NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis in adults

Specification for manufacturer/sponsor submission of evidence

July 2013

Table of contents

Glossary 8
Section A – Decision problem 35
1 Description of technology under assessment 35
2 Context 45
3 Equality 57
4 Innovation 58
5 Statement of the decision problem 60
Section B – Clinical and cost effectiveness 63
6 Clinical evidence 64
7 Cost effectiveness 227
Section C – Implementation 365
8 Assessment of factors relevant to the NHS and other parties 365
9 References 365
10 Appendices 391

List of Tables

Table 1. Annualised Relapse Rate Results from the Basecase MTC 26
Table 2. Three Month Sustained Accumulation of Disability Results from the MTC 26
Table 3. Six Month Sustained Accumulation of Disability Results from the MTC 26
Table 4. Base-case probabilistic cost-effectiveness results within active RRMS 31
Table 5. Probabilistic cost-effectiveness results within HA despite interferon use RRMS 32
Table 6. Probabilistic cost-effectiveness results within RES RRMS 32
Table 7. Estimated annual drug budget impact of introducing alemtuzumab into England and Wales 34
Table A1.1 Clinical development programme for alemtuzumab 39
Table A1.2 Unit costs of technology being appraised 40
Table B6.2.1 Eligibility criteria used in search strategy 66
Table B6.2.2 Alemtuzumab clinical study reference sources 69
Table B6.2.3 List of relevant RCTs 71
Table B6.2.4 Ongoing RCTs/ Extension studies 71
Table B6.3.1 Comparative summary of methodology of the Phase II and Phase III RCTs 74
Table B6.3.2 Summary of methodology of the Phase III extension arm 82
Table B6.3.3 Overview of patient inclusion criteria 84
Table B6.3.4. Baseline characteristics of patients in Phase II and Phase III Alemtuzumab Studies 87
Table B6.3.5 Primary and secondary outcomes of the RCTs 91
Table B6.3.6 Summary of key tertiary endpoints in alemtuzumab Phase III clinical trials 94
Table B6.3.7 Summary of statistical analyses in RCTs 96
Table B6.4.1 Quality assessment results for RCTs 109
Table B6.5.1 (Comparative) summary of results of the Phase II and Phase III RCTs 114
Table B6.5.2. Relapse outcomes in CAMMS223 to month 60 [Coles *et al*, 2012c, Genzyme CAMMS223 CSR] 121
Table B6.5.3. Six-month sustained accumulation of disability event and treatment effect summary by year (Full Analysis Set) [CAMMS223 CSR] 121
Table B6.5.4. Three-month sustained accumulation of disability event and treatment effect summary by year (Full Analysis Set) [CAMMS223 CSR] 122
Table B6.5.5 Proportion of alemtuzumab treated patients without disease activity and EDSS change from baseline to Year 3 in the Extension Study 124
Table B6.5.6. Efficacy of alemtuzumab in patients with rapidly evolving severe disease 125
Table B6.6.1 ARR direct evidence 132
Table B6.6.2 Proportion relapse-free direct evidence 132

Table B6.6.3. Three-month sustained accumulation of disability 132
Table B6.6.4. Six-month sustained accumulation of disability 132
Table B6.6.5 All-cause discontinuation 132
Table B6.6.6 Discontinuation due to adverse events 133
Figure B6.7.1 PRISMA diagram 136
See Additional Appendix 5 for MTC quality assessment table 138
Table B6.7.1 Summary data from the RCTs included in the MTC base case analysis 138
See Additional Appendix 6 for a summary of data used in the MTC analysis and see below. 147
Table B6.7.2 Summary of the trials used to conduct the indirect comparison – part A 148
Table B6.7.3 Summary of the trials used to conduct the indirect comparison – part B 150
Table B6.7.4 Analyses conducted by outcome 158
Table B6.7.5. Annualised relapse rate results from the MTC ≥80% RRMS 160
Table B6.7.6 Proportion relapse-free results from the MTC ≥80% RRMS 161
Three-month SAD 162
Six-month SAD 163
Table B6.7.9. Total discontinuations odds ratio results from the MTC 164
Discontinuations due to Adverse Events 165
Table B6.7.10. Discontinuations due to adverse events odds ratio results from the MTC 165
Table B6.7.11 Inferred rates for (SC IFNβ-1a) 22μg post-2000 166
Table B6.7.12. Comparison of definitions of HA by trial included in the HA subgroup MTC 169
Table B6.7.13. Three-month SAD, sub-group – analysis: HA despite interferon use 171
Table B6.7.14. Annualised relapse rates, sub-group – analysis: HA despite interferon use 171
Table B6.7.15. Comparison of definitions of RES by trial included in the RES subgroup MTC 172
Table B6.7.16. Three-month SAD, sub-group – analysis: RES 174
Table B6.7.17. Annualised relapse rates, sub-group – analysis: RES 174
Table B6.8.1 Summary of relevant non- RCTs 180
Table B6.8.2. Disability outcomes of 87 alemtuzumab – treated patients 184
Table B6.9.1. Overview of adverse events in all active-controlled studies 187
Table B6.9.2. Number (%) of patients with an AE (when incidence ≥5% in any treatment group) by Preferred Term 188
Table B6.9.3 Protocol Risk Minimisation Measures - Genzyme-Sponsored Clinical Studies of Alemtuzumab in Multiple Sclerosis 199
Table B6.9.4. Summary of protocol-specified safety monitoring and prophylactic/concomitant medication administration 200
Table B6.10.1. Proportion of patients treated with 12mg alemtuzumab in Phase II and 3 clinical studies 226
Table B7.1.1 Table detailing two studies identified as potential informants of the alemtuzumab cost-effectiveness model 229
Table B7.2.1 Key features of analysis 236
Table B7.3.1 Mean odds ratios of withdrawal for teriflunomide vs. comparators in the model 246
Table B7.3.2 Annual all-cause rates of withdrawal rates used in the model 247
Table B7.3.3 Mortality multipliers by EDSS score 248
Table B7.3.4 Natural history transition matrix of active RRMS patients. Transition probabilities from EDSS 0 sourced from TOWER and TEMSO placebo arms. Transition probabilities from EDSS 1 to 9 are sourced from London Ontario 249
Table B7.3.5 Natural history transition probabilities of SPMS patients sourced from London Ontario 250
Table B7.3.6 Annual probability of conversion to SPMS from RRMS by EDSS score 251
Table B7.3.7 Natural history transition matrix per EDSS health state and classification based on active RRMS and SPMS transitions from the London Ontario dataset 252
Table B7.3.8 Summary of sources for natural relapse rates 253
Table B7.3.9 Weighted average of relapse rate per year since diagnosis derived by Held et al [Held et al. 2005] 253
Table B7.3.10 Annual relapse rate per year since diagnosis derived from [Patzold et al. 1982] 254
Table B7.3.11 UK MS Survey patient numbers per PDDS / EDSS state by year since diagnosis [Orme et al. 2007] 254

Table B7.3.12 Relapse rates by EDSS score and MS classification 255
Table B7.3.13 Relative risk of relapse compared to placebo sourced from mixed-treatment comparisons 256
Table B7.3.14 Relative effects of treatments on relapses leading to hospitalisation 257
Table B7.3.15 Adverse events of alemtuzumab included in cost-effectiveness model 258
Table B7.3.16 Breakdown of ITP severity from Pool C [Genzyme ISS 2012] 260
Table B7.3.17 Adverse events probabilities used in the model 261
Table B7.3.18 Relative effects of treatments on 3-month sustained accumulation of disability 262
Table B 7.3.19 Example of adjustment of transition probabilities to account for negative probabilities of staying in EDSS states for high hazard ratios where negative probability is N 264
Table B7.3.20 Alemtuzumab transition matrix for EDSS health states and MS classification 265
Table B7.3.21 RRMS transition matrix for alemtuzumab derived using direct trial data (Pooled CARE-MS I and CARE-MS II) 267
Table B7.3.22 RRMS transition matrix for SC IFNβ-1a 44µg derived using direct trial data (Pooled CARE-MS I and CARE-MS II) 268
Table B7.3.23 Comparison between results of natural history method and direct comparison method 268
Table B7.3.24 Summary of variables applied in the base case economic model and explored in sensitivity analysis (SA) 271
Table B7.3.25 Assumptions with justifications, used in the cost-effectiveness model 277
Table B7.4.1 Summary of identified quality of life studies implemented in the model 286
Table B7.4.2 EDSS utilities [Orme et al. 2007] 288
Table B7.4.3 Carer disutility used in the model [Gani, 2008] 289
Table B 7.4.4 Utilities of adverse events, when combined with expected duration of event 290
Table B7.4.5 Summary of quality of life values for cost-effectiveness analysis 294
Table B7.5.1 Acquisition costs of DMTs 299
Table B7.5.2 Acquisition costs for alemtuzumab 301
Table B7.5.3 Annual administration costs associated with DMTs 303
Table B7.5.4 Monitoring resource use associated with DMTs 305
Table B7.5.5 Monitoring costs associated with DMTs 305
Table B7.5.6 Summary of identified cost and resource use studies implemented in the model 308
Table B7.5.7 Annual costs associated with the technologies in the economic model 312
Table B7.5.8 List of health states and associated costs in the economic model 313
Table B7.5.9 Costs of treatment of DMT adverse events 315
Table B7.5.10 Cost calculations for costs associated with relapses [Dee et al. 2012] 319
Table B7.5.11 Costs associated with relapses included in the economic model 319
Table B7.6.1 Structural uncertainty analyses performed for alemtuzumab versus SC IFNβ-1a 44µg in the active RRMS population, fingolimod in the HA RRMS despite treatment with a beta interferon population and natalizumab in the RES RRMS population 320
Table B7.6.2 Deterministic one-way parameter uncertainty analyses performed in the economic model presented through tornado diagrams for alemtuzumab versus SC IFNβ-1a 44µg in the active RRMS population, with abridged analysis also performed for fingolimod and natalizumab 322
Table B7.6.3 Deterministic parameter uncertainty analyses performed in the economic model to test sources of data used 322
Table B7.6.4 Parameters included in probabilistic sensitivity analysis (PSA) 323
Table B7.7.1 Summary of alemtuzumab and SC IFNβ-1a 44µg model results compared with clinical data from CARE-MS I and CARE-MS II 326
Table B7.7.2 Alemtuzumab (mid-year estimates) 327
Table B7.7.3 SC IFNβ-1a 44µg (mid-year estimates) 329
Table B7.7.4 Alemtuzumab and SC IFNβ-1a 44µg accrued deterministic QALYs over time 331
Table B7.7.5 Summary of deterministic LY gain by health state over 50 year time horizon of model 333
Table B7.7.6 Summary of deterministic QALY gain by health state over 50 year time horizon of model 334
Table B7.7.7 Summary of deterministic costs by health state 335
Table B7.7.8 Summary of predicted resource use by category of cost (£) 336
Table B7.7.9 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS ranked by cost 337

Table B7.7.10 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are strongly dominated 338
Table B7.7.11 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are extendedly dominated 338
Table B7.7.12 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS 338
Table B7.7.13 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are strongly dominated 339
Table B7.7.14 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are extendedly dominated 339
Table B7.7.15 One way sensitivity analysis results of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS 343
Table B7.7.16 One way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS 344
Table B7.7.17 One way sensitivity analysis results of alemtuzumab versus natalizumab in active RRMS 344
Table B7.7.18 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (all-years, 80% RRMS) for 3-month SAD, ARR and withdrawal 346
Table B7.7.19 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (all-years, 100% RRMS) for 3-month SAD, ARR and withdrawal 346
Table B7.7.20 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (post-2000, 100% RRMS) for 3-month SAD, ARR and withdrawal 347
Table B7.7.21 Deterministic parameter sensitivity analysis of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS 351
Table B7.7.22 Results of deterministic scenario analysis of dosage of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS 352
Table B7.9.1 RES MTC outcomes for the model, Post 2000 100% RRMS 354
Table B7.9.2 HA disease despite treatment with a beta interferon MTC outcomes for the model, Post 2000 100% RRMS 355
Table B7.9.3 Probabilistic subgroup results for HA RRMS despite treatment with a beta interferon 355
Table B7.9.4 Deterministic subgroup results for HA RRMS despite treatment with a beta interferon 355
Table B7.9.5 One way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon 357
Table B7.9.6 Deterministic parameter sensitivity analysis of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon 359
Table B7.9.7 Probabilistic subgroup results for RES RRMS 359
Table B7.9.8 Deterministic subgroup results for RES RRMS 359
Table B7.9.9 One way sensitivity analysis results of alemtuzumab versus natalizumab for RES RRMS 361
Table B7.9.10 Deterministic parameter sensitivity analysis of alemtuzumab versus natalizumab for RES RRMS 363
Table B7.10.1 Strengths and limitations of the evaluation 364
Table C8.1 Derivation of patient populations eligible for treatment with alemtuzumab 366
Table C8.2 Derivation of total patients receiving alemtuzumab and total patients whose DMT treatment is alemtuzumab 367
Table C8.3 Current MS treatment options and uptake of alemtuzumab 368
Table C8.4 Acquisition costs associated with beta-interferons and glatiramer acetate 369
Table C8.5 Additional cost of administration cost associated with alemtuzumab 370
Table C8.6 Additional monitoring cost associated with alemtuzumab 370
Table C8.7 Additional adverse event cost associated with alemtuzumab 371
Table C8.8 Net budget impact of introducing alemtuzumab into England and Wales assuming the list price with fingolimod 372
Table C10.2.1 PubMed Search Strategy [UBC SLR Protocol, 29 May 2012] 410
Table C10.2.2 CENTRAL Search Strategy [UBC SLR Protocol, 29 May 2012] 411
Table C10.2.3 Embase Search Strategy [UBC SLR Protocol, 29 May 2012] 412
Table C10.5.1 Quality assessment of the studies included in the mixed treatment comparison (except alemtuzumab studies which are shown in section 6.4.3 in the main submission) 418

Table C10.5.1 Quality assessment of the non-RCT studies included in the submission using checklist from Downs and Black 1998 432
Table C10.10.1 Databases searched and interfaces used in the cost- effectiveness systematic review 434
Table C10.10.2 Cost-effectiveness search strategy 436
Table B10.10.3 Eligibility criteria used in the cost-effectiveness systematic review 439
Table C10.11.1 Quality assessment of applicable cost-effectiveness results 442
Table C10.12.1 Databases searched and interfaces used in the quality of life systematic review 448
Table C10.12.2 Quality of life search strategy 450
Table C10.12.3 Eligibility criteria used in the quality of life systematic review 451
Figure B10.12.1 Flow diagram for the quality of life systematic review 453
Table C10.13.1 Databases searched and interfaces used in the cost and resource use systematic review 454
Table C10.13.2 Cost and resource use search strategy 455
Table C10.13.3 Eligibility criteria used in cost and resource use systematic review 457

List of Figures

Figure A2.1 The Expanded Disability Status Scale (Adapted from Kurtze 1883) 47
Figure A2.2 Current treatment pathway for patients with MS 54
Figure B6.2.1 Systematic literature review 68
Figure B6.3.1. CAMMS223 Study and Extension Dosing 81
Figure B6.3.2. Phase II (CAMMS223) and Extension Trial Profile 104
Figure 6.3.4. Phase III CARE-MS I Trial Profile 105
Figure 6.3.5. Phase III CARE-MS II Trial Profile 106
Figure B6.3.6. CAMMS03409 Extension Trial Profile [Fox et al, 2013] 107
Figure B6.3.7. CAMMS03409 Extension Trial Patient Disposition [Fox et al, 2013] 107
Figure B6.5.1. Subgroup analysis of reduction in six-month SAD by number of alemtuzumab cycles received 122
Figure B6.5.2 CAMMS0349 3 ARR results by prior Phase III study [Fox et al, 2013] 124
Figure B6.5.3 Mean EDSS change from baseline to Year 3 in the Extension Study 125
Figure B6.5.4. Summary of Relapse Rate Ratio up to 2 year subgroup analysis (Pooled CAMMS223, CARE-MS I, CARE-MS II CAMMS3409) 128
Figure B6.5.5. Summary of Sustained Accumulation of Disability up to 2 year subgroup analysis (Pooled CAMMS223, CARE-MS I, CARE-MS II CAMMS3409) 129
Figure B6.7.1 PRISMA diagram 136
Figure B6.7.2 ARR Network (Base Case–Recruitment Year 2000 Onward, at least 80% RRMS) 151
Figure B6.7.3 Relapse-free Network (Base Case –Recruitment Year 2000 Onward, at least 80% RRMS) 152
Figure B6.7.4 Three-month SAD Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS) 153
Figure B6.7.5 Six-month SAD network (Base case – Recruitment year 2000 Onward, at least 80% RRMS) 154
Figure B6.7.6 Overall Discontinuation Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS) 155
Figure B6.7.7 DAEs Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS) 156
Figure B6.7.8. Forest Plot: Annualised relapse rate results from the MTC ≥80% RRMS 160
Figure B6.7.9. Forest Plot: Proportion relapse-free results from the MTC 161
Figure B6.7.10. Forest plot: Three-month sustained accumulation of disability results from the MTC ≥80% RRMS 162
Figure B6.7.15 Three-month SAD Network (HA despite interferon use subgroup) 170
Figure B6.7.16 Three-month SAD Network (RES subgroup) 173
Figure B6.9.1. Incidence of AEs over time upto Year 4 for alemtuzumab-treated patients 192
Figure B7.2.1 Schematic of the model 231
Figure B7.2.2 Outcomes in NICE alemtuzumab final scope 232
Figure B7.2.3 Application of treatment effect on relapse segregated by hospitalisation status 235
Figure B7.2.4 Comparators in NICE alemtuzumab final scope 237

Figure B7.3.1 Baseline EDSS distribution used in base case modelling, sourced from UK Risk Sharing Scheme 243
Figure B7.3.2 Baseline EDSS distribution used in modelling alternative scenario, sourced from pivotal alemtuzumab CARE-MS trials 244
Figure B7.3.3 Markov transition matrices for cohort 245
Figure B7.4.1 Health-related quality of life and disability levels [Novartis 2011] 280
Figure B7.4.2 Health-related quality of life and relapses [Novartis, 2011] 281
Figure B7.4.3 Short Form-36 (SF-36) scores in MS patients compared with patients with Parkinson's disease and UK norms [Riazi et al. 2003] 282
Figure B7.4.4 Observed EQ-5D Utility Score in CARE-MS trials 284
Figure B7.5.1 Data extracted from Karampampa et al. [Karampampa et al. 2012] 309
Figure B7.5.2 Data extracted from Tyas et al. [Tyas et al. 2007] 310
Figure B7.5.3 Illustration of the difference in natural history costs from available sources 313
Figure B7.7.1 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS 341
Figure B7.7.2 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS 341
Figure B7.7.3 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus natalizumab in active RRMS 342
Figure B7.7.4 PSA scatter plot of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS 348
Figure B7.7.5 PSA scatter plot of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS 348
Figure B7.7.6 PSA scatter plot of alemtuzumab versus natalizumab in active RRMS 349
Figure B7.7.7 Multi-CEAC of alemtuzumab versus all beta-interferons, glatiramer acetate, fingolimod and natalizumab in active RRMS 350
Figure B7.7.8 CEAF of alemtuzumab versus all beta-interferons, glatiramer acetate, fingolimod and natalizumab in active RRMS 350
Figure B7.9.1 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon 356
Figure B7.9.2 PSA scatter plot of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon 358
Figure B7.9.3 CEAC of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon 358
Figure B7.9.4 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus natalizumab for RES RRMS 360
Figure B7.9.5 PSA scatter plot of alemtuzumab versus natalizumab for RES RRMS 362
Figure B7.9.6 CEAC of alemtuzumab versus natalizumab for RES RRMS 362
Figure B10.10.1 Flow diagram for the cost-effectiveness systematic review 440
Figure B7.5.1 Flow diagram for the cost and resource use systematic review 458

Glossary

Abbreviation	Definition
µg	Microgram
AAN	American Academy of Neurology
ABN	Association of British Neurologists
ACTRIMS	Americas Committee for Treatment and Research in Multiple Sclerosis
AE(s)	Adverse Event(s)
AFFIRM	Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis
ANCOVA	Analysis of Covariance
ANS	American Neurological Society
ARR	Annualised Relapse Rate
B-CLL	B-cell Chronic Lymphocytic Leukaemia
BCMS	British Columbia Multiple Sclerosis
BGR	Brooks-Gelman-Rubin
BNF	British National Formulary
BSC	Best Supportive Care
CC	Complications and Comorbidities
CE	Cost-Effectiveness
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use

CI(s)	Confidence Interval(s)
CMR	Cochrane Methodology Register
CMSC	Consortium of Multiple Sclerosis Centres
CMSMS	Canadian Multiple Sclerosis Monitoring System
CNS	Central Nervous System
CPI	Consumer Price Indices
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Chronic Progressive Multiple Sclerosis
CrI	Credible Interval
CRF	Case Report Form
CSR	Clinical Study Report
DAE	Discontinuation for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DMSR	Danish MS Registry
DMT	Disease Modifying Treatment
DOF	Data on file
DoH	Department of Health
DSA	Deterministic Sensitivity Analysis
EBDiMS	Evidence-based Decision Support in MS
ECG	Electrocardiography
eCRF	Electronic Case Report Forms
ECTRIMS	European Committee for Treatment and Research in Multiple Sclerosis
EDMUS	European Database for Multiple Sclerosis
EDSS	Expanded Disability Status Scale

EEACT	Economic Evaluation Alongside Clinical Trial
EED	Economic Evaluation Database
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
ENS	European Neurological Society
EPAR	European Public Assessment Reports
ERG	Evidence Review Group
EThOS	Electronic Theses Online Service
FA	Full Analysis
FAMS	Functional Assessment of Multiple Sclerosis
FBC	Full Blood Cell Count
FDA	US Food and Drug Administration
GA	Glatiramer Acetate
GAD	Gadolinium Enhancement
GBM	Glomerular Basement Membrane
GP	General Practitioner
HA(D)	Highly Active (disease)
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard Ratio
HRG	Healthcare Resource Groups
HRQL	Health-Related Quality of Life
HRUQ	Health Resource Utilization Questionnaire
HTA	Health Technology Assessment

IAR	Infusion Associate Reaction
ICER	Incremental Cost-Effectiveness Ratio
IFN	Interferon
IFNβ-1a	Interferon Beta-1a
IFNβ-1b	Interferon Beta-1b
IFU	Instructions For Use
IM	Intramuscular
IQR	Interquartile Range
IRIS	Immune Reconstitution Inflammatory Syndrome
ISS	Integrated Safety Summary
ITP	Immune thrombocytopenia
ITT	Intent-To-Treat
IV	Intravenous
IVIG	Intravenous immune globulin
IVRS	Interactive Voice Response Systems
JCV	John Cunningham virus
KOL	Key Opinion Leader
LACTRIMS	Latin American Committee for Treatment and Research in Multiple Sclerosis
LLN	Lower Limit of the Normal range
LY	Life Years
MA(A)	Marketing authorisation (application)
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Score

MedDRA	Medical Dictionary for Regulatory Activities
MESH	Medical Subject Heading
MG	Milligram
ML	Millilitre
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSDN	MS Database Network
MSFC	Multiple Sclerosis Functional Composite
MSM	Multi-State Markov
MTC	Mixed Treatment Comparison
MTR	Magnetization Transfer Ratio
NAB	Neutralising Antibodies
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Not Otherwise Specified
NR	Not recorded
ONS	Office for National Statistics
OR	Odds Ratio
OTC	Over The Counter
PAS	Patient Access Scheme
PASAT	Paced Auditory Serial Addition Test
PbR	Payment by Results
PCR	Polymerase Chain Reaction
PDDS	Patient Determined Disease Steps

PICOS	Population Interventions Comparators Outcomes Study type
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRMS	Progressive-Relapsing Multiple Sclerosis
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
PSS	Personal Social Services
PT	Preferred Term
QALY	Quality-Adjusted Life Year(s)
QUOROM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
RES	Rapidly Evolving Severe (disease)
RMS	Relapsing Multiple Sclerosis
RR	Relapse Rate
RRMS	Relapsing-Remitting Multiple Sclerosis
RSS	Risk Sharing Scheme
RTI	Respiratory Tract Infection
SA	Sensitivity Analysis
SAD	Sustained Accumulation of Disability
SAE	Serious Adverse Event
SC	Subcutaneous
ScHARR	School of Health and Related Research

SD	Standard Deviation
SF-36	Short Form Health Survey
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
S(m)PC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
SRD	Sustained Reduction in Disability
STA	Single Technology Appraisal
SUR	Safety Update Report
TIW	Three times a week
TSH	Thyroid-stimulating hormone
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
WTP	Willingness to Pay

Executive summary

Overview of multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic progressive potentially disabling disorder associated with an increased risk of death and considerable social impact and economic consequences [Pugliatti et al. 2006].

In the UK, approximately 100,000 people have MS [MS Trust 2012]. In England and Wales it is estimated that 88,766 people have MS (based on England and Wales having a population of 56.1 million out of a total UK population of 63.2 million) [ONS 2012]. The mean age of onset of MS symptoms is between 20-50 years [NICE, 2003] with the highest prevalence in the age group 50-64 years [Pugliatti et al. 2006] and it predominantly affects women, with an approximate ratio of 3:1 [Pickin et al. 2009].

In the UK, MS is classified into three key sub-types: relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS).

Relapsing MS (RMS) and relapsing-remitting MS (RRMS)

RMS is a classification encompassing any MS patient who experiences periods of relapse during their disease course. A relapse is a clinically evident 'attack' of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, completely or partially. For two relapses to be considered as such, a period of 30 days must have elapsed between the onset of new symptoms for each event [Coles 2009].

The majority of RMS patients (approximately 85% of all MS patients at diagnosis) have RRMS [Murray, 2006]. Patients with RRMS experience recurring episodes of acute neurological dysfunction (relapses) followed by more or less complete recovery of function. In England and Wales it is estimated that 31,512 people will have RRMS (35.5%) [Kobelt et al. 2006] of which 9,769 (31%) will be treated [Zajicek et al. 2010]. Over time, remission from relapses becomes incomplete and the person with MS is left with some residual effects.

Current pharmacological management includes the use of disease modifying treatments (DMTs), targeted at reducing the frequency and/or severity of relapses and/or slowing disability progression. MS disease should be controlled as early as possible and experience with DMTs indicates that there is a window of opportunity where early use may control the disease in some patients [Coles, 2006; Gold, 2010]. Despite the currently available MS treatments, there is a need for additional convenient, effective and safe treatment options in MS which reduce the level of disability accumulation and reduce the burden of treatment administration.

Burden of MS

MS symptoms include signs of multiple neurological dysfunctions (visual and sensory disturbances, limb weakness, gait problems and bladder and bowel symptoms) followed by recovery or by an increasing disability because of irreversible functional disability over time [Pugliati et al. 2006].

The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability progression although the contribution of the former to the latter is not clear [Confavreux et al. 2006].

Relapse rates in RRMS vary considerably over time for an individual and between individuals but there is a general pattern of periods of more frequent relapses, followed by long periods of lower rates [Richards et al. 2002]. The initial relapse rate can be less than one per year and subsequently declines [Coles 2009]. Relapses may require admission to hospital, are associated with a level of disability and incapacity that disrupts working, family and social life [NICE, 2002], and have a significant impact on quality of life [Orme et al. 2007].

Disability accumulation is a defining feature of RRMS and can be correlated with the extent of axonal injury and further associated with the degree of myelin inflammation [Leray et al. 2010]. It has been hypothesised that a close association between inflammation and neurodegeneration might exist in all disease stages of multiple sclerosis [Kutzelnigg et al. 2005; Frischer et al. 2009].

The impact of disability on patients and society is profound. Costs and utility are highly correlated with disease severity; in particular employment rates reduce substantially with increased EDSS while the costs of care and productivity losses increase more than tenfold between an EDSS score of 0-1 and a score ≥7 [Tyas et al. 2007; Karampampa et al. 2012]. Utility decreases are aligned with increased EDSS scores, and leads to scores worse than death at EDSS 8-9 [Orme et al. 2007].

In the clinical trial programme for alemtuzumab, the outcomes discussed above have been formally assessed by measuring annualised relapse rates, time to six-month sustained accumulation of disability (SAD) (using changes in Expanded Disability Status Scale (EDSS) score), proportion of relapse free patients and quality of life measures.

Measuring disability accumulation

The most accepted tool to measure disability is the EDSS, which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half. A score of six on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with DMTs [Kurtze, 1983].

The clinical trial programme for alemtuzumab reports on sustained accumulation of disability (SAD) for three and six-months as this acknowledges permanent deterioration in patient mobility. Six-month SAD is considered to be a robust measure of sustained disability accumulation, 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”. Not all studies for comparators included the measurement of six-month SAD but they did include SAD outcome data based on a three month definition of sustained disability (hence the HE model uses three-month SAD data).

Alemtuzumab: product details and mechanism of action

Alemtuzumab is a recombinant DNA-derived humanised monoclonal antibody directed against the 21-28 kD cell surface glycoprotein CD52. Alemtuzumab is an IgG1 kappa antibody with human variable framework and constant regions, and complementary-determining regions from a murine monoclonal antibody. The antibody has an approximate molecular weight of 150 kD.

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T ($CD3^+$) and B ($CD19^+$) lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not fully elucidated. However, research suggests immunomodulatory effects through the depletion and repopulation of lymphocytes, including:

- Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment
- Increased representation of regulatory T cell subsets
- Increased representation of memory T- and B-lymphocytes
- Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells)

The reduction in the level of circulating B and T cells by alemtuzumab and subsequent repopulation may reduce the potential for relapse, which ultimately delays disease progression.

Alemtuzumab: indication

Alemtuzumab (Lemtrada®) 12mg concentrate for solution for infusion has a positive CHMP opinion for the treatment of adult patients with RRMS with active disease defined by clinical or imaging features. [EMA, 2013].

The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses.

- Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.

Alemtuzumab treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS.

If additional treatment courses are to be given they must be administered at least 12 months after the prior course [SmPC]. 80-82% of patients did not require retreatment CARE MS I and II extension study data which has reported up to year 3. [redacted] of patients in CAMMS 223 extension study did not need retreatment in years 3-5.

The anticipated list price will be £7,045 per vial.

Place in therapy

In the context of clinical practice in England and Wales, a minimum criteria of two or more relapses in the prior two years is, based on clinical opinion, likely to be used to initiate treatment naïve patients on alemtuzumab in line with ABN guidance defining active disease as it relates to starting patients on interferons and glatiramer acetate. In patients receiving another DMT a definition of active disease which is based either on a clinical definition of active disease (eg. the occurrence of relapses) or one based on imaging will be used to switch patients to alemtuzumab.

In clinical practice in England and Wales, alemtuzumab will be prescribed for patients with active RRMS in the following way

- 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 natilizumab or fingolimod (although the definition of highly active for use of alemtuzumab would not need to be as restrictive as that contained within the licences for these two drugs and would be aligned to the more inclusive definition used amongst clinicians in England and Wales treating MS). Feedback from a number of MS specialists experienced in prescribing alemtuzumab in clinical trials or in off label use shows a trend towards using alemtuzumab earlier in the disease process as experience is gained . This includes patients who are treatment naïve or those with less severe disease. This includes patients who have active RRMS which is not highly active.

- There will be use of alemtuzumab in patients who have active RRMS which is not highly active disease. The extent of this use is an area of uncertainty. However, it is a highly important group to consider because the current discussions amongst MS Specialists about use in this group based on experiential use of alemtuzumab within its broad licence over the medium to long term has the potential to lead to a paradigm shift in the treatment of MS and make a substantial impact on patient's clinical outcomes. Of note in this regard is the following:

    - Some clinicians will choose to use alemtuzumab in place of interferons or glatiramer acetate in active RRMS which is not highly active. This will include first lne use. This includes some clinicians who will use the drug in this way immediately. This is in line with increasing confidence amongst MS specialists about the value of using alemtuzumab in the earlier stages of MS as a means of achieving better outcomes [Coles 2006].
    - Alemtuzumab has demonstrated superiority, in patients with active RRMS, against an interferon (SC INF-1a) in terms of reducing the sustained accumulation of disability and reducing relapses. Alemtuzumab is the first MS treatment to show improved efficacy on disability accumulation endpoints against an active comparator. This active comparator was sc INF-1a [Coles *et al,* 2008; Coles *et al,* 2012b, Cohen *et al,* 2012].
    - The categorisation of MS into an earlier focal inflammatory phase (equating to EDSS 0-3) leading to a later neurodegenerative phase (beyond EDSS 3) has been postulated within the literature [Leroy et al 2010] with the suggestion that this earlier phase may signify a "therapeutic window of opportunity" in which DMTs should be targeted to maximise long term patient outcomes [Leroy *et al*, 2010; Coles *et al,* 2006; Gold *et al,* 2010]; earlier use of alemtuzumab would be aligned to this view of how to achieve optimal outcomes.
    - The broad licence of alemtuzumab supports this compared to the licences of natalizumab and fingolimod which limit them to use in highly active RRMS patients.

Clinical studies support the use of alemtuzumab in all of these subgroups:

Subgroup	Evidence
Treatment naive patients with active RRMS	CAMMS223 (Phase II), CARE-MS I
Treatment experienced patients with active RRMS	CARE-MS II
In patients with highly active disease despite interferon use (in line with the fingolimod licence)	Subgroup analysis
In patients that have RES RRMS	CARE-MS II subgroup analysis

Summary of clinical evidence with relevance to the decision problem

Alemtuzumab is the first MS treatment to show improved efficacy on disability accumulation endpoints against an active comparator [Coles et al, 2008, Coles et al, 2012a, Cohen et al, 2012]. During the clinical trial programme, alemtuzumab demonstrated a significant reduction in the relapse rate compared to SC IFNβ-1a [Coles et al, 2008, Coles et al, 2012a, Cohen et al, 2012].

Additionally, alemtuzumab has the potential to change the way that MS is treated because in longer term studies (up to 5 years) a high proportion of patients after the initial 2 year treatment course did not need retreatment. This compares with other DMTs which are administered on an ongoing, chronic basis.

CAMMS 223 Phase II: active-controlled

The randomised, rater-blinded, active-controlled phase II CAMMS223 study included 334 previously untreated patients with active RRMS. 113 patients received alemtuzumab 12mg dose*, 110 patients received alemtuzumab 24mg dose*, 111 patients received SC IFNβ-1a 44µg. The co primary measures of efficacy were the time to six-month SAD and the rate of relapse. Significant reduction in the relapse rate and the time to six-month SAD was observed and the results were published in a peer reviewed journal [Coles et al. 2008].

- Alemtuzumab 12 mg reduced the relapse rate by 69% compared with SC IFNβ-1a (HR 0.31 [95%CI: 0.18, 0.52] p<0.001) over three years. The ARR at 36 months was 0.36 (95% CI: 0.29, 0.44) for SC IFNβ-1a and 0.11 (95% CI: 0.08, 0.16) for alemtuzumab 12mg [Coles et al. 2008].

- Alemtuzumab 12mg reduced the risk of six-month SAD by 75% over 3 years compared to SC IFNβ-1a (hazard ratio (HR) 0.25 [95% CI: 0.11, 0.57] p<0.001). At Year 3, 26.2% of patients in the SC IFNβ-1a group had experienced six-month SAD, compared with 8.5% in the alemtuzumab group [Coles et al. 2008].

- Patients in the alemtuzumab 12mg arm demonstrated a mean improvement in EDSS of 0.32 points from baseline at Year 3 (95% CI: -0.55, -0.10; p=0.006), whereas SC IFNβ-1a treated patients experienced a mean worsening from baseline of 0.38 (95% CI: 0.13, 0.63; p=0.003). This difference was apparent as early as three months following the initiation of alemtuzumab treatment. [Coles et al. 2008].

At the end of the 36 month treatment period, patients were encouraged to enter the CAMS223 5-year follow up study, which was designed to evaluate the long-term durability (safety and efficacy) of alemtuzumab treatment

---

* Initial course of 12 mg/day or 24 mg/day IV for five days at month 0, and second course of 12 mg/day or 24 mg/day for three days at month 12.

(compared to SC IFNβ-1a) and to establish safety and efficacy of alemtuzumab retreatment in patients who received alemtuzumab during the original three-year treatment period. Alemtuzumab patients were given the option for re-dosing with 12mg per day IV for three days with a “fixed” schedule (once annually) or “as needed” if there was evidence of resumed disease activity (patients had, within the previous year experienced at least one protocol-defined relapse or had, within the previous year or since their last on-study MRI, accumulated at least two unique lesions on brain/spinal cord MRIs comprised of any combination of gadolinium-enhancing lesion(s) or new/enlarging MRI T2 lesion[s]).

- The extension arm of the phase II CAMMS223 study demonstrated long term efficacy for alemtuzumab over five years. Over five years, alemtuzumab 12 mg lowered the risk of six-month SAD by 69% and the rate of relapse by 66% compared with IFNβ-1a (both p<0.001)[Coles et al. 2013]

- Most alemtuzumab patients ([redacted]) did not require a third cycle of alemtuzumab at 5 years [Genzyme, CAMMS223 CSR]

Following the positive phase II trial results, an extensive phase III clinical programme with alemtuzumab was launched.

Phase III: Head-to-head vs. interferon beta-**1a (IFNβ**-1a)

CARE-MS I (ClinicalTrials.gov Identifier: NCT00530348) [Cohen *et al,* 2012]

The CARE-MS I trial was designed to assess the efficacy and safety of first-line alemtuzumab compared with SC IFNβ-1a. This was a randomised, open label, rater blinded, interventional, two arm, active controlled study in 581 previously untreated active RRMS patients over 24 months. Patients enrolled had at least two relapses in the previous 2 years and at least one in the previous year. 376 patients were randomised to receive alemtuzumab 12mg and 187 patients received SC interferon β-1a (IFNβ-1a) 44µg.

The co primary measures of efficacy were relapse rate and time to six-month SAD. A relapse was defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater. Disability was assessed according to the ordinal EDSS score. A sustained accumulation was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more. All scores were confirmed twice during a six month period. Secondary endpoints measured over 24 months included: proportion of relapse-free patients, change in EDSS, percentage change in T2-hyperintense lesion volume and change in multiple sclerosis functional composite (MSFC).

- Alemtuzumab significantly reduced the relapse rate at two years by 55% compared with SC IFNβ-1a (p<0.0001). The estimated relative risk for annualised relapse rate (ARR) at two years was 0.18 for alemtuzumab versus 0.39 for SC IFNβ-1a.
- The percentage of patients experiencing six-month SAD at two years was 11.1% in the SC IFNβ-1a group and 8.0% in the alemtuzumab group. This difference was not statistically significant. The 11.1% six-month SAD rate in the SC IFNβ-1a group was much lower than the expected rate of 20%, which had been observed in study CAMMS223 [Genzyme CARE-MS I CSR 2012].
- Alemtuzumab, when compared with SC IFNβ-1a, significantly reduced the risk of developing Gd-enhancing lesions ([redacted]) and new or enlarging T2-hyperintense lesions over 2 years (48% vs. 58%; p=0.04). Importantly, alemtuzumab -treated patients had significant reductions in the rate of brain atrophy as measured by the brain parenchymal fraction compared with SC IFNβ-1a -treated patients (-0.867% vs. -1.488%, respectively; p<0.0001)
- Patients treated with alemtuzumab in CARE-MS I were significantly more likely to be clinically disease free compared with those treated with SC IFNβ-1a (74% vs. 56%, respectively; p<0.0001)
- Both treatment arms consistently improved from baseline SF-36 and EQ-5D at Year 2 compared to baseline. Improvements seen with alemtuzumab–treated patients were greater than those observed for SC IFNβ-1a -treated patients on SF-36 PCS and EQ-VAS, although these differences were not significant.

CARE-MS II (ClinicalTrials.gov Identifier: NCT00548405) [Coles *et al,* 2012a]

In this second, similarly designed Phase III trial alemtuzumab was compared with SC IFNβ-1a in patients who had experienced at least one relapse on interferon-beta or glatiramer acetate. This was a randomised, open label, rater blinded, interventional, three arm, active controlled study in 1046 patients over 24 months. 436 patients were randomised to receive alemtuzumab 12mg, 173 patients received 24mg, and 231 patients received SC IFNβ-1a 44μg.

The co primary measures of efficacy were relapse rate and time to six-month SAD. A relapse was defined as in CARE-MS I. Secondary outcome measures were: proportion of relapse-free patients at two years, change from baseline in EDSS, acquisition of disability as measured by change in MSFC, MRI-T2 hyperintense lesion volume at year two.

- Compared with SC IFNβ-1a, alemtuzumab 12 mg reduced the relapse rate by 49.4% (RR 0.51 [95% CI: 039, 0.65], p<0.0001). The ARR at two years was 0.26 (95% CI: 0.21, 0.33) for alemtuzumab treated patients versus 0.52 (95% CI: 0.41, 0.66) for SC IFNβ-1a treated patients [Coles et al 2012a].

- Alemtuzumab significantly reduced the risk of six-month SAD at two years by 42% compared with SC IFNβ-1a (HR 0·58 [95% CI: 0.38, 0.87], p=0.0084). The percentage of patients experiencing six-month SAD at two years was 12.7% (95% CI: 9.89, 16.27) in the alemtuzumab group and 21.1% (95% CI: 15.95, 27.68) in the SC IFNβ-1a group [Coles et al 2012a].

- Alemtuzumab significantly increased the proportion of patients who were relapse-free at two years compared with SC IFNβ-1a. At Year 2, 65.4% of patients receiving alemtuzumab remained relapse-free compared with less than half (46.7%) of SC IFNβ-1a -treated patients, which represents a 47% reduction in the risk of relapse over 2 years (HR 0·53 [95% CI: 0·41, 0·69],p<0.0001) [Coles et al. 2012a].

- Patients treated with alemtuzumab significantly lowered (improved) EDSS scores at two years of follow-up by a mean of 0.17 points, while patients receiving SC IFNβ-1a reported a worsening of EDSS score by 0.24 points (p<0.0001).

- Alemtuzumab -treated patients showed significantly greater improvements from baseline than SC IFNβ-1a patients over 2 years on two of the self-reported measures of HRQL: the FAMS (p<0.01 for both Year 1 and Year 2) [Arroyo *et al,* 2013] and the physical component score (PCS) component of the SF-36 (p<0.01 for both Year 1 and Year 2) [Selmaj *et al,* 2012]. In both measures, between-group differences mainly reflected greater improvements on scales pertaining to physical functioning as opposed to mental or social functioning [Selmaj *et al,* 2012, Arroyo *et al,* 2013]

Phase III extension (CAMMS03409, ClinicalTrials.gov Identifier: NCT00930553)

An extension study opened in January 2010 for patients participating in the CARE-MS I or CARE-MS II trials to assess the long-term efficacy and safety of alemtuzumab in patients. Additionally, patients from CAMMS223 trial were recruited to this extension. All patients in this study receive alemtuzumab; alemtuzumab-treated patients with documented evidence of resumed disease activity are able to be re-treated, and SC IFNβ-1a patients who met treatment eligibility criteria, were switched to receive two fixed cycles of alemtuzumab (two treatment courses). The study aims to examine the long term safety and efficacy of alemtuzumab treatment in patients who have either received prior alemtuzumab in a previous study, or are receiving it for the first time following SC IFNβ-1a treatment. After two annual treatment courses, additional annual treatment courses of alemtuzumab are administered on an as-needed basis. During the Extension Study, retreatment criteria are defined as at least one relapse or at least two new emerging or enlarging T2 and/or Gd-enhancing brain or spinal lesions. Estimated study completion date is November 2016 [clinicaltrials.gov].

The study has enrolled 223 patients from CAMMS223, 463 patients from CARE MS I, and 628 patients from CARE MS II.

The latest results are as follows:

- Patients treated with alemtuzumab in the Phase III studies (CARE-MS I and CARE-MS II) experienced similar ARRs as were observed during the Phase III study period [Fox 2013]. ARRs were 0.24 and 0.25 at Year 3 as compared to ARRs of 0.18 and 0.26 at Year 2 in CARE-MS I and CARE-MS II respectively [Fox et al. 2013; Cohen et al 2012; Coles et al. 2012a].

- The proportion of patients in the extension study from CARE-MS I and CARE-MS II who remained relapse free at Year 3 was 67% and 55% respectively [Fox et al. 2013].

- The proportion of patients in the extension study from CARE-MS I and CARE-MS II who were six-month SAD free at Year 3 was 88% and 80% respectively [Fox et al. 2013].

- During Year 3, 18% of patients who had enrolled from CARE-MS 1 and 20% of patients who had enrolled from CARE-MS II received alemtuzumab retreatment [Fox et al. 2013].

Meta analysis

A pooled meta-analysis was performed that included all three phase II and III trials (CAMMS223, CARE-MS I and CARE-MS II). These trials only enrolled patients with active RRMS (as defined by having at least two relapses in the previous two years) and therefore this analysis is in line with licensed indication for alemtuzumab. Results from the meta-analysis indicate that alemtuzumab was significantly superior to SC IFNβ-1a for all efficacy and safety measures. Compared with SC IFNβ-1, alemtuzumab-treated patients relapse less frequently, have an improved chance of remaining relapse-free and are less likely to achieve sustained accumulation of disability for 3 and 6 months:

- ARR (rate ratio) = [redacted]
- Proportion relapse free OR = [redacted]
- SAD (3 months) HR = [redacted]
- SAD (6 months) HR = [redacted]

Statistical and clinical heterogeneity between studies appeared to be small.

Mixed Treatment Comparison (MTC)

A feasibility assessment was performed to determine which trials should be included in the MTC analyses and to account for the evidence of decreased relapse rates over time; KOLs recommended excluding studies with patient recruitment before 2000, taking into consideration:

- Reduction in the untreated ARR rate amongst MS patients at diagnosis in more recent years
- The introduction of new MS diagnostic criteria (McDonald)
- Earlier treatment following the publication of the CHAMPS study [Galetta, 2001]
- Timeframe for the development of the different DMTs

For studies where the year(s) of recruitment were not reported, year of publication was used as a proxy.

In addition, a threshold of ≥80% RRMS was suggested following an Advisory Board meeting after reviewing the distribution of the proportion of RRMS patients in the included trials. Therefore, trials in the base-case network were restricted to studies with patient recruitment after 2000 and with ≥80% RRMS patients. Sensitivity analyses were run on datasets without the post 2000 restriction (≥80% RRMS, all years) and for studies which included only RRMS patients (100% RRMS, post 2000).

Among the trials identified in the systematic literature review, 30 were deemed suitable for the base case MTC analyses. In 21 of these trials, patient recruitment took place after 2000; for the remaining nine trials, recruitment was assumed to be after 2000 on the basis of publication year. Most (25) of the included trials utilised the McDonald diagnostic criteria.

All the relevant comparators were identified in the MTC in studies post 2000 with the exception of Rebif 22 μg, which is a dose used in UK practice. Studies were identified pre-2000 including Rebif 22 μg and are presented as part of a sensitivity analysis which considered all years from 1980 and ≥80% RRMS patient population.

The results of the MTC analysis demonstrated that alemtuzumab was associated with [redacted] for relapse outcomes. A majority of the relationships were statistically significant, with the exception of [redacted]

For three- and six-month SAD, alemtuzumab was [redacted] with [redacted] for three-month SAD. Alemtuzumab showed a [redacted] over [redacted] for three-month SAD and was [redacted] for six-month SAD.

Overall, there were very few signs of heterogeneity among outcomes as evaluated by observation of the random-effect variances (sqrt(τ)) for each outcome.

Table 1. Annualised Relapse Rate Results from the Basecase MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 μg	[redacted]	0.68 [0.52, 0.88]
IM IFNβ-1a 30 μg	[redacted]	0.78 [0.67, 0.91]
SC IFNβ-1a 44 μg	[redacted]	0.62 [0.51, 0.76]
GA 20 mg	[redacted]	0.64 [0.53, 0.76]
Fingolimod 0.5 mg	[redacted]	0.46 [0.4, 0.54]
Natalizumab 300 mg	[redacted]	0.31 [0.25, 0.39]

*not statistically significant

Table 2. Three Month Sustained Accumulation of Disability Results from the MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 μg	[redacted]	1.21 [0.68, 2.16]*
IM IFNβ-1a 30 μg	[redacted]	0.91 [0.61, 1.33]*
SC IFNβ-1a 44 μg	[redacted]	0.79 [0.51, 1.24]*
GA 20 mg	[redacted]	0.93 [0.59, 1.45]*
Fingolimod 0.5 mg	[redacted]	0.75 [0.58, 0.96]
Natalizumab 300 mg	[redacted]	0.58 [0.4, 0.84]

*not statistically significant

Table 3. Six Month Sustained Accumulation of Disability Results from the MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 μg	NA	NA
IM IFNβ-1a 30 μg	[redacted]	[redacted]
SC IFNβ-1a 44 μg	[redacted]	[redacted]

GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

*not statistically significant

MTC results for HA and RES RRMS disease subgroups

In response to the decision problem MTCs were also performed to address the efficacy and safety of therapies in HA and RES disease sub-groups; methodology and results for ARR and three-month SAD to allow comparison with fingolimod and natalizumab respectively.

In the MTC analysis of the RES disease subgroup, the ARR rate ratio [redacted] alemtuzumab versus natalizumab, [redacted]). When compared to placebo, the rate ratios for alemtuzumab and natalizumab were [redacted] respectively. Similarly, [redacted] in the three-month SAD results for alemtuzumab and natalizumab (RR [redacted] alemtuzumab vs natalizumab). When compared to placebo, the three-month SAD rate ratios for alemtuzumab and natalizumab were [redacted]) and [redacted]), respectively.

In the MTC analysis of the HA disease despite beta-interferon subgroup, the ARR rate ratio [redacted] alemtuzumab versus fingolimod, [redacted] When compared to placebo, the rate ratios for alemtuzumab and fingolimod were [redacted], respectively. The three-month SAD rate ratio for alemtuzumab versus fingolimod also favoured [redacted]). When compared to placebo, the three-month SAD rate ratios for alemtuzumab and fingolimod were [redacted]) and [redacted]), respectively.

Safety and adverse events

Alemtuzumab has a manageable and predictable safety profile observed in long term phase II (8.5 year interim analysis) and phase III extension studies and observational studies. For three year follow up data in all active controlled studies, the general adverse event (AE) characteristics (frequency, seriousness, severity) observed in the alemtuzumab treatment groups through all available follow up were similar to those in the active-controlled studies. Most patients reported at least one AE, the majority of which were mild or moderate in severity.

- Adverse events rates were comparable between alemtuzumab and SC IFNβ-1a
- In CAMMS223, AEs were reported in 100% of patients in both treatment groups at Year 3

- In CARE-MS I, AEs were reported in 92.0% of SC IFNβ-1a -treated patients and 96.0% of alemtuzumab-treated patients at Year 2.

- In CARE-MS II, AEs were reported in 94.6% of SC IFNβ-1a -treated patients and 98.4% of alemtuzumab-treated patients at Year 2.

In a pooled analysis of CAMMS223, CARE-MS I and CARE-MS II results, most patients reported at least 1 AE, the majority of which were mild or moderate in severity. AE intensity was graded as follows: grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: very severe; grade 5: fatal. The incidence of grade 3, 4, and 5 AEs were [redacted] and [redacted] respectively. The most common AEs were headache[redacted]rash[redacted]MS relapse [redacted]pyrexia[redacted]. Over all available follow-up, [redacted] of patients treated with alemtuzumab discontinued treatment due to an AE [Genzyme ISS 2012].

Overall the incidence of AEs for alemtuzumab-treated patients was highest in Year 1 (93.6%), with the incidence of AEs decreasing over time to 49.7% in Year 4, highlighting that the AEs experienced by alemtuzumab-treated patients become more manageable over time. In contrast to the overall trend, the incidence of thyroid AEs [redacted] 3 for alemtuzumab -treated patients [redacted] [Genzyme ISS 2012].

The incidence of serious AEs was [redacted] The most frequently reported serious AEs for the alemtuzumab group by Medical Dictionary for Regulatory Activities System Organ Class (MedDRA SOC) were [redacted]. The rate of serious AEs by number of courses received was similar across courses in alemtuzumab-treated group ([redacted] [Genzyme ISS 2012].

Treatment with alemtuzumab may result in the formation of autoantibodies and increase the risk of autoimmune mediated conditions including idiopathic thrombocytopaenia (ITP), thyroid disorders or, rarely, nephropathies. The probabilities of autoimmune adverse events associated with alemtuzumab (consisting of hyperthyroidism [redacted]hypothyroidism[redacted]Grave's disease[redacted] ITP[redacted]) in subsequent years in the health economic model were calculated as averages of the incidence in years 2, 3, 4 and 5 from Pool C safety population.The incidence of autoimmune adverse events plateaued to a rate of approximately [redacted] in the trials after 5 years. This observation is supported by a UK based observational study of patients on alemtuzumab [Cossburn et al, 2011] which reported that novel auto-immune disease developed in 22.2% of patients (N=248). In this cohort autoimmune disease was seen from 2 weeks after initial treatment and was most frequent 12–18 months after first treatment. No new cases of autoimmune disease were identified 60 months or more after initial treatment and risk of AID was independent of total alemtuzumab dose or interval of dosage, consistent with the SmPC requirement to continue monitoring for auto-immune disease for four years after the last dose of

alemtuzumab [SmPC 2013, therefore in the health economic model, patients are not a risk of autoimmune AEs after five years.

Alemtuzumab treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS. Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available. Resources for the management of hypersensitivity and/or anaphylactic reactions should be available. Patients treated with alemtuzumab must be given the Patient Card and Patient Guide and be informed about the risks of alemtuzumab.

Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment as serious varicella zoster virus infections, including primary varicella and varicella zoster re-activation, have occurred more often in patients treated with alemtuzumab 12 mg [redacted] in clinical trials as compared to SC IFNβ-1a [redacted]

The risk management program designed to detect more serious adverse events, e.g. ITP, ensuring early treatment and management was piloted during the pivotal studies will be launched at the time of marketing authorisation. Laboratory tests should be conducted at periodic intervals for 48 months following the last treatment course of alemtuzumab in order to monitor for early signs of autoimmune disease [SmPC, 2013]:

- Full blood count with differential (prior to treatment initiation and at monthly intervals thereafter)
- Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)
- Urinalysis with mircroscopy (prior to treatment initiation and at monthly intervals thereafter)
- A test of thyroid function, such as thyroid stimulating hormone levels (prior to treatment initiation and every three months thereafter until 48 months following last infusion of alemtuzumab). After this period of time testing should be performed based on clinical findings suggestive of thyroid dysfunction.

Before initiation of therapy, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection, according to local guidelines. As for any immune modulating medicinal product, before initiating a course of alemtuzumab treatment, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV [SmPC, 2013].

It is recommended that Human Papilloma Virus (HPV) screening be completed annually for female patients [SmPC, 2013].

Cost effectiveness

The patient population considered in the base case economic evaluation is adults with active RRMS defined by clinical or imaging features. The cost-effectiveness analysis considers a number of comparisons within active RRMS. Firstly, alemtuzumab is compared to beta-interferons, glatiramer acetate, fingolimod and natalizumab as an alternative within active RRMS. This is largely in line with the NICE scope, but with the additions of fingolimod and natalizumab, which according to expert opinion, may either be used in broader RRMS populations outside of NICE guidance. In addition, patients on natalizumab or fingolimod may switch to alemtuzumab when at the point of switching they have active RRMS as opposed to HA despite interferon use or RES which they had when they were initiated on treatment [Genzyme KOL interview report, 2013]. Secondly, alemtuzumab is compared to fingolimod and natalizumab in HAD despite interferon use and RES, respectively. This is in line with the NICE scope and expert opinion, and is presented as a subgroup analysis since these populations represent subgroups of the licensed indication.

A multi-state Markov model was developed which considered health states based on disease classification (RRMS or SPMS) and severity (defined by the EDSS). The model was based on a structure developed by the School of Health and Health and Related Research (ScHARR) in the evaluation of beta-interferons for the treatment of MS. Capturing disease classification and progression through EDSS health states within RRMS and SPMS meant that the costs and quality of life implications could be identified and captured for disability progression and relapses. Therefore, it was deemed that a Markov structure was the most appropriative structure to model the cost-effectiveness of alemtuzumab. Costs and QALYs per patient were calculated over a lifetime horizon (50 years) and discounted at 3.5% per annum. Probabilistic results were considered as the base case analysis since the model is complex and non-linear. The use of a probabilistic base case was recommended by the ERG reviewing the fingolimod single technology appraisal (STA) [Novartis, 2011].

Active RRMS patients entered the model with baseline characteristics collected for RRMS patients in the UK Risk Sharing Scheme (RSS). Clinical data used in the model are based on results from the alemtuzumab trials and MTC for RRMS (in the base case), HA despite interferon use (in the subgroup analysis) and RES (in the subgroup analysis). Patients transition through the model accounting for withdrawal, mortality, disease progression in terms of EDSS, conversion from RRMS to SPMS, and a DMT stopping rule as recommended by ABN guidelines [ABN, 2009]. Treatment effects are included in terms of 3-month SAD and ARR from the MTC. SAD HRs are applied to natural history transition matrices derived from the London Ontario active RRMS dataset and supplemented by the placebo arms of TOWER and TEMSO. Treatment transition matrices are used to estimate progression of patients through the disease scale (EDSS) as well as the disease classification in terms of RRMS and SPMS. Quality of life data used in the model accounted for EDSS level, whether a relapse had occurred, treatment-related adverse events and carer disutility. Costs categories were based on the NHS & PSS perspective and included treatment acquisition costs, administration costs, monitoring costs, adverse event costs, disease costs (associated with EDSS level) and relapse costs split by severity.

Sensitivity analysis for active RRMS, HA despite interferon use and RES populations was conducted to explore parameter and structural uncertainty: one-way sensitivity analysis, parameter uncertainty analysis, and structural scenario analysis. Since the EMA suggested SC IFNβ-1a 44µg was an appropriate comparator for alemtuzumab and results of the MTC demonstrated that SC IFNβ-1a 44µg is the most efficacious of the beta-interferons and glatiramer acetate, full sensitivity analyses are only presented against SC IFNβ-1a 44µg. Furthermore, direct data from the CARE-MS trials is used in the model which compared alemtuzumab to SC IFNβ-1a 44µg.

The probabilistic base case considered an incremental analysis which compared all treatments within active RRMS and used a QALY league table, which ranked treatments by cost (as recommended by the STA template). The mean PSA results found that:

- Alemtuzumab strongly dominated IFNβ-1b, fingolimod (without PAS), fingolimod (assuming a PAS price of £13,000 per year) and natalizumab
- IM IFNβ-1a was strongly dominated by SC IFNβ-1a 44µg
- Alemtuzumab extendedly dominated SC IFNβ-1a 44µg and SC IFNβ-1a 22µg

Consequently, the most relevant comparison when considering the mean PSA results was alemtuzumab vs. glatiramer acetate, which provided an incremental cost-effectiveness ratio (ICER) of £7,017 per QALY. In addition, the cost-effectiveness acceptability curve (CEAF) confirmed that alemtuzumab was the most cost-effective of all treatment alternatives for all willingness to pay (WTP) thresholds above £7,100 per QALY. Determininistic results found the same conclusions in terms of strong and extended dominance, and provided a similar ICER of £8,924 per QALY comparing alemtuzumab vs. glatiramer acetate. Therefore, in the base case analysis, probabilistic and deterministic results agreed that alemtuzumab was the most cost-effective of all treatments in active RRMS when considering WTP thresholds of £20,000 and £30,000 per QALY.

Table 4. Base-case probabilistic cost-effectiveness results within active RRMS

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Glatiramer acetate	484,590	2.887				
Alemtuzumab	494,319	4.273	9,729	1.386	7,017	7,017
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

The EMA believed the choice of SC IFNβ-1a 44µg as a comparator in the clinical programmes was appropriate. In addition, of the interferons and glatiramer acetate provided by the UK RSS, SC IFNβ-1a 44µg has been shown to be the most effective based on the MTC conducted as part of this submission. Hence, it appears that the most

appropriate comparator within active RRMS is SC IFNβ-1a 44µg and not glatiramer acetate. When considering the incremental analysis, alemtuzumab extendedly dominates SC IFNβ-1a 44µg, and when directly comparing alemtuzumab with SC IFNβ-1a 44µg an ICER of £8,445 per QALY was calculated, which strengthens the conclusion that alemtuzumab is the most cost-effective treatment in active RRMS.

In the one-way sensitivity analysis, results were most sensitive to the SAD HRs and withdrawal rates, mildly sensitive to discount rate on outcomes, natural history disease costs and EQ-5D utility values. Scenario analysis showed that the model was sensitive to the assumptions around waning of treatment effect, assumptions of alemtuzumab retreatment, the source of natural history costs and the choice of MTC used for clinical parameters.

In the HA despite interferon use and RES subgroups, the probabilistic incremental analysis compared all treatments within the subgroups using a QALY league table, which ranked treatments by cost (as recommended by the STA template). The mean PSA results found that:

- Alemtuzumab strongly dominated fingolimod (assuming a PAS price of £13,000 per year) in HA despite interferon use
- Alemtuzumab strongly dominated natalizumab in RES RRMS

In addition, the CEAC and CEAF confirmed that alemtuzumab was the most cost-effective of all treatment alternatives for all WTP thresholds. Therefore, alemtuzumab was the most cost-effective of all treatments in both HA despite interferon use and RES RRMS when considering WTP thresholds of £20,000 and £30,000 per QALY.

Table 5. Probabilistic cost-effectiveness results within HA despite interferon use RRMS

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Alemtuzumab	467,667	5.487				
Fingolimod (assumed PAS price £13,000)	493,760	3.669	26,093	-1.818	Dominated	Dominated
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table 6. Probabilistic cost-effectiveness results within RES RRMS

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Alemtuzumab	459,512	5.856				
Natalizumab	509,757	4.325	50,245	-1.531	Dominated	Dominated

ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year

In the sensitivity analysis of the HA despite interferon use and RES RRMS subgroups, the model was sensitive to the SAD HRs, waning of treatment effect and retreatment of alemtuzumab, which was comparable to the active RRMS analysis.

Budget Impact

Uptake of alemtuzumab is expected in four populations: patients with previously untreated RRMS (treatment-naïve) both with and without RES RRMS and patients with treatment-experienced RRMS with and without HA despite interferon use. As discussed previously patients use the following DMTs: beta-interferons, glatiramer acetate, fingolimod and natalizumab. The uptake of alemtuzumab is anticipated to be:

- Primarily from patients with highly active RRMS (as defined within the fingolimod and natalizumab licences):
    - Treatment experienced HA disease despite treatment with a full course of interferon (maximum uptake of [redacted] from a prevalent population of [redacted])
    - Treatment naïve RES (maximum uptake of [redacted] from an annual incident population of [redacted])
- In addition there will be some uptake from patients with active RRMS which is not highly active disease as defined by the fingolimod and natlizumab licences:
    - Treatment experienced excluding patients who are highly active despite treatment with a full course of interferon (maximum uptake of [redacted] from a prevalent population of [redacted])
    - Treatment naïve non RES (maximum uptake of [redacted] from an annual incident population of [redacted])
- The assumed percentage of maximum annual uptake with alemtuzumab was [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5.
- The results show a net annual drug budget impact of [redacted] in year 1, £[redacted] in year 2 [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5.

Table 7. Estimated annual drug budget impact of introducing alemtuzumab into England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
	2014	2015	2016	2017	2018
Total patients receiving alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients whose DMT treatment is alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual drug cost of alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annual net cost to drug budget	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section A – Decision problem

Summary of description of technology under appraisal

- Alemtuzumab is indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features
- The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses.
    - Initial treatment course: 12 mg/day for 5 consecutive days (60 mg total dose)
    - Second treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.
- In open-label follow-up of alemtuzumab clinical trials, some patients received additional "as needed" treatment with alemtuzumab upon documented evidence of resumed MS disease activity. The additional course(s) of alemtuzumab were administered at 12 mg/day for 3 consecutive days (36 mg total dose) at least 12 months after the prior treatment course. If additional treatment courses are to be given they must be administered at least 12 months after the prior course.
- The percentage of patients requiring a subsequent dose in years 3-5 is estimated to be 18% to [redacted] based on clinical trials and observational studies as outlined in Sections 6.5.3.
- It is anticipated that alemtuzumab will be used in a substantial majority of cases instead of natalizumab or fingolimod which are limited by NICE guidance to use in RES and HA despite interferon use patients. Given alemtuzumab's licence being broader than these two groups of patients it is also anticipated that alemtuzumab will also be used in patients with active RRMS which is not highly active and which will involve some use instead of interferons and glatiramer acetate.

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Lemtrada®

Approved name: Alemtuzumab

Therapeutic class: PENDING

ATC Code: PENDING

1.2 What is the principal mechanism of action of the technology?

Alemtuzumab, is a recombinant DNA-derived humanised monoclonal antibody directed against the 21-28 kD cell surface glycoprotein CD52. Alemtuzumab is an IgG1 kappa antibody with human variable framework and constant regions, and complementary-determining regions from a murine (rat) monoclonal antibody. The antibody has an approximate molecular weight of 150 kD.

Alemtuzumab binds to CD52, a cell surface antigen present at high levels on T (CD3+) and B (CD19+) lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes.

The mechanism by which alemtuzumab exerts its therapeutic effects in multiple sclerosis (MS) is not fully elucidated. However, research suggests immunomodulatory effects through the depletion and repopulation of lymphocytes, including:

- Alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment
- Increased representation of regulatory T cell subsets
- Increased representation of memory T- and B-lymphocytes
- Transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells)

The reduction in the level of circulating B and T cells by alemtuzumab and subsequent repopulation, may reduce the potential for relapse, which ultimately delays disease progression [SmPC 2013].

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Genzyme submitted a marketing authorisation application (MAA) for alemtuzumab in May 2012 to the European Medicines Agency (EMA).

On 28th June 2013 the Committee for Medicinal Products for Human Use (CHMP) announced their positive opinion supporting the approval of alemtuzumab in Europe for the treatment of adult patients with relapsing remitting MS with active disease defined by clinical or imaging features. A resulting Commission Decision is expected in September or October 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Genzyme submitted the marketing authorisation application for Lemtrada (alemtuzumab) on 28th May 2012.

The regulatory procedure started on 20th June 2012 and on 28th June 2013 the Committee for Medicinal Products for Human Use (CHMP) announced their positive opinion supporting the approval of alemtuzumab in Europe for "the treatment of adult patients with relapsing remitting MS with active disease defined by clinical or imaging features". However, the EPAR cannot yet be provided.

To date the main topics as identified within the summary of CHMP opinion pertained to the appropriate indication (i.e. target population) for Lemtrada (alemtuzumab), and exploration on safety data supporting the identified and potential risks. Specially, identified risks; autoimmune conditions, infections, infusion associated reactions, and potential risks; cytopenias and malignancies. The appropriate use of risk minimisation activities including educational materials and periodic monitoring has also been discussed. It was stated in this document that the benefits with Lemtrada are its ability to reduce the relapse rate and slow disability progression.

The following conditions for marketing authorisation are provided based on the CHMP positive opinion:

- Alemtuzumab treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS. Specialists and equipment required for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections, should be available
- Resources for the management of hypersensitivity and/or anaphylactic reactions should be available.

- Patients treated with alemtuzumab must be given the Patient Card and Patient Guide and be informed about the risks of alemtuzumab.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Based on positive CHMP opinion granted on 27th June 2013 the following indication is anticipated for the "treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features."

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

A summary of CAMMS03409 extension study (on-going) is provided in table A1.1

Table A1.1 Clinical development programme for alemtuzumab

Study code, patient enrollment and primary end date	Phase and objective	Study design Study Objective	Subject, location, and length	Key inclusion/exclusion criteria	Dose regimens	Primary endpoint(s)	Secondary endpoint(s)	Source
CAMMS03409 Estimated study completion date: September 2014	Phase III Extension of access, safety and efficacy	Open Label, rater blinded Non-randomised, interventional To evaluate long term safety and efficacy	1500 subjects (estimated) 200 international study centers (estimated) 4 years after enrollment	Inclusion: received SC IFNB-1a or alemtuzumab in CAMMS223, CARE-MS I or CARE-MS II, and have not subsequently received an alternative DMT Exclusion: received off-label alemtuzumab, participation in another trial, displays safety concern characteristics	Alemtuzumab patients: retreatment with 12 mg IV daily for 3 consecutive days once annually with evidence of resumed disease activity SC IFNB-1a patients: First treatment with Alemtuzumab 12 mg IV daily for 5 consecutive days, second treatment with 12 mg alemtuzumab IV daily for 3 consecutive days 1 year later	Time to 6-month SAD, relapse rate	Time to sustained reduction in disability, change in EDSS score and MRI findings with time	(Clinical Trials.gov 2011a; Genzyme Extension Study Protocol 2010)

Long term extension study

Patients from the one phase II and two phase III clinical trials investigating the efficacy of alemtuzumab in active MS were eligible to enter a long-term extension study. All patients in this study receive alemtuzumab; alemtuzumab-treated patients with documented evidence of resumed disease activity are able to be re-treated, and SC IFNβ-1a patients who met treatment eligibility criteria, were switched to receive two fixed cycles of alemtuzumab (two treatment courses). The study aims to examine the long term safety and efficacy of alemtuzumab treatment in patients who have either received prior alemtuzumab in a previous study, or are receiving it for the first time following SC IFNβ-1a treatment. After two annual treatment courses, additional annual treatment courses of alemtuzumab are administered on an as-needed basis. Estimated study completion date is November 2014 [clinicaltrials.gov].

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Product commercial availability is expected in [redacted]

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

The technology does not have regulatory approval outside the UK. FDA approval is expected H2 2013.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Alemtuzumab is expected to undergo assessment by the Scottish Medicines Consortium and the National Centre for Pharmacoeconomic Evaluation in Ireland with subsequent advice anticipated to be posted in Q1/Q2 2014.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1.2 Unit costs of technology being appraised

Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate). Each vial contains 12 mg alemtuzumab in 1.2 ml (10 mg/ml) [SmPC, 2013].

Acquisition cost (excluding VAT)	Indicative Price (to be confirmed following agreement with the Department of Health): £7,045 per vial, first 5 vials at £35,225, second 3 vials at £21,135.
Method of administration	Alemtuzumab must be diluted before infusion. The diluted solution should be administered by intravenous infusion over a period of approximately four hours. Treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS [SmPC, 2013].
Dosage and frequency	The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for two treatment courses. • Initial treatment course: 12 mg/day for five consecutive days (60 mg total dose) • Second treatment course: 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course [SmPC, 2013].
Average length of a course of treatment	Alemtuzumab offers an innovation relative to other MS treatments in the mode of administration and the low rates of retreatment. It is administered by intravenous infusion administered over 2 cycles: the first is 12mg per day for 5 consecutive days followed by a second course 12 months later of 12mg per day for 3 consecutive days.
Average cost of a course of treatment	Based on the indicative list price detailed above the cost for the initial two year course of

	alemtuzumab (8 vials) is £56,360
Anticipated average interval between courses of treatments	After the two annual treatments, there remains the option for further future administration at yearly intervals if a patient's clinical assessment suggests need. Experience from the phase III extension study suggests that the majority of patients will not require retreatment with alemtuzumab.
Anticipated number of repeat courses of treatments	The Phase III extension study shows such rates of retreatment to be low at three years (18%-20%). Low rates of retreatment have also been reported up to five years in the extension phase of the CAMMS 223 Phase II study ([redacted]).
Dose adjustments	Not applicable

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable. Alemtuzumab is not a device.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Laboratory tests should be conducted at periodic intervals for 48 months following the last treatment course of alemtuzumab in order to monitor for early signs of autoimmune disease [SmPC, 2013]:

- Full blood count with differential (prior to treatment initiation and at monthly intervals thereafter)
- Serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter)
- Urinalysis with mircroscopy (prior to treatment initiation and at monthly intervals thereafter)

- A test of thyroid function, such as thyroid stimulating hormone levels (prior to treatment initiation and every three months thereafter until 48 months following last infusion of alemtuzumab). After this period of time testing should be performed based on clinical findings suggestive of thyroid dysfunction.

Before initiation of therapy, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection, according to local guidelines. As for any immune modulating medicinal product, before initiating a course of alemtuzumab treatment, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV [SmPC, 2013].

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Alemtuzumab is prescribed within a comprehensive framework of patient education and management providing additional guidance for health care professionals on the treatment of MS and management of any adverse events.The risk management programme associated with alemtuzumab and outlined within its SmPC will allow the identification of autoimmune disorders early and ensure effective management.

Observation for infusion reactions is recommended during and for two hours after alemtuzumab infusion. If an infusion associated reaction occurs, appropriate symptomatic treatment should be given. If the infusion is not well tolerated, the infusion duration may be extended. If severe infusion reactions occur, immediate discontinuation of the intravenous infusion should be considered. Within the clinical trials, anaphylaxis or serious reactions that necessitated treatment discontinuation were very rare [SmPC, 2013].

It is recommended that HPV screening be completed annually for female patients [SmPC, 2013].

No additional monitoring is required for patients receiving alemtuzumab over and above usual clinical practice.

Patients receiving beta-interferons require complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests. In some patients, thyroid function testing is also recommended [SmPCs: Avonex, Betaferon, Rebif, Extavia].

In patients receiving fingolimod, ECG and blood pressure monitoring is necessary around first dosing. Complete blood counts are recommended periodically throughout treatment, liver function tests should be performed three-monthly. An ophthalmological evaluation is recommended at 3-4 months after treatment initiation. [SmPC Gilenya].

Patients receiving natalizumab should have liver function monitoring, anti John Cunningham virus (JCV) antibody testing and regular MRI scanning throughout treatment [SmPC Tysabri].

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Patients should be premedicated with corticosteroids immediately prior to alemtuzumab administration for the first three days of any treatment course. In clinical trials, patients were pretreated with 1,000 mg methylprednisolone for the first three days of each alemtuzumab treatment course.

Additionally, pretreatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered.

Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of one month following treatment with alemtuzumab. In clinical trials, patients were administered aciclovir 200 mg twice a day or equivalent [SmPC, 2013].

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Overview of MS

MS is a chronic disease resulting in disability and premature death [Pugliatti *et al,*2006]. MS is associated with axonal demyelination in the central nervous system (CNS) with considerable social impact and economic consequences and is a major cause of non-traumatic disability in young adults [Trapp *et al,* 2008]. The mean age of onset of MS symptoms is between 20-50 years [NICE, 2003] with the highest prevalence in the age group 50-64 years [Pugliatti *et al,* 2006] and it predominantly affects women, with an approximate ratio of 3:1 [Ramagopalan *et al,* 2010]. Although considerable scientific progress has been made throughout a century of research, the underlying cause of MS is still unknown [Dutta *et al,* 2011].It is thought that there is no single cause for MS but interplay between environmental triggers and genetic susceptibility is increasingly accepted as a valid aetiology of MS [Trapp *et al,* 2008].

In the UK, MS is classified into three key sub-types: relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS). The course of MS in an individual patient is largely unpredictable, but may lead ultimately to progressive disability and premature death.

<u>Primary-progressive MS</u>

Primary-progressive MS occurs in about 15% of patients at presentation. Patients with PPMS do not experience relapses but show a slowly progressive disease course [Murray 2006].

<u>Relapsing-remitting MS</u>

Relapsing-remitting MS (RRMS) is the most common form of the disease occurring in about 85% of patients at diagnosis [Murray 2006]. Patients with RRMS experience recurring episodes of acute neurological dysfunction (relapses) followed by more or less complete recovery of function. A relapse is a clinically evident 'attack' of demyelination, characterised by gradual onset of symptoms over days, stabilising over days or weeks and then gradually resolving, completely or partially. For two relapses to be considered as such, a period of 30 days must have elapsed between the onset of new symptoms for each event [Coles 2009].

<u>Secondary-progressive MS</u>

After many years approximately most patients with RRMS will enter a phase of progression with or without relapses, called secondary progressive multiple sclerosis [Murray 2006]. Approximately 65% of people with RRMS will develop SPMS within 15 years of diagnosis [NICE Final Scope].

Epidemiology of MS

The National Institute for Health and Care Excellence (NICE) estimates that MS is diagnosed in 3.5 to 6.6 people per 100,000 of the population each year with a prevalence of 100 to120 per 100,000 (in comparison, the incidence of stroke is 240 per 100,000 each year) in England and Wales [NICE, 2003]. Other estimates have been higher including an estimation carried out by the London School of Hygiene and Tropical Medicine which suggested a prevalence of 100 to 140 per 100,000 patients and equates to approximately a total prevalent population of approximately 100,000 patients in the UK [Multiple Sclerosis Trust. 2012].

Natural History of MS

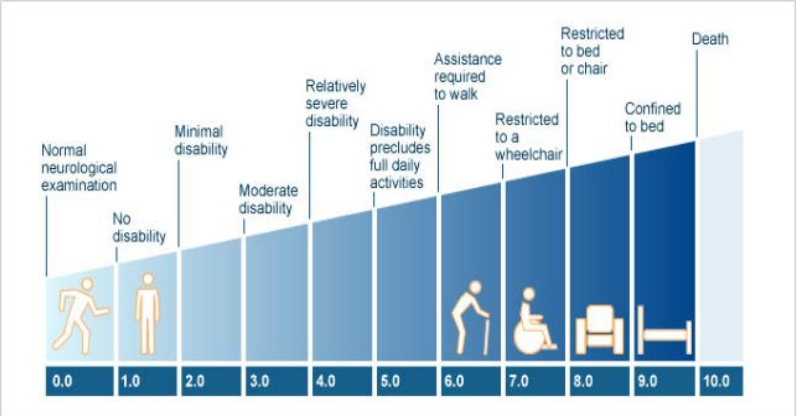
The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability accumulation although the contribution of the former to the latter is not clear [Confavreux *et al,* 2006].

Whilst disability progression in the absence of relapse activity is a defining feature of primary and secondary progressive MS, disability accumulation is a defining feature of RRMS and can be correlated with the extent of axonal injury and further associated with the degree of myelin inflammation [Leray *et al,* 2010]. It has been hypothesised that a close association between inflammation and neurodegeneration might exist in all disease stages of multiple sclerosis [Kutzelnigg *et al,* 2005; Frischer *et al,* 2009].

Whilst frequent and prolonged relapses with incomplete recovery at onset and a short interval between the initial episode and first relapse are adverse prognostic features; the onset of the progressive phase of the disease course is the main determinant of disability [Compston *et al,* 2002]. Relapse rates in RRMS vary considerably over time for an individual and between individuals but there is a general pattern of periods of more frequent relapses, followed by long periods of lower rates [Richards *et al,* 2002]. The initial relapse rate is usually less than one per year and subsequently declines [Coles 2009].This makes assessment of the effects of treatments in any individual extremely difficult.

The most accepted tool to measure disability is the Expanded Disability Status Scale (EDSS), which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half (Figure A2.1). A score of six on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with disease-modifying treatments (DMTs) [Kurtze 1983].The distribution of EDSS scores of patients being initiated on DMTs through the UK Risk Sharing Scheme is bimodal with peaks around EDSS two and six (no patients start treatment at EDSS seven or greater) [Pickin *et al,* 2009].

Figure A2.1 The Expanded Disability Status Scale (Adapted from Kurtze 1883)



Burden of disease

Accumulation of disability clearly presents a challenge to patients and their carers, alongside the very real representation of worsening disease. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that disrupts working, family and social life. Relapses can have a significant impact on quality of life [Orme *et al,* 2007]. Quality of life is significantly correlated with EDSS and has been seen to decrease from a utility score of 0.92 (close to perfect health) at an EDSS score of 0 to a state considered to be worse than death in the most severe state of MS (utility score -0.18 at an EDSS score of 9)[Orme *et al*, 2007]. There are some key elements of MS as a disease process that are of high importance to a patient: suffering relapses, becoming increasingly disabled with time and maintenance of an acceptable quality of life on both a daily and long-term basis.

Patients with MS may also experience hidden disabilities which are symptoms and disabilities that are not obviously apparent or visible. Hidden disabilities include difficulties with cognition, memory, mood, affect, pain, fatigue, sleep, bowel, bladder and sexual function as well as osteopenia and osteoporosis. They can adversely affect an MS patient's health related quality of life (HRQL) and their ability to function at home, at work and in society [Giovanonni *et al,* 2012]. These symptoms can be interrelated: one symptom can exacerbate another or can be caused by the treatment of another symptom.

The combination of hidden disabilities and other physical symptoms of MS creates a huge burden in terms of psychological, emotional, social and financial issues, for patients. Notably, it has been estimated that two-thirds of patients are unable to maintain employment [Honarmand *et al,* 2010]. This burden can extend to families and caregivers resulting in distress and potentially straining relationships between patients and their partners, carers and relatives [Fisk *et al,* 2005]. Chronic illness creates stress and strain in a relationship, potentially resulting in marital problems and divorce. A greater probability of divorce or separation has been observed among MS patients relative to the background population [Pflegger *et al,* 2010].

Current treatment options for patients with RMS

The treatment of RRMS is based on the use of DMTs and current opinion supports the use of early treatment with DMTs to try and reduce the accumulation of disability and subsequent neurodegeneration, in the hopes of delaying onset of progressive MS states [Gold *et al,* 2010; Comi *et al,* 2010].

There is currently no cure for MS, and as such the ultimate goal of treatment for MS is to prevent or delay long-term disability [Tremlett *et al,* 2012]. The available DMTs have demonstrated efficacy in reducing relapse rates and in some cases delaying disability progression in patients with RRMS, however, the response in these patients is variable and many ultimately continue to experience relapses, accumulate disability and ultimately progress to secondary progressive disease which is characterised by neurodegeneration.

In general, patients with RRMS (and an EDSS score <6.5) are likely to be started on interferon-beta or glatiramer acetate [Rio *et al,* 2011].These may be prescribed provided patients meet the requirement of two clinically significant relapses in the previous two years in line with Association of British Neurology (ABN) guidelines and the Department of Health Risk Sharing Scheme [DoH 2002, ABN 2009].The ABN Guidelines represent a consensus of British neurologists regarding the appropriate use of DMTs in patients with multiple sclerosis [ABN 2009].These were last updated in 2009 prior to licensing of fingolimod. This is the definition of active disease based on clinical features used by UK clinicians to initiate patients with RRMS on interferons or glatiramer acetate.

The interferon-betas and glatiramer acetate are self-injected therapies which are administered from once a day to once a week dependent on the treatment chosen. Some patients experience problems with these therapies due to the inconvenient mode of administration (regular injections) and poor tolerability, specifically injection-site reactions, flu-like symptoms, fatigue and depression [Costello 2008]. Moreover, not all RRMS patients will respond to the existing disease-modifying treatments (DMTs) and many will discontinue treatment [Rio *et al,* 2011].

The marketing authorisations for fingolimod and natalizumab are limited to use in patients with highly active RRMS. NICE guidance further restricts their use:

- Fingolimod as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with IFN-β [NICE 2012, SMC 2012]

- Natalizumab as a treatment for rapidly evolving severe RRMS, defined by two or more disabling relapses in one 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 [NICE 2007,SMC 2007]

As stated in its SmPC, “use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability”. As a result, the benefits and risks of natalizumab treatment should continue to be considered on a case by case basis by the specialist physician and the patient. The risk factors

associated with an increased risk of PML are the presence of anti-JCV antibodies, treatment duration especially beyond 2 years and immunosuppressant use prior to receiving natalizumab.

An estimated 47%-68% of MS patients are JCV positive [Ollson et al 2013].

As stated in the natalizumab SmPC, disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of natalizumab and an increased incidence of hypersensitivity reactions

Initiation of fingolimod results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete atrioventricular block. All patients should have an ECG and blood pressure measurement performed prior to and six hours after the first dose of fingolimod. All patients should then be monitored for a period of six hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurements. Continuous (real time) ECG monitoring during this six hour period is recommended [Gilenya SmPC]. Patients who develop cardiac abnormalities during the first dose monitoring period may require an overnight hospital stay [Gilenya SmPC].

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Based on the positive CHMP opinion, alemtuzumab is anticipated to be indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Whilst the majority of patient uptake is assumed to come from highly active disease groups, i.e. HA and RES disease, alemtuzumabs improved efficacy compared to SC IFNβ-1a and its broad indication based on a positive CHMP opinion, provides an opportunity to address the unmet need of a wider range of patients. Having such a drug available for use within a broad licence may shift existing treatment paradigms and this is a key uncertainty in the projected patient numbers presented in table A2.1 which currently assume relatively small uptake from interferons or glatiramer acetate. This potential shift in the treatment paradigm needs to be seen in the context of a debate amongst clinicians around whether earlier treatment with high efficacy drugs may be the way to optimise patient outcomes as referred to in Section 2.5

In the UK, approximately 100,000 people have MS [Multiple Sclerosis Trust 2012].

- In England and Wales it is estimated that 88,766 people have MS (based on England and Wales having a population of 56.1 million out of a total UK population of 63.2 million) [ONS, 2012]

It is estimated that 35% of the prevalent MS population will be diagnosed with RRMS [Kobelt et al, 2006]. Therefore, the estimated prevalence of patients with RRMS in England and Wales in 2013 will be 31,512. Of the prevalent RRMS patients, 31% (9,769) will be prevalent active RRMS currently treated or treated within the last 12 months patients (treatment-experienced), and could potentially receive alemtuzumab [Zajicek et al, 2010].

Also in England and Wales there are 1,588 [Boggild *et al,* 2009] patients initiated on treatment each year.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

MS has been associated with an almost threefold increase in the risk for death, with excess mortality rates from other diseases such as cardiovascular disease and infectious and respiratory disease. The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of approximately 10 years [Bronnum-Hansen *et al,* 2004].

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE guidance

- TA32 - Beta interferon and glatiramer acetate for the treatment of multiple sclerosis: Although both glatiramer acetate and interferon-beta were found not to be cost-effective both are available as long as prescribing is in line with ABN guidelines and the Department of Health Risk Sharing Scheme

NICE guidance is also available for fingolimod and natalizumab in patients with highly active disease and rapidly evolving severe disease respectively. It is not anticipated that alemtuzumab will be routinely used in these subgroups of MS:

- TA254- Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis: Fingolimod as an option for the treatment of highly active RRMS in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with IFN-β [NICE 2012]
- TA127: Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis: Natalizumab as a treatment for rapidly evolving severe RRMS, defined by two or more disabling relapses in one 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 [NICE 2007]

NICE guidelines:

- CG8: Multiple sclerosis: Management of multiple sclerosis in primary and secondary care : Guidelines were published in 2003 and are currently under review for planned publication in 2014 [NICE, 2003]

There are ongoing NICE appraisals regarding relapsing-remitting multiple sclerosis for new therapies: teriflunomide, laquinimod and dimethyl fumarate.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

As stated above in Section 1.5 based on positive CHMP opinion granted on 27th June 2013, marketing authorisation for alemtuzumab is anticipated in the following indication:

> "Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features."

In the context of clinical practice in England and Wales, as a minimum requirement for initiation of treatment of alemtuzumab in treatment naïve patients, active disease would be defined as patients meeting the ABN eligibility criteria for initiation with beta interferons and glatiramer acetate which is two or more relapses in the prior two years. Alemtuzumab would also be anticipated to be used in patients who have failed existing therapies such as interferons and glatiramer acetate. We would anticipate that in clinical practice in England and Wales active disease defined by clinical features (e.g. the occurrence of relapse) or imaging features will be used to initiate treatment experienced patients on alemtuzumab. This would include, for example, those circumstances where a neurologist will switch treatment to alemtuzumab in patients who have demonstrated a new brain lesion on MRI whilst receiving beta interferon even in the absence of clinical relapses.

The efficacy of alemtuzumab in active RRMS is reflected in its broad licence which allows it to be used as an alternative to interferons and GA unlike other treatment options such as fingolimod and natalizumab which are restricted to patients with a specific definition of highly active RRMS as outlined in their licences (e.g. RES and HAD despite treatment with interferon use). This reflects the favourable risk benefit profile across patients with active RRMS based upon its clinical programme attributed to alemtuzumab by the EMA.

Genzymes' assumption is that alemtuzumab would:

- 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 natilizumab or fingolimod (although the definition of highly active for use of alemtuzumab would not need to be as restrictive as that contained within the licences for these two drugs and would be aligned to the more inclusive definition used amongst clinicians in England and Wales treating MS). Feedback from a number of MS specialists experienced in prescribing alemtuzumab in clinical trials or in off label use shows a trend towards using alemtuzumab earlier in the disease process as experience is gained. This includes patients who are treatment naïve or those with less severe disease. This includes patients who have active RRMS which is not highly active.

- There will be use of alemtuzumab in patients who have active RRMS which is not highly active disease. The extent of this use is an area of uncertainty. However, it is a highly important group to consider because the current discussions amongst MS Specialists about use in this group based on experiential use of alemtuzumab within its broad licence over the medium to long term has the potential to lead to a paradigm shift in the treatment of MS and make a substantial impact on patient's clinical outcomes. Of note in this regard is the following:

    - Some clinicians will choose to use alemtuzumab in place of interferons or glatiramer acetate in active RRMS which is not highly active. This will include first lne use. This includes some clinicians who will use the drug in this way immediately. This is in line with increasing confidence amongst MS specialists about the value of using alemtuzumab in the earlier stages of MS as a means of achieving better outcomes [Coles 2006].
    - Alemtuzumab demonstrated superiority, in patients with active RRMS, against an interferon (SC INF-1a) in terms of reducing the sustained accumulation of disability and reducing relapses. Alemtuzumab is the first MS treatment to show improved efficacy on disability accumulation endpoints against an active comparator. This active comparator was sc INF-1a [Coles *et al,* 2008, Coles *et al,* 2012b, Cohen *et al,* 2012].
    - The categorisation of MS into an earlier focal inflammatory phase (equating to EDSS 0-3) leading to a later neurodegenerative phase (beyond EDSS 3) has been postulated within the literature [Leroy et al 2010] with the suggestion that this earlier phase may signify a "therapeutic window of opportunity" in which DMTs should be targeted to maximise long term patient outcomes [Leroy et al 2010] [Coles et al 2006][Gold et al 201]; earlier use of alemtuzumab would be aligned to this view of how to achieve optimal outcomes.

- The broad licence of alemtuzumab supports this compared to the licences of natalizumab and fingolimod which limit them to use in highly active RRMS patients.

Interviews conducted with neurologists in England and Wales to ascertain existing treatment pathways and how this may be impacted by the uptake of alemtuzumab were carried out (see Section B7.3.5 for details of interviews). Having reviewed publicly available trial evidence for alemtuzumab, the clinicians stated they would, subject to guidance, expect to use alemtuzumab primarily in RRMS patients after first line interferon or glatiramer acetate use [Genzyme KOL interview report, 2013]. Clinicians also said they would also consider using alemtuzumab as a treatment in patients with rapidly evolving disease as a first line treatment [Genzyme KOL interview report 2013].

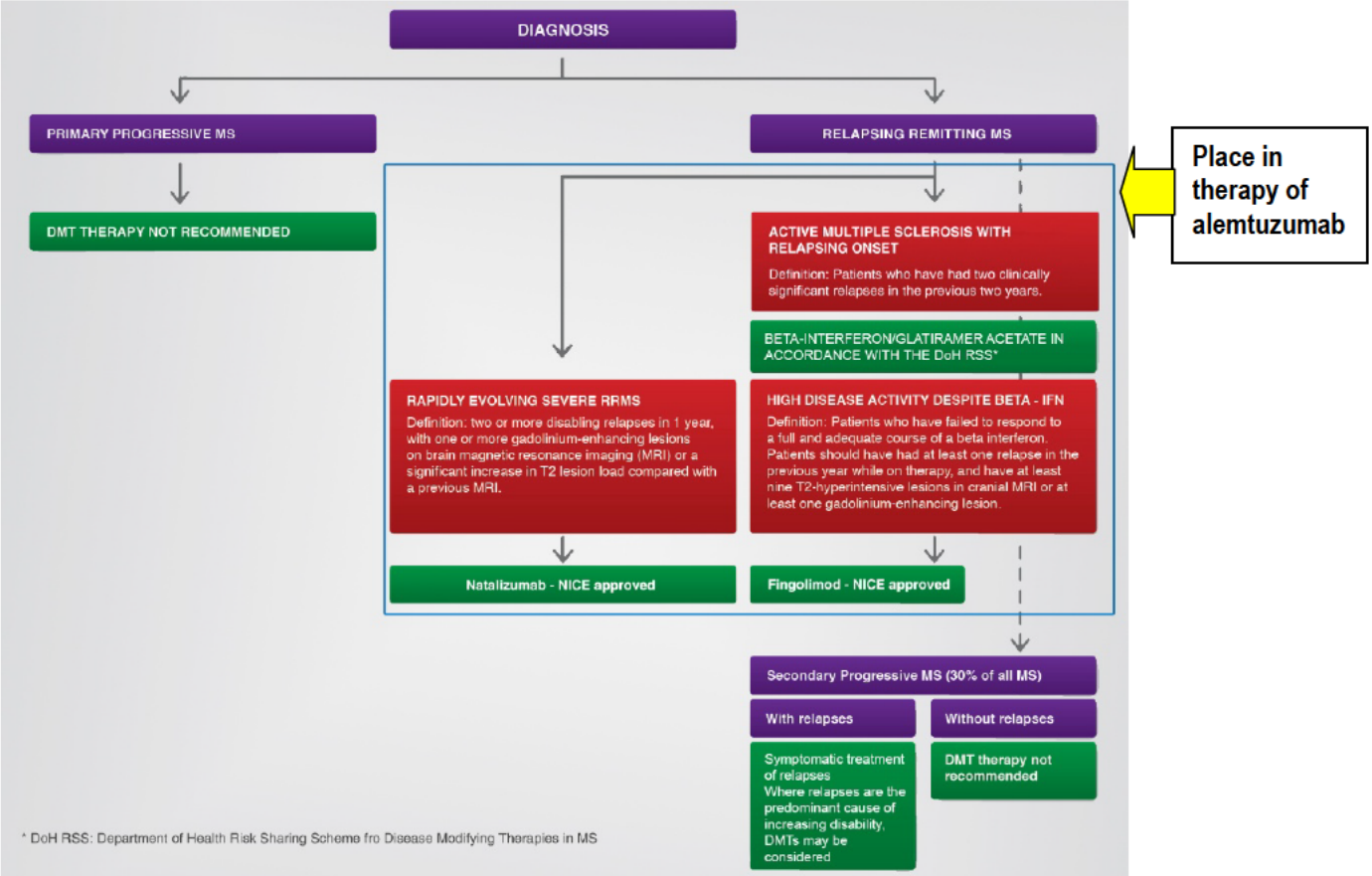
In summary it is anticipated that alemtuzumab will largely be considered in practice as an alternative to current therapies in the following groups:

- Patients with active RRMS including in place of beta interferons or glatiramer acetate
- Initially, most use will be in patients with more highly active RRMS including:
  - Those with rapidly evolving severe RRMS (including as an alternative treatment to treatment naïve or treatment experienced RES RRMS patients who would otherwise receive natalizumab,)
  - Those with high disease activity despite beta-interferon and glatiramer acetate use (including as an alternative treatment to fingolimod in those with high disease activity despite beta interferon use)
  - Use of alemtuzumab in highly active RRMS would not be limited to the definitions contained within the licences for natalizumab or fingolimod and would be aligned to the more inclusive definition of highly active disease employed by clinicians treating MS in England and Wales
- Patients who have an increased risk profile with existing DMTs:
  - In particular, natalizumab patients may be switched by clinicians to alemtuzumab, particularly where they are concerned about the risk benefits associated with JCV positive patients on natalizumab for two years. (see Section A2.5). An estimated 47%-68% of MS patients are JCV positive [Ollson et al 2013]. This in line with the natalizumab SPC which notes the following:
    - Use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of natalizumab treatment should be individually reconsidered by the specialist physician and the patient. The risk factors are associated with an increased risk of

PML are the presence of anti-JCV antibodies, treatment duration, especially beyond 2 years and immunosuppressant use prior to receiving natalizumab.

- Patients switched from natalizumab because high circulating NABs to this drug raise concerns about its continued efficacy. As stated in the natalizumab SmPC, disease exacerbations or infusion related events may indicate the development of antibodies against natalizumab. In these cases the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of natalizumab and an increased incidence of hypersensitivity reactions

Figure A2.2 Current treatment pathway for patients with MS



2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Pharmacological therapies for MS have been reviewed by influential bodies in England and Wales (i.e. NICE and the ABN); however these guidelines require updating to reflect newly available therapeutic entities. Whilst an element of clinical decision making will always be used to deviate from these guidelines, as befits individual situations, we are unaware that these best practice guidelines are being routinely breached.

2.7 Please identify the main comparator(s) and justify their selection.

Comparators will be:

- Interferon beta and glatiramer acetate and natalizumab and fingolimod in active RRMS
- Fingolimod for patients with highly active RRMS who have an unchanged or increased relapse rate or ongoing relapses compared with the previous year despite treatment with interferons (in line with the definition of highly active RRMD within the fingolimod licence and the associated NICE recommendation)
- Natalizumab for patients with RES (in line with the natalizumab licence and the associated NICE recommendation).

Interferon beta and glatiramer acetate are used, in line with a clinical definition of active disease, when patients meet the requirement of two clinically significant relapses in the previous two years in line with ABN guidelines (a consensus of British Neurologists regarding the appropriate use of DMTs) and the Department of Health Risk Sharing Scheme and we anticipate this is where alemtuzumab will be used [DoH 2002; ABN 2009].

Natalizumab is currently used for RRMS patients with rapidly evolving severe (RES) disease (i.e. two or more disabling relapses in one year with 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.) Patients with RES were included in clinical trials for alemtuzumab and this subgroup is another area where alemtuzumab is expected to be used.

Fingolimod is currently used for RRMS patients with high disease activity despite interferon-beta (i.e. patients who have failed to respond to a full and adequate course of interferon-beta. Patients should have had at least one relapse in the previous year while on therapy and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion). Patients with high disease activity were included in clinical trials for alemtuzumab and this subgroup is another area where alemtuzumab is expected to be used.

It should be noted that in order to estimate ICERs within a health economic model which includes fingolimod (either as a direct comparator or within a treatment sequence model), Genzyme needed to be made aware of fingolimod's discounted PAS price.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The main adverse reactions to alemtuzumab that require treatment as described in the phase III trials and the SmPC are autoimmune thyroid diseases, ITP, and nephropathies i.e. anti-GBM.

The thyroid gland is the most common target, being affected in 20 to 30% of patients, most frequently with the development of Grave's disease [Coles et al, 2012a]. All thyroid disorders were managed with conventional medical therapy; one patient underwent thyroidectomy for goitre, and another had radioiodine treatment [Coles et al, 2012a].

Serious events of ITP have been observed in approximately 1% of patients treated in controlled clinical trials in MS [Lemtrada SmPC]. In the phase III clinical trials, patients generally received corticosteroids to manage the ITP, or intravenous immunoglobulin [Coles et al, 2012a; Cohen et al, 2012].

Nephropathies, including anti-GBM disease, have been observed in 0.3% of patients in clinical trials in MS [SmPC]. In the phase III trial, glomerulonephritis was treated with plasmapheresis, cyclophosphamide, and intravenous steroids [Cohen et al, 2012].

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

It is anticipated that alemtuzumab will be administered in a secondary care day-case infusion setting at the recommended dose of 12 mg/day administered by intravenous infusion for two treatment courses[†]. This would cost £473.83 per day of infusion (National Reference Costs 2011-12 Day Cases. Service code AA30B: Medical Care of Patients with Multiple Sclerosis without CC).

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure will be required to be put in place. Stakeholder consultation has confirmed that patients are currently able to access day-case infusion chairs for rituximab when used outside of the context of its product licence as a treatment for MS.

[†] Initial treatment course of 12 mg/day for five consecutive days (60 mg total dose) and a second treatment course of 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

We have no concerns regarding equality issues at this time however it should be noted that alemtuzumab is not recommended for use in patients below 18 years of age since the safety and efficacy of alemtuzumab in children and adolescents aged 0 to 18 years has not yet been established; no data are available.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

During the natural course of the condition, a large proportion of patients with MS will experience substantial sustained accumulation of disability over time. This is currently observed to occur despite the use of existing DMTs and results in a substantial deterioration in quality of life [Orme *et al*, 2007]. MS should be controlled as early as possible, and experience with DMTs indicates that there is a window of opportunity where early use may control the disease in some patients [Coles 2006; Gold 2010].

Key clinical outcomes for alemtuzumab supporting the claim that it provides a "step change" in patient care are:

- Alemtuzumab is the first MS treatment to show improved efficacy on disability accumulation endpoints against an active comparator [Coles et al, 2008, Coles et al, 2012a, Cohen et al, 2012]. Treatment with alemtuzumab significantly reduced sustained accumulation of disability compared to SC IFNβ-1a.
- Alemtuzumab demonstrated reversal in mean EDSS against baseline in all pivotal studies.

In addition, alemtuzumab also demonstrated a significant reduction in the relapse rate compared to SC IFNβ-1a [Coles *et al,* 2008, Coles *et al,* 2012a, Cohen *et al,* 2012].

The broad licence provided by the EMA for alemtuzumab indicates a favourable benefit risk ratio across a broad range of patients with active RRMS in a drug that has shown improved efficacy on disability accumulation endpoints compared to an interferon (the commonest class of drugs used in active RRMS).

Additionally, alemtuzumab has the potential to change the way that MS is treated because in longer term studies (up to 5 years) a high proportion of patients after the initial 2 year treatment course did not need retreatment. This compares with other DMTs which are administered on an ongoing, chronic basis.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The benefits to both patients and carers of the finite, annual administration schedule vs. a chronically, frequently administered oral or parenteral therapy cannot be fully captured within the QALY calculation. We would also comment that the societal impact of MS in terms of loss of productivity, patient and carer burden and ability to work etc. is much wider than accounted for in the analysis and not fully captured within the perspective adopted by NICE of the NHS and PSS.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The benefits achieved relating to finite versus chronic, frequent administration has been assumed from commonly accepted beliefs.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with relapsing-remitting multiple sclerosis	People with active relapsing-remitting multiple sclerosis based on clinical or imaging features	Decision problem addressed aligned to CHMP positive opinion licence wording
Intervention	Alemtuzumab	Alemtuzumab	
Comparator(s)	• Beta-interferon • Glatiramer acetate • Natalizumab (for treatment-naïve or previously treated patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)	• Beta-interferon • Glatiramer acetate • Natalizumab (for treatment-naïve or previously treated patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • Fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon) In addition natalizumab and fingolimod included as comparators for active RRMS	Natalizumab and fingolimod included as comparators for active RRMS to capture the situation where patients treated on these drugs will be switched to alemtuzumab. Such patients may have active RRMS but not necessarily highly active RRMS at the time of being switched.

Outcomes	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale [EDSS]) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom from disease activity • Mortality • Adverse effects of treatment • Health-related quality of life.	• Relapse rate • Severity of relapse • Disability (for example, expanded disability status scale [EDSS]) • Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • Freedom of disease activity • Mortality • Adverse effects of treatment • Health related quality of life • Hospitalisation (as a result of relapses).	For alemtuzumab, we will also include the following outcome which was prospectively evaluated in the Phase III programme of CARE-MS II study • Resource utilisation: hospitalisation (as a result of relapses).
Economic analysis	• The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life. • The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs should be considered from an NHS and Personal Social Services Perspective. • The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS (See Health Service Circular 2002/2004)	• Incremental cost per quality-adjusted life year. • The time horizon considered is lifetime (50 years). • Costs will be considered from an NHS and Personal Social Services perspective. • Costs of beta interferon and glatiramer acetate are obtained from the UK Risk Sharing Scheme. • If details of the patient access scheme discount for fingolimod are available to the manufacturer, these will be taken into account.	

Subgroups to be considered	If the evidence allows, the following subgroups of patients will be considered: • Treatment experienced patients with relapsing-remitting multiple sclerosis • Treatment naïve patients with relapsing-remitting multiple sclerosis • Patients with highly active relapsing-remitting multiple sclerosis whose disease has inadequately responded to or are intolerant to treatment with disease modifying therapy • Patients with rapidly evolving severe relapsing-remitting multiple sclerosis	• Patients with highly active relapsing-remitting multiple sclerosis despite an adequate course of interferon (in line wiyth the fingolimod licence) • Patients with rapidly evolving severe relapsing-remitting multiple sclerosis (in line with the natalizumab licence)	• These subgroups are included in the section titled "Other Considerations" in the scope. • The clinical effectiveness in the treatment naïve studies (CARE MS I and CAMMS 223) and the treatment experienced study (CARE MS II) are described separately. No subgroup treatment experienced or naïve CE analysis is provided because it is thought that the CE analysis of active RRMS using the pooled results from both the treatment naïve and experienced studies captures more appropriately use across the broad range of the licence. • Patients with highly active relapsing-remitting multiple sclerosis despite a full couse of interferon (vs fingolimod in line with its licence) and patients with rapidly evolving severe relapsing-remitting multiple sclerosis (vs natlaizumab in line with its licence) are covered in a subgroup analysis. It is thought these comparators alone are appropriate for these subgroups since they are subgroups defined by the wording of the licences of these two comparator drugs.
Special considerations, including issues related to equity or equality			

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Summary of evidence

Alemtuzumab is the first treatment for RRMS to demonstrate a reduction in sustained accumulation of disability compared with an active comparator (see Section 6.5.3).

Alemtuzumab has demonstrated maintained reduction of sustained accumulation of disability compared with an active comparator for up to 5 years (see Section 6.5.3).

The percentage of patients requiring a subsequent dose in years 3-5 is estimated to be 18% to [redacted] based of clinical trials and observational studies (see Section 6.5.3).

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic review was conducted to identify published studies demonstrating the efficacy and safety of alemtuzumab for the treatment of RRMS in relation to currently available therapies, including glatiramer acetate (henceforth referred to as glatiramer), interferon-beta, natalizumab and fingolimod. The full search strategy can be found in Section 10.2 Appendix 2. Searches were conducted in MedLine, Embase, and the Cochrane Collaboration Central Register of Clinical Trials (CENTRAL) from 1st January 1980 to 12th November 2012.

Additional searches were conducted in FDA and EMA websites to search for unpublished clinical trial information and safety data.

Any high quality recently conducted systematic reviews, (i.e. new publications in higher tiered journals for example, Filippini et al, 2011; Smith et al, 2010) NICE guidelines and technology appraisals had their bibliographies reviewed. This was done by

running supplemental, targeted, searches using words to describe the disease as well as the study type (systematic reviews and meta-analyses). We are aware that Canadian Agency for Drugs and Technologies in Health (CADTH) are currently undertaking a project to examine the comparative efficacy and safety of drug therapies for RRMS. The draft materials including a list of included studies for the review are no longer in the public domain since the consultation period closed and as such were not included in the review.

Proceedings from several key conferences held from 2009 to 2012 were reviewed for relevant abstracts:

- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)
- Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS)
- American Academy of Neurology (AAN)
- American Neurological Society (ANS)
- European Neurological Society (ENS)
- European Federation of Neurological Societies (EFNS)
- Consortium of Multiple Sclerosis Centres (CMSC)

Bibliographies of review articles were searched to obtain relevant references.

Two reviewers reviewed studies for inclusion according to pre-specified inclusion and exclusion criteria.

Supplemental Targeted Literature Search

In addition to the narrow and deep systematic search of the literature on the clinical efficacy and safety of DMTs for RRMS and progressive MS, one trial of natalizumab and one trial of teriflunomide in relapsing MS were also included [O'Connor *et al*. 2011; Rudick *et al*. 2006] as part of a supplemental targeted review of the literature. The SENTINEL trial [Rudick *et al*. 2006] did not meet the inclusion criteria for this systematic review because it investigated natalizumab and IFNβ-1a combination therapy. It was included in a targeted fashion because of the critical data the study provided regarding the safety of natalizumab although excluded from the MTC analysis.

After the last literature searches were completed, alemtuzumab data were presented at the 2013 Annual Meeting of the Consortium for Multiple Sclerosis Centres, May 29–June 1, Orlando, FL and the 23rd Annual Meeting of the European Neurological Society, 8–11 June, 2013, Barcelona, Spain. For completeness, data from the relevant abstracts/presentations has been included in the submission.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

A full systematic literature review was performed to identify relevant RCTs involving *any* disease modifying treatment (DMT) used for treating RRMS/PMS in adults (see Section 10.2 Appendix 2). From these results, trials involving alemtuzumab were extracted as a final step.

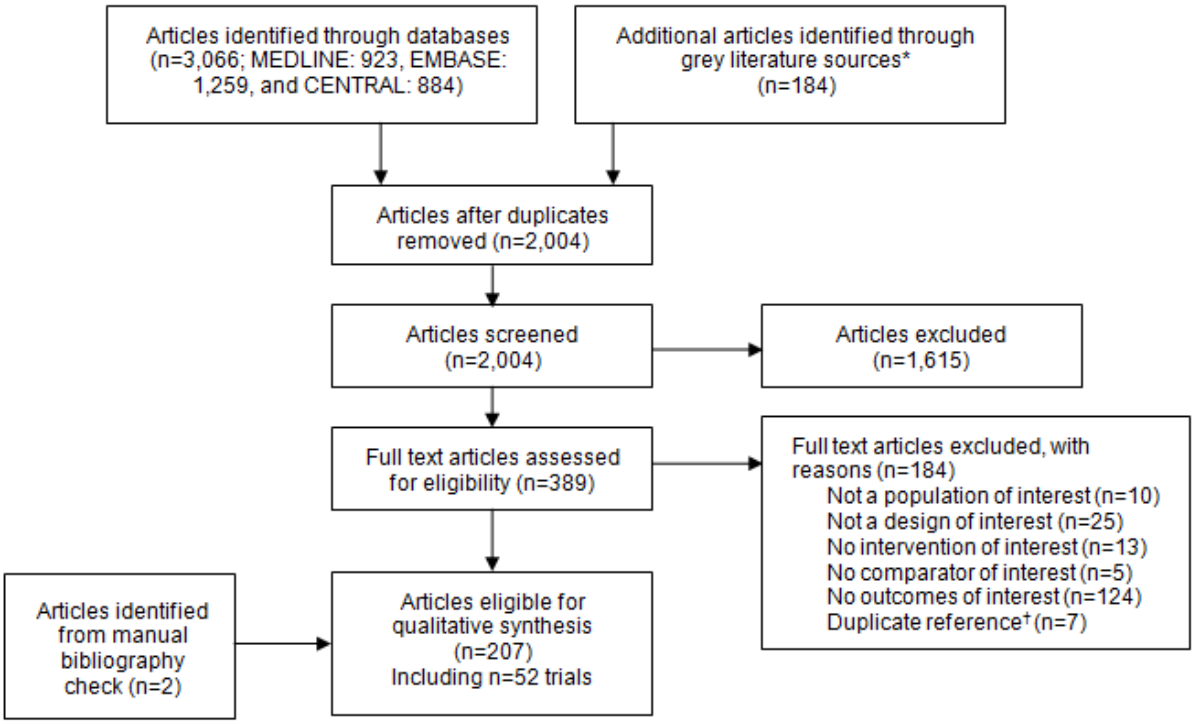
Table B6.2.1 Eligibility criteria used in search strategy

Inclusion criteria
Population Adult patients with RRMS. Interventions/Comparators The choice of comparators was to include all possible MS DMTs: • Alemtuzumab • BG00012 • Daclizumab • Fingolimod • Glatiramer acetate • Interferon-1a • Interferon-1b • Laquinimod • Mitoxantrone • Natalizumab • Rituximab • Teriflunomide Outcomes (detailed information on outcomes extracted is provided in Section 10.2 Appendix 2) • Relapse • Proportion relapse free • 3-month and 6-month Disability Accumulation • MRI Outcomes – Number of new or newly enlarging T2 hyperintensive lesions – Volume of T2 hyperintensive lesions – Number of T1 or Gd-enhancing lesions • Discontinuation and Adverse Events Study design • Single- or double-blind randomised controlled trials (RCTs) and open-label extension phase of these trials Language restrictions • English

Exclusion criteria
Population • People who do not have MS Interventions/Comparators • Not DMTs Outcomes • No relevant data on any of the outcomes of interest Study design • Studies that are not randomised, letters to the editor, citations with no abstract • Studies that are open label from the outset • Studies that were continuing to recruit • Studies where patient numbers treated with a specific intervention or disease status (RRMS, or PMS with relapse) could not be determined Language restrictions • Studies not written in English

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Figure B6.2.1 Systematic literature review



*Includes the FDA and EMA websites as well as proceedings from the following key conferences between 2009 and 2012: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), American Academy of Neurology (AAN), American Neurological Society (ANS), European Neurological Society (ENS), European Federation of Neurological Societies (EFNS), Consortium of Multiple Sclerosis Centers (CMSC)
†These seven citations were conference proceedings that were duplicates of abstracts published in journal supplements and brought in through the MEDLINE, EMBASE and CENTRAL searches.

Of the 52 trials identified for the qualitative synthesis, three included alemtuzumab as an intervention. A total of 24 publications relating to the alemtuzumab studies were identified in the SLR. An additional 2 references were presented at conference following the completion of the literature search.

In addition to the data available in the public domain, Genzyme have provided unpublished data from the extension phases of the RCTs.

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Table B6.2.2 Alemtuzumab clinical study reference sources

Trial	Primary Reference Source	Additional References
Phase II CAMMS223 study plus an open label extension to this trial:	Two peer reviewed articles [Coles *et al*. 2008; Coles *et al*. 2012c extension]	1 peer reviewed article [Coles *et al,* 2011] and 9 conference abstracts [Coles 2009; Wingerchuk 2010; Wynn 2010; Twyman 2011; Twyman and Group 2010; Wray and Group 2011; Cascione 2011; Boyko *et al.* 2011; Coles 2010]. Further data presented here is from the Clinical Study Report held at Genzyme.
Phase III CARE MS I trial	One peer-reviewed article [Cohen *et al*. 2012]	Five conference abstracts [Coles *et al,* 2011; Coles *et al,* 2012b; Fox *et al,* 2012; Giovannoni *et al,* 2012; Wray *et al,* 2012]. Further data presented here is from the Clinical Study Report held at Genzyme.
Phase III CARE MS II trial	One peer-reviewed article [Coles *et al*. 2012]	Five conference abstracts [Fox *et al,* 2012; Confavreux *et al,* 2012; Freedman *et al,* 2012; Giovannoni *et al,* 2013; Hartung *et al,* 2012]. Further data presented here is from the Clinical Study Report held at Genzyme.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The clinical development program for alemtuzumab has evaluated the safety and efficacy of alemtuzumab in the treatment of MS in three pivotal studies, and two open-label extension studies. These studies have:

1) examined the hypothesis that RRMS patients with active disease treated at an early stage of disease will have reduced accumulation of disability and lower rate of relapses

2) investigated whether alemtuzumab improves outcomes for both for treatment-naïve patients and for those who relapsed while receiving another treatment for MS.

The alemtuzumab Phase II and III studies were active-controlled, randomised, rater-blinded, studies comparing the safety and efficacy of alemtuzumab to high-dose SC IFNβ-1a in patients with active RRMS.

In the context of clinical practice in England and Wales, a minimum criteria of two or more relapses in the prior two years is, based on clinical opinion, likely to be used to initiate treatment naïve patients on alemtuzumab in line with ABN guidance defining active disease as it relates to starting patients on interferons and glatiramer acetate. In patients receiving another DMT a definition of active disease which is based either on a clinical definition of active disease (e.g. the occurrence of relapses) or one based on imaging will be used to switch patients to alemtuzumab.

All three studies only included patients with active RRMS, consistent with practice in England and Wales and as reflected in the (CHMP approved) licensed indication.

Two studies, one Phase II (CAMMS223) and one Phase III (CARE-MS I), enrolled treatment-naïve patients, while the Phase III study CARE-MS II enrolled patients who had at least one relapse during prior treatment (for ≥ 6 months) with IFNβ or glatiramer acetate.

All three RCTs and their extension phases are relevant to the decision problem:

Table B6.2.3 List of relevant RCTs

Study reference	Phase	Study Design	Interventions	Dosage duration
NCT0050778 (CAMMS223) New England Journal of Medicine 2008 [Coles *et al*. 2008] Extension Study [Coles al. 2012 extension]	Phase II	Randomised, rater blinded trial investigating the effectiveness of alemtuzumab compared with SC IFNβ-1a in treatment naïve RRMS patients with active disease	Alemtuzumab (IV) 12mg/day, or alemtuzumab (IV) 24mg/day, or SC IFNβ-1a 44µg.	Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment course two at Month 12. Treatment with a third course of alemtuzumab was optional, and could be given if peripheral CD4+ T-cell count was ≥100/µL. SC IFNβ-1a administered three times per week after dose titration.
NCT00530348 (CAMMS323, CARE-MS I) The Lancet 2012 [Cohen *et al*. 2012]	Phase III	Randomised, rater-blinded, phase III trial investigating the efficacy and safety of first-line alemtuzumab compared with SC IFNβ-1a in treatment naïve RRMS patients with active disease	Alemtuzumab (IV) 12mg/day, or SC IFNβ-1a 44µg.	Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment course two at Month 12. SC IFNβ-1a administered three times per week after dose titration.
NCT00548405 (CAMMS324, CARE-MS II) The Lancet 2012 [Coles *et al*. 2012 (b)]	Phase III	Randomised, rater-blinded, controlled phase III trial investigating the efficacy and safety of alemtuzumab compared with SC IFNβ-1a in patients with RRMS with active disease despite first-line treatment.	Alemtuzumab (IV) 12mg/day or alemtuzumab (IV) 24mg/day, or SC IFNβ-1a 44µg.	Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment course two at Month 12. SC IFNβ-1a administered three times per week after dose titration.

Table B6.2.4 Ongoing RCTs/ Extension studies

Study	Title:	Interventions:	Start/End Date:	Outcome Measures:
NCT00930553 (CAMMS03409)	An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab	Patients previously treated with SC IFNβ-1a received alemtuzumab IV 12 mg/day for two treatment courses (12mg/day for 5 consecutive days at study entry and for 3 consecutive days 12 months later and for any subsequent as need retreatment. Patients previously treated with alemtuzumab: received cycles of alemtuzumab IV as needed (i.e.: upon documented evidence of resumed disease activity	Jan 2010 – Feb 2016	Sustained accumulation of disability (SAD), Relapse Rate

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Alemtuzumab was compared with high dose SC IFNβ-1a (Rebif®) in phase II and phase III clinical trials. Beta interferons are identified within the scope as a key comparator for RRMS patients.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

N/A. All of the studies identified above are included within this submission.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Two further studies were considered relevant to the decision problem and are summarised in section 6.8. Due to the weight of evidence derived from RCTs a systematic reviews of non-RCT evidence was not undertaken. However, the two studies provide supportive evidence for the long-term efficacy of alemtuzumab, number of patients requiring retreatment and the rates of auto-immune adverse effects in alemtuzumab treated patients.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

See Tables B6.3.1 and B6.3.2.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

See Tables B6.3.1 and B6.3.2. Please note that although a 24mg dose was initially studied in clinical trials, the licensed dose of alemtuzumab will be the12 mg dose (IV five times daily at month 0 and three times daily at month 12). See section 6.3.8 for further details.

Table B6.3.1 Comparative summary of methodology of the Phase II and Phase III RCTs

Trial no. (acronym)	NCT0050778 (CAMMS223) [Coles *et al*. 2008; clinicaltrials.gov; CAMMS223 CSR; Coles *et al*. 2012(a)]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen *et al*. 2012; clinicaltrials.gov]	NCT00548405 (CAMMS324, CARE-MS II) [Coles *et al*. 2012 (b); clinicaltrials.gov]
INTRODUCTION Background	Previous open label studies in RRMS showed that alemtuzumab stabilised and even improved existing deficits. On the basis of these observations emerged hypotheses that that the secondary progressive phase of the disease might be attributable to post inflammatory neurodegeneration and that immunotherapy would influence long-term disability only if administered early in the disease course. These concepts informed the design of the CAMMS223 trial, designed to compare two doses of alemtuzumab with SC IFNβ-1a in previously untreated patients with early RRMS.	Following positive results from the Phase II CAMMS223 trial in reducing disease activity, the CARE-MS I trial was designed to assess the efficacy and safety of first-line alemtuzumab compared with SC IFNβ-1a.	Open label studies showed that alemtuzumab is efficacious in patients with RRMS for individuals who had not been previously treated and for patients with secondary autoimmunity the main safety concern. These finding s were substantiated in the randomised rater-masked Phase II (CAMS223) and subsequent Phase III comparison (CARE-MS I) trials. In this second Phase III trial alemtuzumab was compared with SC IFNβ-1a in patients who had recently relapsed while taking a standard disease-modifying therapy.
Objectives	Comparison of alemtuzumab and SC IFNβ-1a safety and efficacy.	Comparison of alemtuzumab and SC IFNβ-1a safety and efficacy.	Comparison of alemtuzumab and SC IFNβ-1a safety and efficacy.
METHODS Study design	Randomised, open label, rater blinded, interventional, three arm, active controlled study.	Randomised, open label, rater blinded, interventional, two arm, active controlled study.	Randomised, rater and dose blinded, interventional, three arm, active controlled study.
Location	49 centres in 5 countries (Croatia, Poland, Russia, United Kingdom, United States).	101 academic medical centres and clinical practices in 16 countries (Argentina, Australia, Brazil, Canada, Croatia, Czech Republic, France, Germany, Mexico, Poland, Russia, Serbia, Sweden, Ukraine, United Kingdom, United States).	194 academic medical centres and clinical practices in 23 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Croatia, Czech Republic, Denmark, France, Germany, Israel, Italy, Mexico, Netherlands, Poland, Russia, Serbia, Spain, Sweden, Ukraine, United Kingdom, United States).
Recruitment	334 patients were enrolled into the study. Enrolment occurred between December 2002	581 patients were enrolled into the study. Enrolment occurred between 07 September	1046 patients were enrolled into the study. Enrolment occurred between 20 October 2007

	and July 2004. 198 patients participated in the extension period. 47 from the SC IFNβ-1a arm, 72 from the alemtuzumab 12mg/day arm and 79 from the alemtuzumab 24mg/day arm.	2007 and 17 April 2009.	and 18 September 2009.
Study duration	The original study plan called for a three year treatment period, which was later extended by a follow-up period of four years from final alemtuzumab dose (making the total study period five or more years from entry). On 16 Sep 2005, dosing of alemtuzumab was suspended after three alemtuzumab-treated patients developed ITP, including one case that was fatal. Dosing of alemtuzumab in CAMMS223 was later resumed. During the dosing suspension, alemtuzumab patients continued with scheduled safety, efficacy, and PK assessments and participated in a safety monitoring program comprised of patient and investigator education, monthly monitoring of full blood cell counts (FBCs), and completion of monthly monitoring surveys for ITP signs and symptoms. Patients in the SC IFNβ-1a group continued with assigned study drug treatment and scheduled assessments.	24 months.	24 months.
Method of randomisation	Patients randomly allocated using an interactive voice response system in a 1:1:1 ratio to receive alemtuzumab (12mg/day), alemtuzumab (24mg/day), or SC IFNβ-1a (44µg). Pocock and Simon minimisation algorithm used	Patients randomly allocated using an interactive voice response system in a 2:1 ratio to receive alemtuzumab (12mg/day) or SC IFNβ-1a (44µg). Randomisation was stratified by site.	Patients randomly allocated using an interactive voice response system in a 2:2:1 ratio to receive alemtuzumab (12mg/day), alemtuzumab (24mg/day), or SC IFNβ-1a (44µg).

	to balance the study groups with regard to age, sex (<30 years or ≥30 years), sex, and baseline EDSS score (<2.0 or ≥ 2.0). Randomisation was stratified by site.		Randomisation was stratified by site.
Method of Blinding	Differences in the timing, mode of administration and side effect profiles for alemtuzumab and SC IFNβ-1a made a true double-blind design unfeasible. To minimise potential for bias, key assessments, including the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) and evaluation of on-study relapses were performed by blinded evaluating neurologists. All cranial MRIs (except screening MRIs) were evaluated by blinded neuroradiologists at an independent, central facility. After Year Three, evaluation of on-study relapses and EDSS were performed by blinded personnel; the MSFC was not done. Unblinded neuroradiologists at an independent central facility evaluated MRIs performed after Year Three.	Both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and SC IFNβ-1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo. Clinical data integrity was therefore secured by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments.	Both study drugs have adverse effects that precluded masking of patients and treating clinicians to treatment assignment, and SC IFNβ-1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo. Clinical data integrity was therefore secured by stringent rater masking and independent adjudication of relapses. Raters completed a questionnaire assessing quality of the masking at each EDSS assessment. In the absence of a masked rater, unmasked raters could submit EDSS assessments.
Interventions	Alemtuzumab: 12mg dose: n=113 24mg dose: n=110 Comparator: SC IFNβ-1a 44µg: n=111 Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment	Alemtuzumab: 12mg/day: n=376 Comparator: SC IFNβ-1a 44µg: n=187 Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment course two at Month 12.	Alemtuzumab: 12mg/day: n=436 24mg/day: n=173 Comparator: SC IFNβ-1a 44µg: n=231 Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment

	course two at Month 12. Treatment with a third course of alemtuzumab was optional, and could be given if peripheral CD4+ T-cell count was ≥100/µL. SC IFNβ-1a administered three times per week after dose titration. A follow-up period was added to the study under a protocol amendment, with alemtuzumab retreatment of up to two additional 12 mg courses (12 mg alemtuzumab IV given on three consecutive days), separated by at least 12 months OR SC IFNβ-1a self-administered injections of 44µg, tiw (three times per week) after an initial dose titration over four weeks. See below for further detail on the retreatment schedule.	SC IFNβ-1a administered three times per week after dose titration. After a protocol amendment in January 2009, alemtuzumab patients received oral acyclovir 200mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infection.	course two at Month 12. SC IFNβ-1a administered three times per week after dose titration. A protocol amendment in December 2008 discontinued randomisation in the alemtuzumab 24mg group to accelerate recruitment to the other two study groups. The 2:1 randomisation allocation was maintained between alemtuzumab 12mg and SC IFNβ-1a. Under this amendment, patients in the alemtuzumab arm also received acyclovir 200mg twice daily during alemtuzumab infusion and for 28 days thereafter as prophylaxis against herpes infection.
OUTCOMES Primary outcomes (including scoring methods and timings of assessments)	The co primary measures of efficacy were the time to 6-month SAD and the rate of relapse. Disability was assessed according to the ordinal EDSS score. A sustained accumulation was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more. All scores were confirmed twice during a six month period. The onset of a sustained level of disability was timed to the first recorded increase in the EDSS score aside from	The co primary measures of efficacy were relapse rate and time to 6-month SAD. A relapse was defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination assessed by a masked rater. The relapse adjudication panel decided the status of suspected relapses on the basis of the protocol definition and their masked review of	The co primary measures of efficacy were relapse rate and time to 6-month SAD. Relapse and SAD were defined as in CARE-MS I. Sustained reduction in disability was defined as a decrease from baseline by at least one EDSS point confirmed over six months for patients with baseline EDSS scores of at least 2.0.

	relapse. A relapse was defined as new or worsening symptoms with an objective change in neurological examination attributable to multiple sclerosis that lasted for at least 48 hours, that were present at normal body temperature, and that were preceded by at least 30 days of clinical stability.	all data collected by the site, including whether there was an objective change corresponding to current relapse symptoms [one point on two functional system scales or two points on one functional system scale or increase in EDSS score]. SAD was defined as in CAMMS223, confirmed over six months.	
Secondary outcomes (including scoring methods and timings of assessments)	Secondary outcomes were: the proportion of patients who did not have a relapse at three years, changes in lesion burden (as seen on T_2-weighted MRI) brain volume (as measured by the Losseff method on T_1-weighted MRI). MRI scans were performed annually.	Secondary endpoints measured over 24 months included: proportion of relapse-free patients, change in EDSS, percentage change in T2-hyperintense lesion volume and change in MSFC.	Secondary outcome measures were: proportion of relapse-free patients at two years, change from baseline in EDSS, acquisition of disability as measured by change in MSFC, MRI-T2 hyperintense lesion volume at year two.
Tertiary outcomes	Proportion of patients without SAD; time to SAD using a 3-month criterion; time to first relapse; changes in EDSS scores; disability accumulation (absolute change in MSFC complemented by quantitative visual assessment of contrast sensitivity [Pelli-Robson chart]); MRI magnetisation transfer ratio (MTR) and changes in Medical Outcome Study 36-Item Short-Form Health Survey (SF-36; Version 1) scores.	Several tertiary and additional endpoints were derived from the clinical relapse, disability, MRI, and HRQL assessments (FAMS, SF-36, EQ-5D, Health Resource Utilisation Questionnaire [HRUQ])	Several tertiary and additional endpoints were derived from the clinical relapse, disability, MRI, and HRQL assessments (FAMS, SF-36, EQ-5D, HRUQ).
Safety outcomes	Assessments measured quarterly included thyroid function, levels of antithyrotropin-receptor antibodies and lymphocyte subpopulations.	To assess safety the following was done monthly (every three months in the SC IFNβ-1a group): patient questionnaires, full blood counts, serum creatinine, urinalysis and microscopy. Thyroid function tests were done every three months.	Safety assessments were performed as in CARE-MS I.
Duration of follow up	The primary analyses of safety and efficacy were performed on data from the initial 3 years of treatment/follow-up. A follow-up period was	Per the protocol, Genzyme required follow-up for alemtuzumab-treated patients for safety for at least four years from their last cycle of	Per the protocol, Genzyme required follow-up for alemtuzumab-treated patients for safety for at least four years from their last cycle of

	added to the study and retreatment with alemtuzumab with up to 2 additional 12 mg cycles, separated by at least 12 months, and if patients met qualifying criteria for each retreatment, was implemented. The remaining post-treatment follow-up is being performed as part of a separate protocol, the CAMMS03409 Extension Study.	treatment at Month 12. As the study duration was two years, additional follow-up was arranged as part of the extension study.	treatment at Month 12. As the study duration was two years, additional follow-up was arranged as part of the extension study.

Retreatment of patients during the CAMMS223 Extension Study

The original study plan called for a three year treatment period. Eligible patients were randomly assigned 1:1:1 to receive SC IFNβ-1a, low- (12 mg) or high- (24 mg) dose alemtuzumab (Figure B6.3.1). On 16 Sep 2005, dosing of alemtuzumab was suspended after three alemtuzumab-treated patients developed immune thrombocytopenic purpura (ITP), including one case that was fatal. Dosing of alemtuzumab in CAMMS223 was later resumed.

During the dosing suspension, alemtuzumab patients continued with scheduled safety, efficacy and pharmacokinetic assessments and participated in a safety monitoring program comprised of patient and investigator education, monthly monitoring of full blood cell counts (FBCs), and completion of monthly monitoring surveys for ITP signs and symptoms. Patients in the SC IFNβ-1a group continued with assigned study drug treatment and scheduled assessments. The study was extended by a two year follow-up period (making the total study period five years from entry) to support long-term monitoring of safety and efficacy outcomes.

After the alemtuzumab dosing suspension ended (07 Apr 2008), consenting alemtuzumab patients who were free of disqualifying criteria (listed in table B.5) could receive additional doses of alemtuzumab in either:

- a “fixed” (annual) retreatment arm (two annual cycles of 12 mg alemtuzumab IV given on three consecutive days)
- an “as needed” retreatment arm (two annual cycles of 12 mg alemtuzumab IV given on three consecutive days upon documented evidence of resumed MS disease activity),

The study period was extended for an additional four years. Patients were either randomised in a 1:2 ratio (Amendment 8) or could choose to (as revised under Amendment 10) have alemtuzumab retreatment on either a “fixed” (annual) or an “as-needed” (≥12 months) basis. Alemtuzumab patients were eligible for a first retreatment cycle in the “as-needed” retreatment arm if they met at least one of the criteria listed below and provided they had met none of the disqualifying criteria as stated above:

- Had, within the previous year experienced at least one protocol-defined relapse.
- Had, within the previous year or since their last on-study MRI, accumulated at least two unique lesions on brain/spinal cord MRIs comprised of any combination of gadolinium-enhancing lesion(s) or new/enlarging MRI T2 lesion(s).

All retreated patients received the 12 mg alemtuzumab dose; the 24 mg alemtuzumab dose was not used in the retreatment period. Under Amendment 10 (March 2009), alemtuzumab patients could elect to be in the “fixed” (annual) retreatment arm or an “as needed” retreatment arm, regardless of their treatment assignment under

Amendment 8 (April 2008). Patients could continue follow-up under Amendment 6 and not participate in Amendments 8 and 10. Full details of protocol amendment 6, 8 and 10 are listed in Additional Appendix 1.

Figure B6.3.1. CAMMS223 Study and Extension Dosing

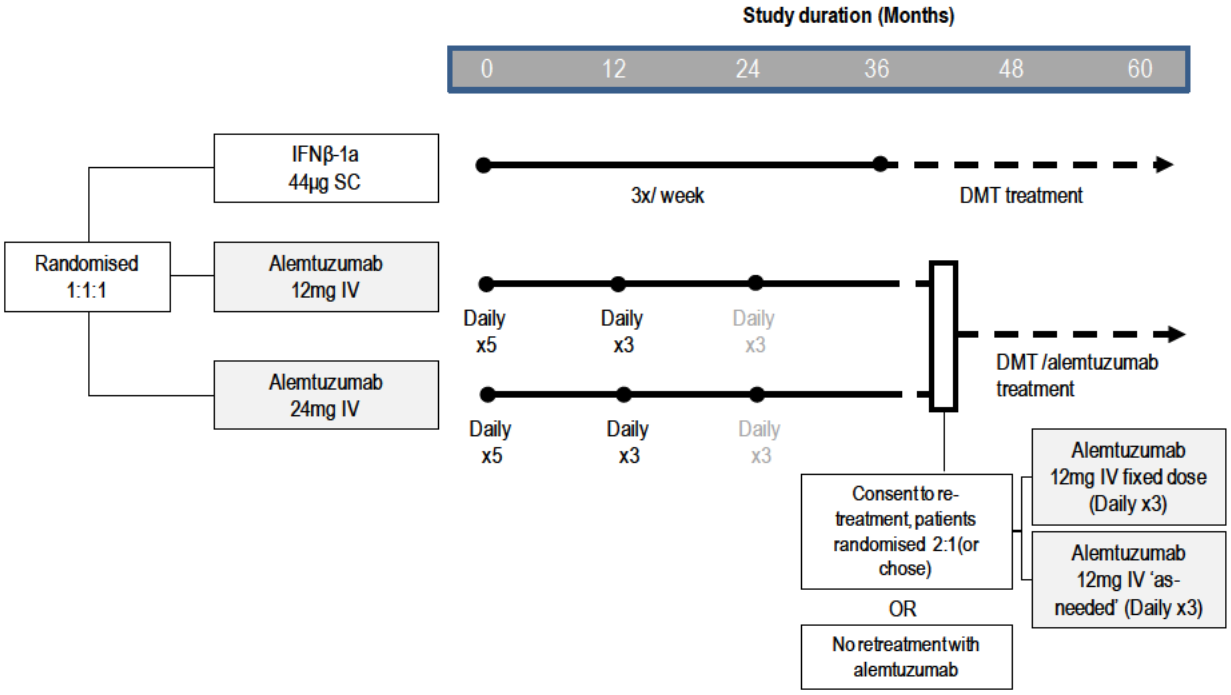


Table B6.3.2 Summary of methodology of the Phase III extension arm

Trial no. (acronym)	NCT00930553 (CAMMS03409) [Fox *et al*. 2013; clinicaltrials.gov; extension study protocol]
INTRODUCTION Background	An extension study opened in January 2010 for patients participating in the CARE-MS I or CARE-MS II trials. Additionally, patients from CAMMS223 trial were recruited to this extension.
Objectives	To examine: 1. The long-term safety and efficacy of alemtuzumab in MS patients who received alemtuzumab during prior Genzyme-sponsored studies including CAMMS223, CAMMS323, or CAMMS324. 2. The safety and efficacy of as-needed alemtuzumab retreatment in these previously alemtuzumab-treated patients. 3. The safety and efficacy of two fixed annual alemtuzumab cycles followed by optional as-needed retreatment in patients who previously received SC IFNβ-1a during these studies.
METHODS Study design	Open label, rater blinded, non-randomised and interventional.
Location	176 international centres.
Study duration	Ongoing since January 2010. Scheduled to complete February 2016. Patients in the trial for four years after enrolment.
Recruitment [Coles et al, 2012c; Fox *et al*. 2013; Havrdova *et al*. 2013]	

	From CAMMS223		From CARE-MS I		From CARE-MS II	
	Prior SC IFNβ-1a	Prior alemtuzumab 12mg	Prior SC IFNβ-1a	Prior alemtuzumab 12mg	Prior SC IFNβ-1a	Prior alemtuzumab 12mg
Patients enrolled	111 (100)	112 (100)	187 (100)	376 (100)	202 (100)	426 (100)
Completed prior study, n (%)	74 (66.7)	94 (83.9)	173 (92.5)	367 (97.6)	175 (86.6)	416 (97.7)
Entered Extension, n (%)	47 (42.3)	72 (64.3)	144 (77.0)	349 (92.8)	145 (71.8)	392 (92.0)

Method of randomisation	N/A
Method of blinding	Raters blinded to patients' treatment history.

Trial no. (acronym)	NCT00930553 (CAMMS03409) [Fox *et al*. 2013; clinicaltrials.gov; extension study protocol]
Interventions	Alemtuzumab 12mg/day‡ The alemtuzumab dose was based on safety and efficacy data from the CAMMS223 Phase II study's three year results. The 12mg/day and 24mg/day dosing regimen‡ were both significantly more effective than SC IFNβ-1a at year three and had similar overall safety profiles. Thus, the minimal effective dose was selected in keeping with standard practise. Eligible patients receive two annual cycles of alemtuzumab. SC IFNβ-1a patients who cannot receive alemtuzumab at study entry should be re-assessed at the discretion of the investigator and must qualify for and receive alemtuzumab treatment by the end of the Month 2 visit window or they will be discontinued from the study. A sub-study to assess the potential effects of a five-day, 12 mg/day, IV alemtuzumab treatment cycle on cardiac repolarisation as detected by prolongation of the QT corrected (QTc) interval ("QT sub-study") will be performed at select sites.
OUTCOMES Primary outcomes (including scoring methods and timings of assessments)	The co primary measures of efficacy are time to six month SAD and relapse rate. Efficacy assessments: • EDSS - quarterly • Relapses – as needed
Secondary /tertiary outcomes (including scoring methods and timings of assessments)	Secondary outcomes include: time to sustained reduction in disability, change in EDSS score and MRI findings with time • MRI – annually (T1-weighted with and without gadolinium [Gd], T2-weighted) Patient-reported HRQL is a tertiary outcome and is assessed using the SF-36, FAMS, and EQ-5D.
Follow-up	Once the extension study ends, any additional safety follow-up may occur via a separate mechanism.

‡ Alemtuzumab administered as five daily IV infusions during treatment course one at Month 0, and three daily IV infusions during treatment course two at Month 12.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Patients in all three active-controlled studies had active RRMS, but patients in CARE-MS II had relapsed on prior disease modifying therapy (DMT) for MS, whereas patients in CAMMS223 and CARE-MS I were treatment-naïve (Table B6.3.3).

In all studies, patients must have had active disease with ≥2 clinical episodes within the past two years (and, in CARE-MS I and CARE-MS II, ≥1 clinical episode within the past year).

The treatment-naïve patients in CAMMS223 and CARE-MS I were required to have early, active RRMS upon study entry, as defined by low EDSS scores (≤3) and relatively brief disease duration (≤3 or 5 years, respectively). In comparison, patients in CARE-MS II could have an entry EDSS of up to 5.0, and a longer disease duration (≤ 10 years).

For full inclusion /exclusion criteria see Additional Appendix 2.

Table B6.3.3 Overview of patient inclusion criteria

Inclusion Criteria	CAMMS223	CARE-MS I	CARE-MS II
Patient age (years)	18–50	18–50	18–55
Criteria for MS disease diagnosis	McDonald's update of the Poser criteria	McDonald's criteria	McDonald's criteria
Onset of MS symptoms prior to study	Within past 3 years	Within past 5 years	Within past 10 years
Screening EDSS score	0.0 to 3.0	0.0 to 3.0	0.0 to 5.0
MS episode history	At least 2 relapses in the 2 years prior to the study	At least 2 relapses in the 2 years prior to the study plus at least 1 episode in year prior, with objective neurological signs	At least 2 relapses in the 2 years prior to the study plus at least 1 episode in year prior, with objective neurological signs
MS treatment history	Treatment-naïve	Treatment-naïve	≥1 MS relapse during treatment with a beta interferon or glatiramer acetate after having been on that therapy for ≥6 months

Inclusion Criteria	CAMMS223	CARE-MS I	CARE-MS II
MRI findings	At least 1 Gd- enhancing lesion during any of up to 4 monthly screening MRIs	Cranial MRI scan demonstrating white matter lesions attributable to MS	Cranial MRI scan demonstrating white matter lesions attributable to MS plus at least 1 of the following • ≥9 T2 lesions ≥3 mm in any axis, • a Gd-enhancing lesion ≥3 mm in any axis plus ≥ 1 brain T2 lesions, • a spinal cord lesion consistent with MS plus ≥1 brain T2 lesions

SOURCE: (Genzyme CAMMS223 CSR 2010; Genzyme CARE-MS I CSR 2012; Genzyme CARE-MS II CSR 2012)

EDSS: Expanded Disability Status Scale; Gd: Gadolinium; MRI: Magnetic resonance imaging; MS: Multiple sclerosis

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The baseline characteristics between trials were generally well matched. However, as a result of key inclusion criteria relating to previous exposure to previous DMT's and time since RRMS diagnosis, there were three instances where variation is observed:

1. Implicit from the trial design, all patients in the CARE-MS II trial had received previous DMT, whereas none in the CARE-MS I and CAMMS223 had received prior DMT.
2. Patients in the CARE-MS II trial had a greater time since first relapse compared to CARE-MS I and CAMMS223 trial participants.

The treatment-naïve patients in CAMMS223 and CAMMS323 were required to have early, active RRMS upon study entry, as defined by low EDSS scores (≤3) and relatively brief disease duration (≤3 or ≤5 years, respectively) with at least two clinical episodes within the past two years (and, in CAMMS323, ≥1 clinical episode within the past year). Patients in CAMMS223 were additionally required to have ≥1 Gd-enhancing lesion on cerebral MRI, which is indicative of inflammatory disease activity.

In comparison, patients in CAMMS324 had relapsed on prior therapy (interferon beta or glatiramer acetate taken for at least six months). Compared with the CAMMS223 and CAMMS323 study populations, patients in CAMMS324:

- Could have had MS symptoms for longer (up to 10 years)
- Could have a higher EDSS score (up to five).

Table B6.3.4. Baseline characteristics of patients in Phase II and Phase III Alemtuzumab Studies

Trial	NCT0050778 (CAMMS223) [Coles *et al*. 2008; CSR]			NCT00530348 (CAMMS323, CARE-MS I) [Cohen *et al*. 2012; CSR]		NCT00548405 (CAMMS324, CARE-MS II) [Coles *et al*. 2012(b); CSR]		
Baseline characteristics	SC IFNβ-1a (44µg 3x/week)	Alemtuzu-mab (12mg annual cycle)	Alemtuzu-mab (24mg annual cycle)	SC IFNβ-1a (44µg 3x/week)	Alemtuzu-mab (12mg annual cycle)	SC IFNβ-1a (44µg 3x/week)	Alemtuzu-mab (12mg annual cycle)	Alemtuzu-mab (24mg annual cycle)
Number of patients	111	112	110	187	376	202	426	170
Mean age in years (SD)	32.8 (8.8)	31.9 (8.0)	32.2 (8.8)	33.2 (8.5)	33.0 (8.0)	35.8 (8.77)	34.8 (8.36)	35.1 (8.40)
Female (%)	64.0	64.3	64.5	65.2	64.6	64.9	66.0	70.6
White (%)	90.1	91.1	89.1	96.3	93.6	92.6	90.4	88.4
Mean time since first episode in years (SD)	[redacted]	[redacted]	[redacted]	2.0 (1.3)	2.1 (1.4)	4.7 (2.86)	4.5 (2.68)	4.3 (2.77)
Mean time since last episode in years (SD)				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time since first relapse (yrs)	1.4	1.3	1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of relapses	293	301	290	-	-	-	-	-
Relapse in previous 2 years (%)								
0	0	2 (1.8)	1 (0.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	8 (7.2)	6 (5.4)	13 (11.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	73 (65.8)	58 (51.8)	56 (50.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	30 (27.0)	46 (41.1)	40 (36.4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration of previous MS drug use in months (SD)	-	-	-	-	-	36 (23.7)	35 (25.0)	37 (23.9)
Mean number of previous MS drugs used (SD)	-	-	-	-	-	1 (0.6)	1 (0.7)	1 (0.6)
No. of patients with alternative MS drug use	-	-	-	-	-	202	426	170
Generic name of previous MS drug								
SC IFNβ-1a	-	-	-	-	-	108	232	102
Intramuscular interferon beta 1a	-	-	-	-	-	46	120	52

Subcutaneous IFNβ-1a (22µg or 44µg)	-	-	-	-	-	73	146	58
IFNβ-1b	-	-	-	-	-	63	154	55
Interferon beta	-	-	-	-	-	-	-	-
Glatiramer	-	-	-	-	-	69	146	59
Natalizumab	-	-	-	-	-	7	15	5
Immunoglobulin	-	-	-	-	-	1	11	2
Rituximab	-	-	-	-	-	-	-	-
Azathioprine	-	-	-	-	-	5	6	0
Fampridine	-	-	-	-	-	2	1	0
Mean EDSS score	1.9 (0.83)	1.9 (0.74)	2.0 (0.73)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	8 (7.2)	4 (3.6)	5 (4.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>0-1.5	37 (33.3)	40 (35.7)	36 (32.7)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>1.5-2.0	28 (25.2)	30 (26.8)	30 (27.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>2.0-4.0	38 (34.2)	38 (33.9)	39 (35.5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>4.0-6.5	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gadolinium-enhancing lesions								
Patients with baseline lesions	-	-	-	51.0%	46.0%	44.0%	42.0%	45.0%
Mean no. of lesions on T1-weighted images (SD)	-	-	-	2.2 (4.9)	2.3 (5.1)	2.10 (4.95)	2.28 (6.02)	2.88 (8.57)
T1 lesion volume, cm^3								
Mean (SD)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2 lesion volume, cm^3								
Mean (SD)	[redacted]	[redacted]	[redacted]	7.3 (9.9)	7.4 (9.0)	9.04 (10.42)	9.94 (12.25)	9.47 (9.66)
Median (min, max)	[redacted]	[redacted]	[redacted]	3.8 (0.1-55.5)	4.2 (0.0-49.0)	5.6 (0.0-70.3)	6.0 (0.0-77.6)	6.2 (0.1-52.2)
Brain parenchymal fraction								
Mean (SD)	-	-	-	0.818 (0.021)	0.821 (0.022)	0.817 (0.022)	0.813 (0.023)	0.816 (0.024)
Median (min, max)	-	-	-	0.818	0.821	0.817	0.816	0.816

				(0.763-0.865)	(0.686-0.878)	(0.738-0.862)	(0.730-0.863)	(0.729-0.866)

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

We believe all the trial outcomes reported below to be relevant to the decision problem.

A number of tertiary endpoints were investigated in the alemtuzumab Phase III clinical trials. A selection of the key tertiary endpoints, defined as those published in two Lancet publications [Cohen *et al*. 2012, Coles *et al*. 2012 (b)] as well as a few selected endpoints presented at ACTRIMS 2013, ENS 2013, EFNS 2012 and ECTRIMS 2010 are summarised in Table 6.3.6.

Table B6.3.5 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
NCT0050778 (CAMMS223) [Coles *et al*. 2008; Coles *et al*. 2012(a)]	The co-primary measures of efficacy were: • Time to SAD • Rate of relapse Patients in CAMMS223 were invited to participate in an extension of CAMS223 to explore 1) the continued durability of the treatment effect of alemtuzumab and 2) the long-term safety profile.	Time to SAD (6 month) The EDSS is the most accepted tool to measure disability and is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half [Kurtzke, 1983]. A score of six on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with DMTs [ABN, 2009]. In the study SAD was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more; all scores were confirmed twice during a six month period. The onset of a SAD was timed to the first recorded increase in the EDSS score aside from relapse. Patients with an increased level of disability could be discontinued from the study. Relapse rate Relapses are a defining feature of RRMS. Relapses may require admission to hospital, and are associated with a level of	Clinical outcome measures were the proportion of patients who did not have an MS relapse MRI outcome measures included changes in lesion burden (as seen on T_2-weighted MRI), and brain volume (as measured by the Losseff method on T_1-weighted MRI).	MRI Magnetic resonance imaging (MRI) is a highly sensitive technique used for the detection of brain tissue changes in patients with MS. As a result, MRI has been extremely valuable to monitor both disease activity and progression in clinical trials. T2-weighted MRI can identify a broad spectrum of pathological changes, including inflammation, oedema, demyelination, gliosis, and axonal loss. New areas of gadolinium (Gd) enhancement on T1-weighted MRI suggest recent inflammatory demyelination with disruption of the blood-brain barrier. Chronic hypointense lesions on T1-weighted images (“black holes”) are indicators of persistent damage. MRI scans were performed annually and interpreted by a neuroradiologist who was unaware of assignments to study groups. Clinical measure See primary outcomes validity column for relapse definition.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
		disability and incapacity that disrupts working, family and social life. Relapses can have a significant impact on quality of life [Orme *et al*. 2007]. In addition, studies have demonstrated a significant effect of relapses in producing disability early in the disease course [Lublin, 2011]. A higher relapse rate has been shown to be associated with a shorter time to fixed disability (EDSS 6) and to onset of secondary progressive disease [Lublin *et al*. 2011].		
NCT00530348 (CAMMS323, CARE-MS I) [Cohen *et al*. 2012]	The co-primary measures of efficacy were: • Time to 6 month SAD • Rate of relapse	See details above for the CAMMS223 trial (time to SAD and relapse rate).	Clinical outcome measures included the proportion of relapse-free patients and change in EDSS. MRI outcome measures included change in T2-hyperintense lesion volume. Change in MSFC.	See detail above for CAMMS223 clinical and MRI measures. The MSFC is a composite (3-part) measure of disability in MS patients with component tests of ambulation, arm coordination and dexterity, and cognitive function. Increases from baseline in MSFC represent improvement.
NCT00548405 (CAMMS324,	The co-primary measures of efficacy were: • Time to 6 month SAD	See details above for the CAMMS223 trial (time to SAD and relapse rate).	Clinical outcome measures included the proportion of relapse-	See detail above for CAMMS223 clinical and MRI measures.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
CARE-MS II) [Coles *et al*. 2012(b)]	• Rate of relapse		free patients and change in EDSS. MRI outcome measures included change in T2-hyperintense lesion volume. Change in MSFC.	MSFC measure - See detail above for CARE-MS I.
NCT00930553 (CAMMS03409) [Fox *et al*. 2013]	The primary objective was to assess the long-term safety and efficacy of alemtuzumab in patients with RRMS. Efficacy assessments: • EDSS - quarterly • Relapses – as needed • MRI – annually	See details above for the CAMMS223 trial (EDSS, relapses and MRI). Long-term monitoring and assessment of safety and tolerability for a new therapeutic product is standard practice.	Clinical outcome measures included the time to sustained reduction in disability and change in EDSS. MRI outcome measures included change in T2-hyperintense lesion volume. Change in MSFC.	Clinical and MRI measures - See detail above for CAMMS223. MSFC measure - See detail above for CARE-MS I.

Table B6.3.6 Summary of key tertiary endpoints in alemtuzumab Phase III clinical trials

Tertiary endpoint	Description
Time to SAD (Three month criterion)	A patient was considered to have reached three month SAD when the following conditions were met: • If the baseline EDSS was 0, and EDSS score increased by at least 1.5 points and remained at least 1.5 points above baseline during the next assessment (i.e., 3 consecutive months); • If the baseline EDSS score was greater than or equal to 1, and EDSS score increased by at least 1 point and remained at least 1 point above baseline during the next assessments (i.e., 3 consecutive months).
Time to Sustained Reduction in Disability (SRD) based on EDSS scores	Time to SRD is defined as a ≥1 point decrease on the EDSS sustained for six consecutive months for patients with baseline EDSS ≥2.
Clinically disease free	Patients were classified as disease free if they did not experience a relapse or six month SAD from baseline.
New and enlarging T2-hyperintense lesion count	Changes in T2-hyperintense lesion number and size based on annual MRI. These changes reflect cumulative disease activity within the preceding 12 months.
New T1 hypointense lesions	New T1-hypointense lesions include foci where axonal density has been permanently reduced by MS-related tissue destruction and also a subset of Gd-enhancing lesions. Lesions were scored using signal hypointensity thresholds of 75% and 85%.
Gd-enhancing lesions	Gd-enhancing lesions result from blood-brain barrier disruption secondary to acute inflammation and represent active inflammation at the time of the MRI scan. Both total and new Gd-enhancing lesions are counted on each scan.
T1-hypointense lesion volume	Changes in the volume of T1-hypointense lesions were assessed using two thresholds expressed as a percent hypointensity relative to surrounding normal appearing white matter. Lesions were scored using signal hypointensity thresholds of 75% and 85%. Volumes corresponding to the 85% threshold were used for analysis, as they are the more standard measure.
Brain parenchymal fraction*	Brain parenchymal fraction is the ratio of brain matter to total cerebral volume. Its serial measurement provides a sensitive indication of brain atrophy.
MRI disease free	Patients were classified as MRI disease free if they did not experience a new Gd-enhancing lesion or a new or enlarged T2 hyperintense lesion from baseline.
SF-36	Generic, general self-assessment instrument for measuring HRQL, which captures broad effects of health problems for patients with MS. Groups 36 items into eight scales: physical function, physical role limitation, bodily pain, general health, vitality, social function, emotional role limitations, and mental health. This generates two scores for physical and mental health which are quantified on a scale of 0-10, with lower scores representing lower HRQL.
EQ-5D	The health dimensions sampled in the EQ-5D are mobility, self-care, usual activities (role limitations), pain/discomfort, and anxiety/depression. Each dimension contains just three levels, yielding a total of 245 health states.

	The EQ-5D covers five domains of HRQL (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with three levels of answers (no, some, and severe problems). The resulting combination of answers can then be translated into utilities via a social tariff established with the general population by using decision–analytical methods (time trade-off).
Functional Assessment of Multiple Sclerosis (FAMS)	An MS specific quality of life instrument consisting of 59 questions regarding mobility, symptoms, depression/emotions, well-being, cognitive function, and social interaction.

SOURCE: Adapted from Genzyme CARE-MS I CSR 2012 and Genzyme CARE-MS II CSR 2012.
*only measured in CARE-MS I
Note: This does not represent an exhaustive list of the tertiary and exploratory endpoints investigated in the alemtuzumab Phase III clinical trials

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B6.3.7 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT0050778 (CAMMS223) [Coles *et al*. 2008; Coles *et al*. 2012(a)]	To determine the effectiveness of alemtuzumab in patients with previously untreated, early RRMS. Patients in CAMMS223 were invited to participate in an extension of CAMS223 to explore 1) the continued durability of the treatment effect of alemtuzumab and 2) the long-term safety profile.	Preplanned interim analyses were performed when most patients had completed at least one year and two years with a prespecified alpha spending function. After the interim analyses, P values of <0.016 and 0.004 were considered to have statistical significance for the rates of sustained disability and relapse, respectively. Treatment effects were compared with respect to the time to SAD with the use of a proportional-hazards model and to the rate of relapse with the use of the Andersen–Gill model with robust variance estimation. The proportion of patients with relapse-free survival was assessed with the use of logistic regression. The estimated percentage of patients with sustained disability or relapse was generated by the Kaplan–Meier method. The annualised rate of relapse was estimated with the use of Poisson regression. A proportional-odds model was used to estimate improvement, stabilisation, and worsening of the EDSS score, as compared with baseline. The percent change from baseline on MRI was analysed with the use of the Wilcoxon–Mann–Whitney test and the multivariate Wei–Lachin test during the entire 36-month period. Fisher's exact test and Poisson regression were used for the analysis of adverse events and event rates, respectively.	On the basis of the literature it was determined that 285 patients would be needed to provide a power of 75% to detect treatment effect at 36 months, assuming a rate of sustained disability of 12% in the alemtuzumab group and of 30% in the group receiving SC IFNβ-1a with a two sided test and a significance level of 2% (with a Bonferroni adjustment for two alemtuzumab groups and a significance level of 1% for the comparison of relapse rates). 334 patients underwent randomisation, 111 were assigned to receive SC IFNβ-1a and 223 were assigned to receive alemtuzumab (113 receiving 12mg/day and 110 receiving 24mg/day). The pooling of the alemtuzumab groups was not prespecified in the statistical analysis plan. Extension	The protocol was designed by the lead academic authors and was approved by local review boards or the ethics committee at each centre. Genzyme employees analysed the data in accordance with the statistical plan and with additional suggestions from the writing committee. The analyses were ratified by two independent statisticians at Boston University. The primary analysis was on an intent-to-treat basis for all randomised patients. Efficacy observations from early discontinuation and unscheduled visits were used in the efficacy analyses [CAMMS223 CSR]. Extension The analysed intention-to-treat dataset included patients with continuous follow-up and those who discontinued during the original study period but re-enrolled in the extension. Post hoc analyses were performed at 60 months after randomisation. Supplemental efficacy analyses were conducted using all available data (complete follow-up). Safety results used all available data up to the closing of CAMMS223.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		The reported P values are two-sided and were not adjusted for multiple testing. Extension Sensitivity analyses were conducted, censoring patients at the time when they received any nonstudy DMT during the first 36 months of the trial and any DMT, including SC IFNβ-1a or alemtuzumab retreatment, during the extension phase. Because of incomplete follow-up and the possibility of informative dropout biasing the estimated treatment effects, sensitivity analyses were conducted using inverse probability weighting methodology. AEs were summarised using all evaluable data from treated patients' baseline to complete follow-up ending in January 2010. The event rate per 100 patient-years for AEs was calculated and accompanied by an exact Poisson confidence interval.	In the extension study n=198	
NCT00530348 (CAMMS323, CARE-MS I) [Cohen *et al*. 2012]	To assess the effect of alemtuzumab compared with SC IFNβ-1a in a Phase III trial of previously untreated patients with early, active RRMS.	The primary efficacy analysis was adjusted for multiple comparisons with the Hochberg procedure. Treatment effects on relapse rate were assessed using a proportional means model. SAD effects were assessed using a proportional hazards model. Geographical regions (USA, Canada, Australia, Latin America, European Union and non-European Union) were categorised and included as covariates. Yearly relapse rate was estimated with a negative	On the basis of previous trials16–19 and the Phase II study, at least 20% of patients in the SC IFNβ-1a group were expected to meet the disability endpoint by 24 months. Therefore, 525 patients randomly allocated 2:1 to alemtuzumab and SC IFNβ-1a were expected to provide at least 95% power to detect a	Data was captured by electronic case report forms (eCRF), all of which were made available to Genzyme for data management and analysis. Intent-to-Treat Population: The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all patients who are randomised to treatment and who have received at least one dose of study drug. . Patients were compared for efficacy according to the treatment they were randomised to receive, irrespective of the treatment they actually

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		bimodal regression model. The proportion of patients with SAD was estimated with the Kaplan-Meier method. Secondary endpoints for multiple comparisons were controlled by testing sequentially the proportion of relapse free patients, EDSS change, T2-hyperintense lesion volume change, and MSFC change. Changes from baseline in EDSS and MSFC were analysed at specific time points with a mixed model for repeated measures. Changes in T2-hyperintense lesion volume and brain volume were analysed with a ranked ANCOVA model. Patients with new or enlarging T2-hyperintense lesions or gadolinium-enhancing lesions, and those who were free from disease activity were analysed with logistic regression.	60% alemtuzumab treatment effect on time to SAD with a two-sided significance level of 5% and assuming a 10% discontinuation rate. This sample size was also expected to provide at least 95% power to detect a 60% treatment effect on relapse rate, assuming 40% of patients in the SC IFNβ-1a group relapsed within 24 months. 563 patients were randomised with 526 completing the study on their assigned treatment.	received. All patients who received at least one dose of study drug were included in the safety analyses. For the assessment of the co-primary efficacy endpoints and other time-to-event endpoints patients were censored at their last visit if the respective event (e.g. SAD or relapse) had not occurred. For the assessment of continuous, repeated measures efficacy endpoints (e.g., change from baseline in EDSS), missing at random were assumed and methods appropriate to the assumption were used. For the assessment of change from baseline to a specific time point (e.g., percent change from baseline in MRI-T2 hyperintense lesion volume at Year 2), the last post-treatment observation will be used for the analysis if data are missing. For the assessment of binary or categorical efficacy endpoints, the last known status of the efficacy measure will be used for the analysis if data are missing.
NCT00548405 (CAMMS324, CARE-MS II) [Coles *et al*. 2012 (b)]	To compare alemtuzumab with SC IFNβ-1a in patients with RRMS who have recently relapsed while taking a standard disease-modifying therapy.	The primary efficacy analysis was adjusted for multiple comparisons with the Hochberg procedure. Treatment effects on relapse rate were assessed using a proportional means model. SAD effects were assessed using a proportional hazards model. Treatment group and geographical region were covariates.	On the basis of previous trials and the Phase II study, we expected at least 20% of patients in the SC IFNβ-1a group to meet the disability endpoint by two years. Therefore, 573 patients, randomly allocated 2:1 to alemtuzumab 12 mg or SC	Data was captured by electronic case report forms (eCRF), all of which were made available to Genzyme for data management and analysis. Intent-to-Treat Population: The population on which primary, secondary, and tertiary efficacy analyses will be performed consists of all patients who are randomised to treatment and who have received at least one dose of study drug. Patients were compared for efficacy according to the

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		Secondary endpoints were controlled for multiple comparisons by testing in the following order: proportion of relapse-free patients, changes in EDSS, T2 lesion volume, and MSFC. Changes from baseline in EDSS and MSFC were analysed at specific time points with a mixed model for repeated measures, and treatment comparisons with all available assessments were assessed with a non-parametric test for repeated measures. Changes in T2-hyperintense lesion volume were analysed with a ranked ANCOVA model. The proportion of patients with new or enlarging T2-hyperintense lesions or gadolinium-enhancing lesions, and those who were free from disease activity were analysed with logistic regression.	IFNβ-1a provided 80% or more power to detect a 50% treatment effect in time to sustained disability with a two-sided significance of 5%, assuming 10% discontinuation. This sample size provided 95% or more power to detect a 40% treatment effect on relapse rate, assuming 68% of patients in the SC IFNβ-1a group relapsed over two years. 840 patients were randomised.	treatment they were randomised to receive, irrespective of the treatment they actually received. All patients who received at least one dose of study drug were included in the safety analyses. For the assessment of the co-primary efficacy endpoints and other time-to-event endpoints patients will be censored at their last visit if the respective event (e.g. SAD or relapse) has not occurred. For the assessment of continuous, repeated measures efficacy endpoints (e.g., change from baseline in EDSS), missing at random will be assumed and methods appropriate to the assumption will be used. For the assessment of change from baseline to a specific time point (e.g., percent change from baseline in MRI-T2 hyperintense lesion volume at Year 2), the last post-treatment observation will be used for the analysis if data are missing. For the assessment of binary or categorical efficacy endpoints, the last known status of the efficacy measure will be used for the analysis if data are missing. Nine patients originally assigned alemtuzumab 24mg received actually received the 12mg per day dose; these patients were included in the 24mg cohort for efficacy, but in the 12mg per day group for safety analyses

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT00930553 (CAMMS03409) [Fox *et al*. 2013; extension study protocol]	To examine: 1. The long-term safety and efficacy of alemtuzumab in MS patients who received alemtuzumab during prior Genzyme-sponsored studies including CAMMS223, CAMMS323, or CAMMS324. 2. The safety and efficacy of as-needed alemtuzumab retreatment in these previously alemtuzumab-treated patients. 3. The safety and efficacy of 2 fixed annual alemtuzumab cycles followed by optional as-needed retreatment in patients who previously received SC IFNβ-1a during these studies.	Efficacy Analysis The long-term effects of alemtuzumab in patients who received alemtuzumab prior to the extension study (e.g., in studies CAMMS223, CAMMS323, or CAMMS324) will be examined by: • Summarising the efficacy endpoints, including sustained accumulation of disability (SAD), relapse rate, sustained reduction in disability (SRD) and change in EDSS, MRI, and HRQL, from prior study baseline to Extension Month 36 • Summarising the percentage of patients meeting criteria for as-needed retreatment (MRI vs. relapse), and time to meeting criteria for retreatment. The efficacy of alemtuzumab in patients who received SC IFNβ-1a prior to the extension study will be evaluated using pre vs. post alemtuzumab comparisons on the efficacy endpoints noted above. Analyses comparing the effect of immediate alemtuzumab treatment with delayed alemtuzumab treatment on the efficacy endpoints noted above will be restricted to patients in CAMMS323 and CAMMS324 and use an integrated dataset consisting of all data from study onset in these prior studies to Extension Month 24. All efficacy analyses will be 2-sided and performed at the 0.05 level of significance, unless otherwise specified. Estimates of treatment effect on efficacy parameters will be accompanied by 2-sided 95% confidence interval (CI) for the effect size. Summary statistics will be computed	Not applicable.	Data was captured by electronic case report forms (eCRF), all of which were made available to Genzyme for data management and analysis. Efficacy analyses were performed on the intent-to-treat population, consisting of all patients who were randomised to treatment in CAMMS223, CAMMS323 and CAMMS324 and who have received study drug. All patients in the extension study were included in the safety population.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		and displayed by treatment group and scheduled assessment time. Summary statistics for continuous variables will minimally include n, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.		

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analyses of trials

RRMS populations outlined in the scope as considerations

The evidence for alemtuzumab supports use in all patients with active RRMS, however, in line with the scope for this submission, evidence to support use in all of the following subgroups of active RRMS can be found:

Treatment-experienced patients with RRMS

Evidence from CARE-MS II supports the efficacy of alemtuzumab in previously treated patients.

Treatment-naive patients with RRMS

Evidence from CAMMS223 and CARE-MS I support the efficacy of alemtuzumab in treatment-naive patients.

Rapidly evolving severe MS

Both the CAMS223 and CARE-MS II studies have had analyses completed on a subgroup of patients with rapidly evolving severe disease. In CAMMS223 and CARE MS II, pre-planned analyses on the RES subgroup included ARR and SAD; post-hoc analyses were conducted on other endpoints including sustained reduction in disability, clinical disease activity free, and MRI activity free. Rapidly evolving severe disease criteria was defined as:

- ≥2 relapses in the year prior to treatment
- At least one gadolinium-enhancing lesion at baseline

This criteria approximates to the definition of RES RRMS in the licensed indication and NICE guidance for natalizumab [Biogen Idec 2013; NICE 2007] as follows:

- Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The results are presented in Section 6.3.5.

Further subgroup analyses

Pooled subgroup analyses were conducted to assess the influence of gender, age, geographic region, and other baseline or demographic factors on relapse rate and sustained accumulation of disability.

Results are shown in Section 6.3.5.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Please note: two alemtuzumab doses (12mg and 24mg) have been tested during the clinical development programme. These doses were used during the initial three year treatment period of CAMMS223 to identify dose-dependent relationships in terms of efficacy or safety variables.

Data relating to alemtuzumab 12mg dosing was submitted to the CHMP for consideration of use in practice. Therefore, although CONSORT diagrams are shown including the 24mg dose, the clinical data discussed within this submission relates to the 12mg dose only.

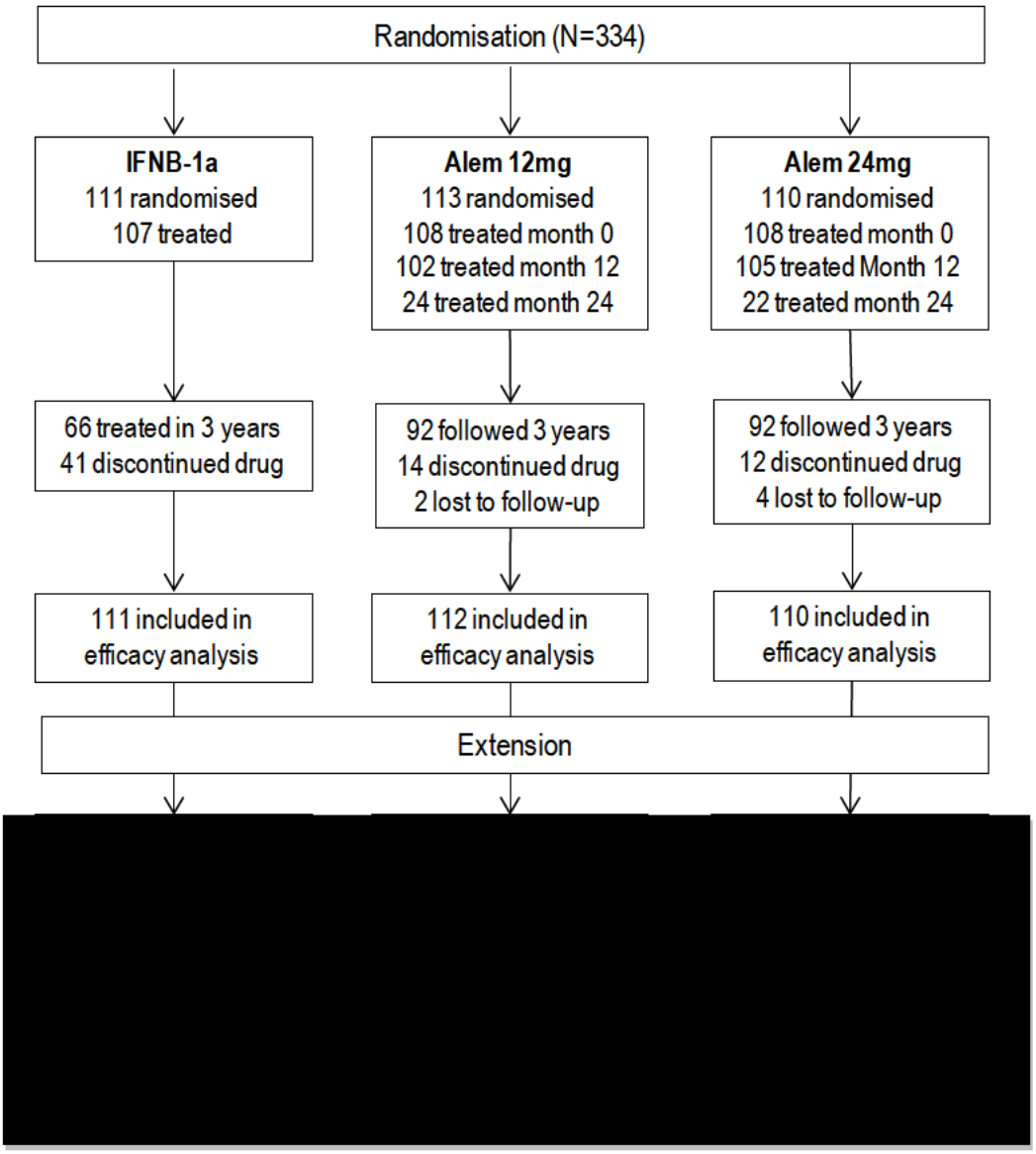
Phase II – CAMMS223

Patients were not permitted to cross to another treatment group during the course of the study, however during the extension phase the use of DMTs including IFNβ-1a was permitted in any treatment arm.

A higher proportion of patients withdrew (largely due to lack of efficacy or adverse events) from the SC IFNβ-1a vs. alemtuzumab 12 or 24mg such that only 59% of the original group of patients receiving SC IFNβ-1a completed the 36 month study compared to 83% of patients receiving alemtuzumab.

At the end of the study review, 90% and 91% of raters remained unaware of assignment to the group receiving SC IFNβ-1a and the group receiving alemtuzumab, respectively [Coles *et al,* 2008].

Figure B6.3.2. Phase II (CAMMS223) and Extension Trial Profile



Source: Coles et el 2008, CAMMS223 CSR

The extension phase started in August 2006. All CAMMS223 patients were encouraged to participate, including those who had previously withdrawn. More alemtuzumab patients participated in the extension study than SC IFNβ-1a patients. An analysis for informative drop-out indicated that a sustained accumulation of disability event was marginally related to not participating in the extension period ($p<0.1$). The total number of relapses was not significantly related. The risk of SAD throughout complete follow up, adjusted by estimated probability of a patient dropping out, still yielded a significant treatment effect (67% reduced risk of the pooled alemtuzumab group vs. SC IFNβ-1a; p=<0.0001) [Coles et al, 2012c].

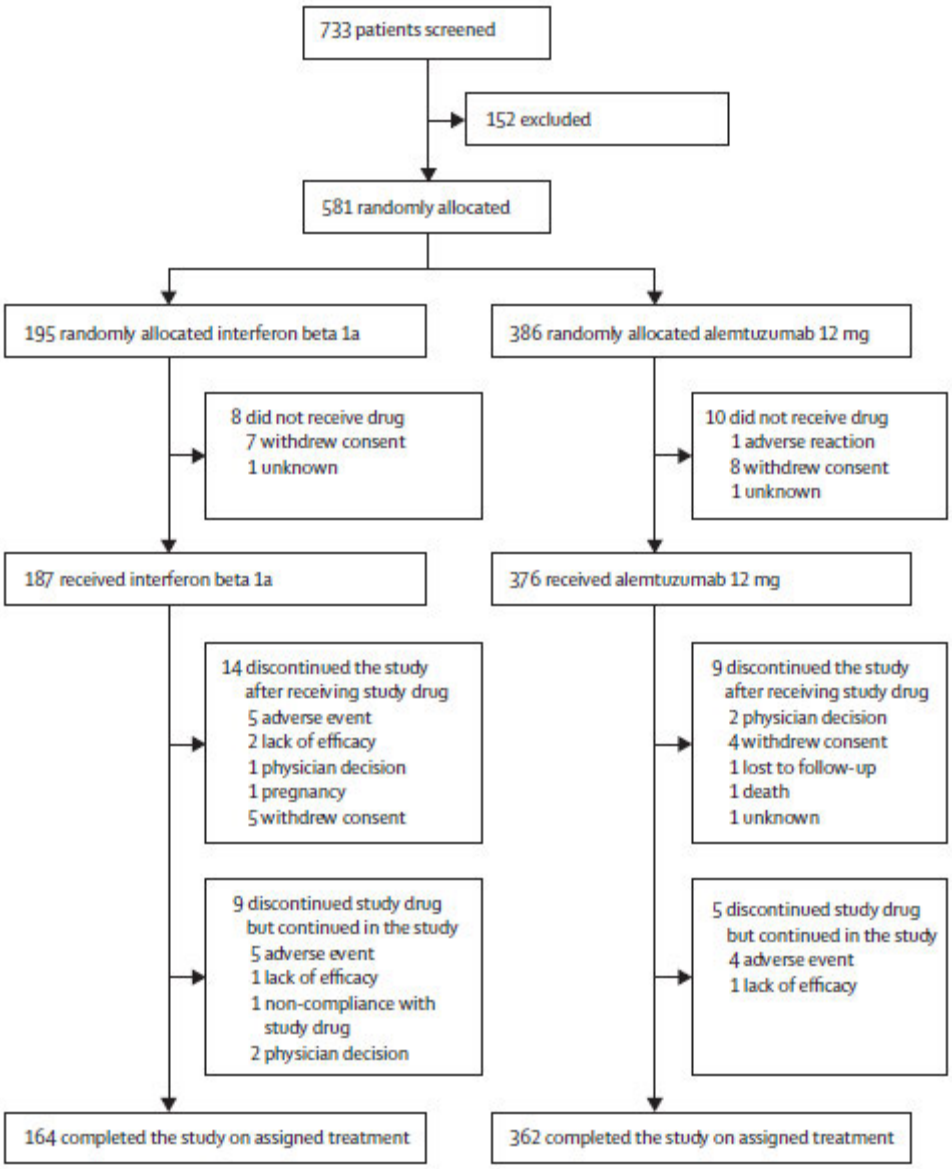
Phase III – CARE-MS I

Patients were not permitted to cross to another treatment group during the course of the study.

526 (93%) of the 581 patients randomly allocated treatment completed the study on assigned treatment allocation.

A higher proportion of patients withdrew from treatment with SC IFNβ-1a compared to alemtuzumab 12mg per day during the course of the study; withdrawal due to adverse events was significantly higher in the SC IFNβ-1a arm versus alemtuzumab. Of the patients who discontinued the study medication prematurely, nine and five patients in the SC IFNβ-1a and alemtuzumab 12mg per day arm, completed the planned follow-up.

Figure 6.3.4. Phase III CARE-MS I Trial Profile



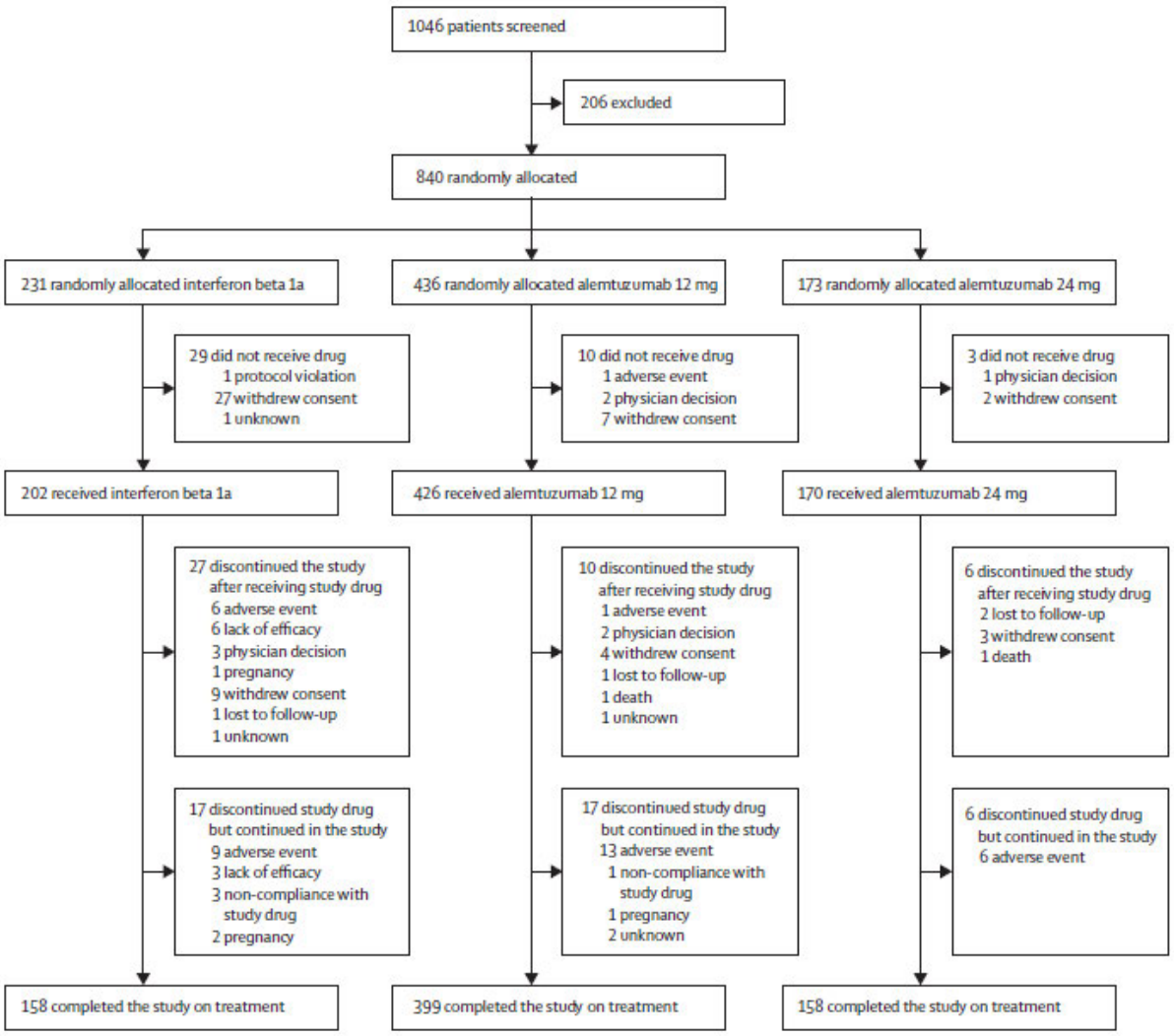
Phase III – CARE-MS II

Patients were not permitted to cross to another treatment group during the course of the study.

755 (90%) of the 840 patients randomly allocated treatment remained in the study until month 24. More patients randomly allocated SC IFNβ-1a than alemtuzumab discontinued the trial before treatment.

A higher proportion of patients receiving SC IFNβ-1a than alemtuzumab withdrew from treatment during the course of the study; withdrawal due to adverse events was also more frequent in the SC IFNβ-1a than alemtuzumab arms. Of the patients who discontinued the study medication prematurely, 17, 17, and 6 patients in the SC IFNβ-1a, alemtuzumab 12mg per day, and alemtuzumab 24mg per day groups, respectively, completed the planned follow-up.

Figure 6.3.5. Phase III CARE-MS II Trial Profile



Number of patients at each time point includes all patients who have at least one Expanded Disability Status Scale (EDSS) assessment on or after that visit. Number of patients participating in extension includes all patients who have at least one EDSS assessment during the extension period. ABCR Avonex, Betaseron, Copaxone, and Rebif; IFNβ-1a interferonβ-1a. *One patient who received alemtuzumab (12-mg group) was excluded from the efficacy analyses (but was included in the safety analysis) because the initial diagnosis of MS was incorrect. The patient did not participate in the extension period.

CAMMS0349 extension study

Study CAMMS03409 is an on-going, 3-year extension study for eligible patients who participated in the Phase II and Phase III studies. The study includes collection of additional follow-up data and treatment/re-treatment with alemtuzumab. The full patient disposition for CAMMS3409 is shown in Table B6.3.2. All patients from CAMMS223 extension are included in the CAMMS3409 follow up, and the results for this subgroup have previously been reported [Coles 2013]. The extension study profile and patient disposition for the cohort of patients who entered from CARE MS-I and II were recently published and are shown in Figures B6.3.6 and B6.3.7 below. No data for the full population is currently available.

Figure B6.3.6. CAMMS03409 Extension Trial Profile [Fox *et al*, 2013]

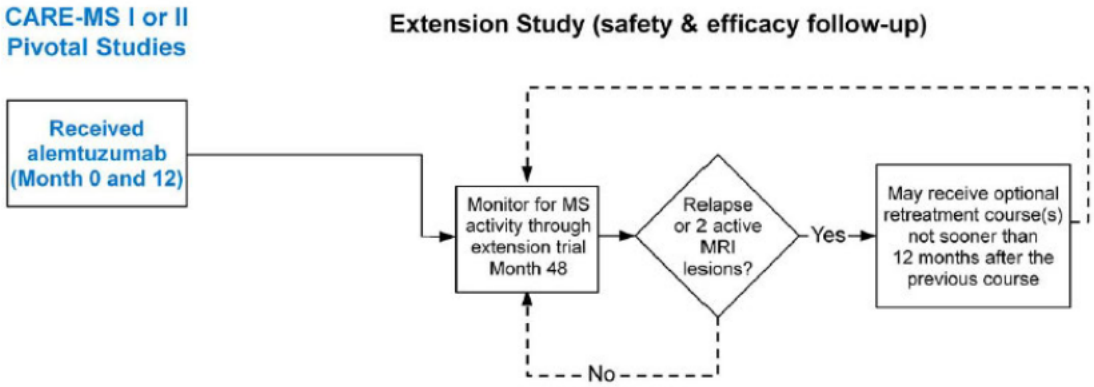


Figure B6.3.7. CAMMS03409 Extension Trial Patient Disposition [Fox *et al*, 2013]

	CARE-MS I	CARE-MS II
	173 received SC IFNβ-1a 367 received 12mg alemtuzumab	175 received SC IFNβ-1a 416 received12mg alemtuzumab
Entered extension	144 prior SC IFNβ-1a 349 prior 12mg alemtuzumab	145 prior SC IFNβ-1a 392 prior 12mg alemtuzumab
Discontinued extension Year 1	6 prior SC IFNβ-1a (1 death) 7 prior 12mg alemtuzumab (1 death)	5 prior SC IFNβ-1a (1 due to an adverse event) 6 prior 12mg alemtuzumab

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B6.4.1 Quality assessment results for RCTs

Trial no. (acronym)	NCT0050778 (CAMMS223) [Coles *et al*. 2008]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen *et al*. 2012]	NCT00548405 (CAMMS324, CARE-MS II) [Coles *et al*. 2012(b)]
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Allocation to treatment was randomly assigned by IVRS. Treatment group was not concealed from patients and clinicians as study drugs had distinctive adverse effects that precluded masking assignment. Clinical data integrity was however secured by stringent clinical and MRI rater masking	Allocation to treatment was randomly assigned by IVRS. Treatment group was not concealed from patients and clinicians as study drugs had distinctive adverse effects that precluded masking assignment. Clinical data integrity was however secured by stringent clinical and MRI rater masking	Allocation to treatment was randomly assigned by IVRS. Treatment group was not concealed from patients and clinicians as study drugs had distinctive adverse effects that precluded masking assignment. Clinical data integrity was however secured by stringent clinical and MRI rater masking
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, differences in timing, mode of administration and side effect profiles made a true double-blind design unfeasible. Also SC IFNβ-1a was available only in proprietary prefilled syringes that could not effectively be duplicated for placebo. The key assessments were however performed by blinded evaluating neurologists.	No, for the same reasons as previous column. Clinical data integrity was secured by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists.	No, for the same reasons as previous column. Clinical data integrity was secured by stringent clinical and MRI rater masking, and adjudication of relapses by a committee comprising six independent and masked neurologists.
Were there any unexpected imbalances in drop-outs between groups?	Yes, there were more discontinuations in the SC IFNβ-1a group, principally because of lack of efficacy and AEs.	Yes, there were more discontinuations in the SC IFNβ-1a group, principally because of lack of efficacy and AEs.	Yes, there were more discontinuations in the SC IFNβ-1a group, principally because of lack of efficacy and AEs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis	For all efficacy analyses,	All efficacy analyses were	All efficacy analyses were

include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	the Full Analysis (FA) Set (all randomised patients who had a diagnosis of MS) was the primary Population and missing data was accounted for.	performed on the FA Set, consisting of all treated patients according to the treatment to which they were randomised and missing data were accounted for.	performed on the FA Set, consisting of all treated patients according to the treatment to which they were randomised and missing data were accounted for.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.

- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Alemtuzumab offers superior reduction in annualised relapse rates compared with an active comparator.

- In CAMMS223, alemtuzumab reduced the relapse rate at 3 years by 69% compared with SC IFNβ-1a in treatment-naïve patients.
- In CARE-MS I, alemtuzumab significantly reduced the relapse rate at 2 years by 55% compared with SC IFNβ-1a in treatment-naïve patients.
- In CARE-MS II, alemtuzumab significantly reduced the relapse rate at 2 years by 49% compared with SC IFNβ-1a in patients who have relapsed on prior disease modifying therapy.

Alemtuzumab has shown reduction in sustained accumulation of disability compared with an active comparator.

- In CAMMS223, alemtuzumab significantly reduced 6-month SAD by 75% at 3 years compared with SC IFNβ-1a.
- In CARE-MS I, a lower proportion of alemtuzumab-treated patients experienced 6-month SAD compared with patients treated with SC IFNβ-1a (8.0% vs. 11.1%), although this difference was not significant.
- In CARE-MS II, alemtuzumab significantly reduced 6-month SAD by 42% at 2 years compared with SC IFNβ-1a.

Alemtuzumab demonstrated significant improvement in mean EDSS against an active comparator.

- In CAMMS223, alemtuzumab reversed disability, with patients demonstrating a mean improvement of 0.32 EDSS points from baseline at Year 3, compared with a mean worsening of 0.38 EDSS points for SC IFNβ-1a-treated patients.
- In CARE-MS I, both alemtuzumab and SC IFNβ-1a experienced a mean reduction of -0.14 in EDSS score from baseline at Year 2.

- In CARE-MS II, alemtuzumab 12 mg reversed disability, with patients demonstrating a mean improvement of 0.17 EDSS points from baseline at Year 2, compared with a mean worsening of 0.24 EDSS points for SC IFNβ-1a-treated patients.

Alemtuzumab offers improvements in MRI imaging outcomes compared to SC **IFNβ**-1a

- In CARE-MS I, alemtuzumab significantly reduced the risk of developing Gd-enhancing lesions from baseline at Year 2 compared with SC IFNβ-1a ([redacted])
- In CARE-MS I, alemtuzumab significantly reduced the risk of developing new or enlarging T2-hyperintense lesions over 2 years compared with SC IFNβ-1a (48% vs. 58%, respectively; p=0.04)
- In CARE-MS I, alemtuzumab significantly reduced the rate of brain atrophy as measured by median change in brain parenchymal fraction over 2 years compared with SC IFNβ-1a (median -0.867% vs. -1.488%, respectively; p<0.0001)
- In CARE-MS II, significantly fewer patients treated with alemtuzumab reported new or enlarging T2-hypointense lesions compared with SC IFNβ-1a (46% vs. 68%, respectively; p<0.0001)
- In CARE-MS II, significantly fewer patients treated with alemtuzumab reported Gd-enhancing lesions to Year 2 compared with SC IFNβ-1a (34.2% vs. 18.5%, respectively; p<0.0001)
- In CARE-MS II, alemtuzumab significantly reduced the rate of brain atrophy as measured by median change in brain parenchymal fraction over 2 years compared with SC IFNβ-1a (-0.615% vs. -0.810%, respectively; p=0.01)

In the majority of patients, the effect of alemtuzumab has been shown to last for up to five years without the need for retreatment.

- In CAMMS223, alemtuzumab, when compared with SC IFNβ-1a, produced a sustained reduction in ARR (0.12 vs. 0.35, respectively; p<0.0001) and reduced the risk of 6-month SAD by 67% to up to 5 years of follow-up.
- Results from the Extension Study show that patients treated with alemtuzumab in CARE-MS I and CARE-MS II experienced similar ARRs at Year 3 (0.24 and 0.25, respectively) compared with the ARR experienced during the original 2 year study period (0.13 and 0.25 respectively)
- Results from the Extension Study also show that the proportion of patients treated with alemtuzumab in CARE-MS I and CARE-MS II who remain free of 6 month SAD remained similar at Year 3 (88% and 80% respectively) compared with the original 2 year study period (92% and 87% respectively)
- 82% and 80% respectively of CARE MS I and II alemtuzumab-treated patients did not need retreatment in year 3 of the extension study. Criteria for retreatment with alemtuzumab required that the patient experienced either at least one protocol-defined relapse or at least two new or enlarging T2 and/or gadolinium enhancing brain or spinal lesions
- [redacted] of patients in CAMMS 223 extension did not need retreatment (the criteria for retreatment was a mix of scheduled and "as needed" upon documented evidence of resumed MS disease activity

Alemtuzumab has shown to improve the quality of life in patients with MS compared with an active comparator.

- In CAMMS223, alemtuzumab [redacted]

- In CARE-MS I, alemtuzumab-treated patients reported significant improvements in HRQL compared with SC IFNβ-1a at as measured by FAMS total score
- In CARE-MS II, alemtuzumab-treated patients reported significant improvements in HRQL compared with SC IFNβ-1a at as measured by FAMS total score and the SF-36 PCS

Table B6.5.1 (Comparative) summary of results of the Phase II and Phase III RCTs

Please note: Expanded trial results reporting primary and secondary outcomes of all trials are available in Additional Appendix 3.
Presented results are for the licensed dose of alemtuzumab (12mg) unless otherwise stated. Alemtuzumab 24mg though used within the clinical trial setting is not licensed for use.

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
Patient numbers	SC IFNβ-1a n=111 Alemtuzumab 12mg/day n=113 (112 included in the efficacy analysis) Alemtuzumab 24mg/day n=110	SC IFNβ-1a n=187 Alemtuzumab 12mg/day n=376	SC IFNβ-1a n=231 Alemtuzumab 12mg/day n=436 Alemtuzumab 24mg/day n=173
Analyses	ITT Extension The analysed ITT dataset included patients with continuous follow-up and those who discontinued during the original study period but re-enrolled in the extension. Post hoc analyses were performed at 60 months after randomisation.	ITT	ITT
Primary trial outcome	Time to SAD and rate of relapse.	Time to six months SAD and rate of relapse.	Time to six months SAD and rate of relapse.
Relapse rate	Alemtuzumab 12mg reduced the rate of relapse by 69% (HR 0.31; CI: 0.18 to 0.52) compared with SC IFNβ-1a (p<0.001). The ARR at 36 months was 0.36 (95% CI: 0.29 to 0.44) for SC IFNβ-1a and 0.11 for 12mg dose (95% CI: 0.08 to 0.16).	Alemtuzumab 12 mg reduced the rate of relapse compared with SC IFNβ-1a. 75 (40%) patients in the SC IFNβ-1a group relapsed (122 events) compared with 82 (22%) patients in the alemtuzumab group (119 events; rate ratio 0·45 [95% CI 0.32–0.63]; p<0.0001), corresponding to a 54·9% improvement with	Alemtuzumab 12 mg reduced the rate of relapse compared with SC IFNβ-1a. 104 (53%) patients in the SC IFNβ-1a group relapsed (201 events) compared with 147 (35%) patients in the alemtuzumab group (236 events; rate ratio 0.51 [95% CI 0.39–0.65]; p<0·0001), corresponding to a 49.4% improvement with

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
	The proportion of patients who remained relapse-free at 36 months was 51.6% for SC IFNβ-1a and 77.0% for the12-mg dose (p<0.001). The number of patients who would need to be treated with alemtuzumab instead of SC IFNβ-1a to prevent one patient from having a relapse at 36 months was 3.9 for the 12-mg dose.	alemtuzumab. The ARR was 0.18 (95% CI: 0.13 to 0.23) with alemtuzumab treatment compared with 0.39 (95% CI: 0.29 to 0.53) in the SC IFNβ-1a group. Based on Kaplan-Meier estimates, 77.6% of patients in the alemtuzumab group were relapse-free at two years compared to 58.7% in the SC IFNβ-1a group (p<0.0001). In a subgroup analyses conducted to assess the influence of baseline or demographic factors on relapse rate the rate ratios comparing alemtuzumab to SC IFNβ-1a for each of the subgroups all favoured alemtuzumab [Fox et al. 2012].	alemtuzumab. The ARR was 0.26 (95% CI: 0.21 to 0.33) with alemtuzumab treatment compared with 0.52 (95% CI: 0.41 to 0.66) in the SC IFNβ-1a group. 65.4% of patients in the alemtuzumab group were relapse-free at 2 years compared to 46.7% in the SC IFNβ-1a group (p<0.0001). In a subgroup analyses conducted to assess the influence of baseline or demographic factors on relapse rate the rate ratios comparing alemtuzumab to SC IFNβ-1a for each of the [redacted] Alemtuzumab 12 mg reduced relapse rate to a greater extent than did SC IFNβ-1a in all subgroups defined by previous therapy, with or without beta-interferons, and those treated specifically at any one time with subcutaneous SC IFNβ-1a or glatiramer. Alemtuzumab's superior efficacy compared with SC IFNβ-1a was unaffected by the presence of anti-interferon antibodies at baseline or month 24.
Severity of relapse	Not reported.	Alemtuzumab treated patients demonstrated a 61% reduction in risk of severe relapse compared with SC IFNβ-1a–treated patients	Alemtuzumab treated patients demonstrated a 47.8% risk reduction in annualised rate of severe relapses compared with SC IFNβ-1a-

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
		(ARR 0.03 vs. 0.08, respectively, p=0.0056). Relapse severity was based on extent of relapse-associated change in EDSS and Functional System Score (FSS), as scored by blinded raters. Severe relapses were defined as: an EDSS increase ≥2 points; >2-point change in ≥1 FSS or; ≥1-point change in ≥4 FSS. For alemtuzumab treated patients, there was a 57% reduction in the risk of relapses treated with corticosteroids compared with SC IFNβ-1a-treated patients (ARR 0.11 vs. 0.39 respectively, p<0.0001). In addition, only a small number of relapses in either group required hospitalisation, with no significant differences between groups (p=0.34).	treated patients (ARR 0.04 vs. 0.08, respectively, p=0.0121) [Twyman *et al*. 2013]. Severe relapses were defined as an EDSS increase greater than or equal to 2 points, greater than 2-point change in more than one FSS, or greater than 1-point change in more than FSS. There was a 56.2% reduction in risk of relapses treated with corticosteroids observed in patients in the alemtuzumab treatment arm versus the SC IFNβ-1a group (ARR 0.19 vs. 0.43 respectively, p<0.0001) [Twyman *et al*. 2013]. Alemtuzumab also reduced the risk for relapses that led to hospitalisation vs. SC IFNβ-1a by 54.9% (ARR 0.05 vs. 0.11, respectively, p=0.0045) [Twyman *et al*. 2013].
Disability – Change in EDSS	Patients in the SC IFNβ-1a group experienced a mean worsening in EDSS of 0.38 from baseline (95% CI, 0.13 to 0.63; p=0.003). Patients in the alemtuzumab 12 mg group had an estimated mean improvement from baseline in the EDSS score of 0.32 points at Year 3 (95% CI: −0.55 to −0.10; p=0.006). Improvement in the EDSS score was already	Mean change in EDSS score from baseline did not differ between groups, improving by -0.14 points in both cases.	Mean disability improved from baseline by –0.17 EDSS points after alemtuzumab 12 mg (p=0.004) compared with a 0.24 EDSS point deterioration for SC IFNβ-1a (p=0.0064), a net benefit for alemtuzumab of 0.41 EDSS points (p<0.0001 vs. SC IFNβ-1a).

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
	detectable at Month 3 in both alemtuzumab groups and the difference to the SC IFNβ-1a group was maintained over the 3 Year study period. 58 (54.2%) of patients in the alemtuzumab 12mg dose had an improvement in EDSS score from baseline compared to 35 (33.7%) SC IFNβ-1a patients. EDSS score worsened in 43 (41.3%) patients in the SC IFNβ-1a group, compared to 24 (22.4%) alemtuzumab12mg patients. As compared with SC IFNβ-1a, the estimated odds ratio for worsening disability versus either improved or stable disability was 0.41 (95% CI, 0.24 to 0.69) for the 12-mg dose of alemtuzumab (p<0.001).		
Disability: SAD /SRD	Alemtuzumab 12 mg significantly reduced the risk of six –month SAD by 75% as compared to SC IFNβ-1a (HR 0.25; 95% CI: 0.11, 0.57; p<0.001). The percentage of patients experiencing six-month SAD at 3 years was 26.2% in the SC IFNβ-1a group, and 8.5% in the 12 mg group. Alemtuzumab 12 mg significantly reduced the risk of three–month SAD by 75% as compared to SC IFNβ-1a (HR 0.42; 95% CI 0.23 -0.77; p<0.005). The percentage of patients experiencing six-month SAD at 3 years was 32.7% in the SC IFNβ-1a	Rates of SAD did not significantly differ between groups.	40 (20%) patients in SC IFNβ-1a group had SAD compared with 54 (13%) in the alemtuzumab group, corresponding to a 42% improvement in the alemtuzumab group (HR 0·58, 95% CI 0.38–0.87; p=0·008). 18 (9%) patients in SC IFNβ-1a group had SRD compared with 92 (22%) in the alemtuzumab group (HR 2.57, 95% CI 1.57 to 4.20; p=0·0002). Alemtuzumab's superior effect on disability was

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
	group, and 16.3% in the 12 mg group.		seen in all subgroups defined by previous therapy or anti-interferon antibodies (either present at baseline or emerging subsequently).
Mortality	There were two deaths, both in the alemtuzumab group. One patient who had several pre-existing cardiac risk factors died of cardiovascular disease. The other death was attributable to ITP. Extension No additional deaths were reported in the alemtuzumab group, but one additional death due to an accident occurred in the SC IFNβ-1a group.	There was one death in the alemtuzumab group that was [redacted]	There were two deaths in the study. Both deaths occurred in the alemtuzumab 12 mg group [redacted]
Discontinuation rate	41 patients in the SC IFNβ-1a group (37% of the treated population) discontinued study drug compared to 14 patients (13%) in the 12mg alemtuzumab group.	23 patients in SC IFNβ-1a group (11% of the treated population) discontinued the study or study drug compared to 14 in the alemtuzumab arm (4% of the treated population).	44 patients in the SC IFNβ-1a group (22% of the treated population) discontinued the study drug compared to 27 (6%) in the 12mg alemtuzumab group and 12 (7%) in the 24mg alemtuzumab group.
Health-related quality of life	[redacted]	Alemtuzumab treated patients showed significantly greater improvements from baseline than SC IFNβ-1a-treated patients on two self-reported measures of HRQL over two years: the functional assessment of Multiple Sclerosis (FAMS) ($p<0.05$ for both Year 1 and Year 2)[Gupta et al, 2012] and the SF-36 (between group differences observed at Year 1 only for physical component summary (PCS), $p=0.0002$) [Selmaj *et al*, 2012].	Alemtuzumab treated patients showed significantly greater improvements from baseline than SC IFNβ-1a patients over two years on two of the self-reported measures of HRQL: the FAMS ($p<0.01$ for both Year 1 and Year 2)[Arroyo *et al,* 2012] and the PCS component of the SF-36 ($p<0.01$ for both Year 1 and Year 2) [Selmaj *et al*, 2012]. [redacted]

Outcomes of relevance to the decision problem			
Trial	NCT0050778 (CAMMS223) [Coles et al. 2008; Coles et al. 2012(a); CSR]	NCT00530348 (CAMMS323, CARE-MS I) [Cohen et al. 2012; Fox et al. 2012; CSR]	NCT00548405 (CAMMS324, CARE-MS II) [Coles et al. 2012; CSR]
			[redacted] Using the FAMS scale, alemtuzumab treated patients significantly improved from baseline at all-time points, whereas SC IFNβ-1a did not improve at any time point assessed (p≤0.01) [Arroyo *et al,* 2012] . [redacted]

Alemtuzumab Long-term Data

Efficacy associated with retreatment with alemtuzumab in CAMMS223 (Phase II study):

The effectiveness of alemtuzumab in reducing the relapse rate and accumulation of disability compared with SC IFNβ-1a in early active RRMS has been demonstrated in the extended follow-up study of CAMMS223 (up to five years from baseline).

As described in Section 6.3 above, after the alemtuzumab dosing suspension ended (07 Apr 2008) in the CAMMS223 study, consenting alemtuzumab patients could receive additional doses of alemtuzumab in either a "fixed" (annual) retreatment arm or an "as needed" retreatment arm, and the study period was extended for an additional four years. Patients in the fixed retreatment arm could receive two annual three day cycles of 12 mg/day alemtuzumab; patients in the as-needed retreatment arm could receive up to two annual three day cycles of 12 mg/day alemtuzumab upon documented evidence of resumed MS disease activity, defined by the following criteria:

- Had, within the previous year experienced at least one protocol-defined relapse.
- Had, within the previous year or since their last on-study MRI, accumulated at least two unique lesions on brain/spinal cord MRIs comprised of any combination of gadolinium-enhancing lesion(s) or new/enlarging MRI T2 lesion(s).

The study profile for the CAMS223 extension is shown in section 6.3.8. Criteria for retreatment with alemtuzumab in the extension phase are described in Section 6.3. In the extension phase of the CAMM223 study [redacted] of patients received a 3rd dose of alemtuzumab (12mg) [CAMMS223 CSR]: at complete follow-up [redacted] patients from the alemtuzumab 12mg treatment arm (safety set) received three of more alemtuzumab cycles. [redacted] patients originally assigned to alemtuzumab 12mg received a third cycle, with [redacted] receiving the third cycle at Month 24, and [redacted] receiving the third cycle after retreatment was in place under Amendments 8 or 10. [redacted]). [redacted] [Genzyme, CAMMS223 CSR]. The reason for the high percentage of patients receiving a third dose of alemtuzumab arises from the original trial design which stipulated retreatment at month 24 at the treating physicians discretion if CD4+ T-cell count was >100x10^6 cells per litre.

Relapse endpoints

Over five years, alemtuzumab 12mg lowered the rate of relapse by 66% compared with SC IFNβ-1a ($p < 0.0001$). The ARR from baseline to month 60 was 0.12 for alemtuzumab and 0.35 for SC IFNβ-1a. A similar ARR reduction was seen for alemtuzumab patients who received only two cycles during the original study period compared with SC IFNβ-1a patients [Coles *et al*, 2012c].

Table B6.5.2. Relapse outcomes in CAMMS223 to month 60 [Coles *et al*, 2012c, Genzyme CAMMS223 CSR]

	Patients with event		ARR (95% CI)		Rate ratio vs. SC **IFNβ**-1a (95% CI)	p-value
	SC IFNβ-1a (n=111)	Alemtuzumab 12 mg (n=112)	**SC IFNβ**-1a (n=111)	Alemtuzumab 12 mg (n=112)		
Year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	51	30	0.35 (0.29, 0.42)	0.12 (0.09,0.16)	0.34 (0.20, 0.57)	<0.0001

Source: CSR Table 14.2.1.2.1.1 and Table 14.2.1.2.5.1

Disability endpoints

The effects of alemtuzumab on SAD appeared to be durable since the difference between the alemtuzumab groups and the SC IFNβ-1a group was maintained at 5 years of follow-up. After five years, alemtuzumab 12 mg reduced the risk of 6-month SAD by 69% as compared to SC IFNβ-1a (HR 0.31; 95% CI [0.16, 0.60]; p = 0.0005, Table B6.5.3) [*Coles et al, 2012c*]. A similar reduction in the risk of SAD was seen in those patients who received only 2 cycles of alemtuzumab during the original study period, at months 0 and 12. In the group treated with alemtuzumab the mean EDSS scores remained lower than baseline after five years compared to an increase in the SC IFNβ-1a group (-0.15 vs. 0.46, p=0.0056) [*Coles et al, 2012c*].

Table B6.5.3. Six-month sustained accumulation of disability event and treatment effect summary by year (Full Analysis Set) [CAMMS223 CSR]

	Patients with event		HR vs. SC IFNβ-1a (95% CI)	p-value
	SC IFNβ-1a (n=111)	Alemtuzumab 12 mg (n=112)		
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	30	13	0.31 (0.161,0.598)	0.0005

Source: CSR Table14.2.1.1.1.1, Table 14.2.1.1.5.1

Table B6.5.4. Three-month sustained accumulation of disability event and treatment effect summary by year (Full Analysis Set) [CAMMS223 CSR]

	Patients with event		HR vs. SC IFNβ-1a (95% CI)	p-value
	SC IFNβ-1a (n=111)	Alemtuzumab 12 mg (n=112)		
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]

Source: CSR Table14.2.3.6.1.1, Table 14.2.3.6.2

An additional analysis focusing on patients who received exactly 2 treatment courses of alemtuzumab 12mg during the original 36-month study period (N=161) has also been performed. The results suggest that the effects of alemtuzumab on relapse rate and 6-month SAD are able to be maintained up to at least 5 years (4 years after last treatment). In these analyses, alemtuzumab patients who had received exactly 2 treatment courses were censored at the time of retreatment during the extension period. The rate of relapse was reduced by 67% in patients who received 2 treatment courses of alemtuzumab 12mg compared with the SC IFNβ-1a arm (RR 0.33; 95% CI [0.18, 0.60]; p=0.0003) [Coles et al, 2012c, Supplementary App]. Similarly, two treatment courses of alemtuzumab 12mg reduced the risk of 6-month SAD by 61% at Year 5 compared with the SC IFNβ-1a group (HR 0.39; 95% CI [0.20, 0.77]; p=0.0062)) [Coles et al, 2012c, Supplementary Web App].

In addition, subgroup analysis from the inital three year study period shows that the efficacy of alemtuzumab in reduction of six-month SAD is not affected by number of cycles of therapy received [Figure B6.5.1]

[redacted] Subgroup analysis of reduction in six-month SAD by number of alemtuzumab cycles received

[redacted]

Source: CAMMS223 CSR

Retreatment with alemtuzumab in CAMMS03409 Extension Study

CAMMS03409 is an on-going Extension Study for patients from CAMMS223, CARE-MS I, and CARE-MS II, providing continuous follow-up up to 6 years from CARE-MS study entry. The objectives of this study are to examine:

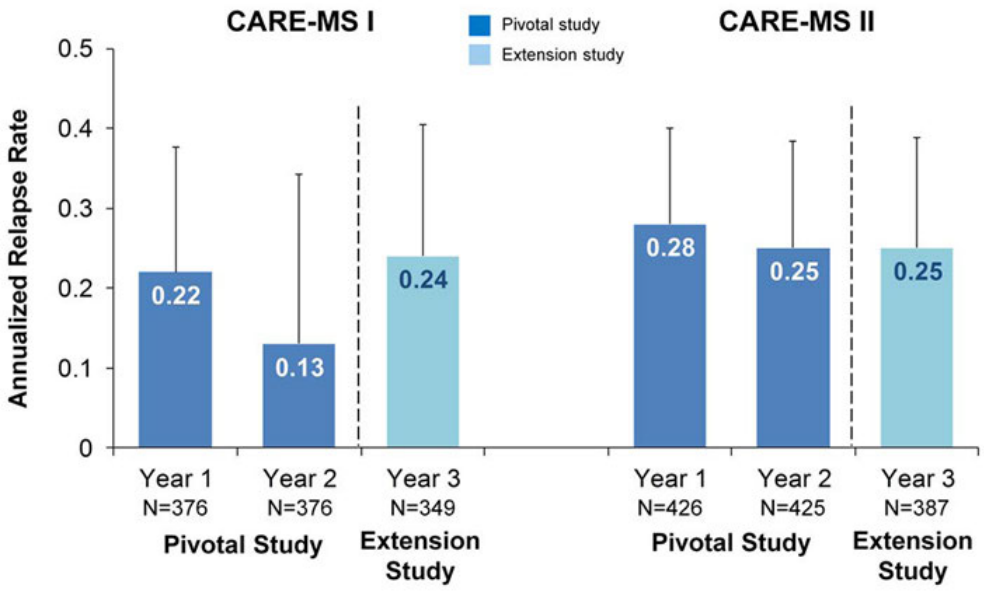
- The long-term safety and efficacy of alemtuzumab in MS patients who received alemtuzumab during prior studies including CAMMS223, CARE-MS I, and CARE-MS II
- The safety and efficacy of as-needed alemtuzumab retreatment in these previously alemtuzumab-treated patients
- The safety and efficacy of 2 fixed annual alemtuzumab cycles followed by optional as-needed retreatment in patients who previously received SC IFNB-1a during these studies

The patient disposition for the Extension Study for patients entering from CARE-MS I and CARE-MS II is summarised in Table B6.3.2 and Figure B6.3.7. Greater than 90% of patients who completed the Phase III studies entered the Extension Study, and less than 5% of the patients enrolled in the study dropped out [Fox *et al*, 2013]

During the Extension Study, retreatment criteria were defined as at least one relapse or at least two new emerging or enlarging T2 and/or Gd-enhancing brain or spinal lesions. During Year 3, 18% of patients who had enrolled from CARE-MS 1 and 20% of patients who had enrolled from CARE-MS II received alemtuzumab retreatment [Fox *et al*, 2013].

Results from the Extension Study show that patients treated with alemtuzumab 12 mg in the Phase III studies (CARE-MS I and CARE-MS II) experienced similar ARRs at Year 3 as were observed during the Phase III study period (Figure B6.5.2) [Fox *et al*, 2013].

Figure B6.5.2 CAMMS0349 3 ARR results by prior Phase III study [Fox *et al*, 2013]



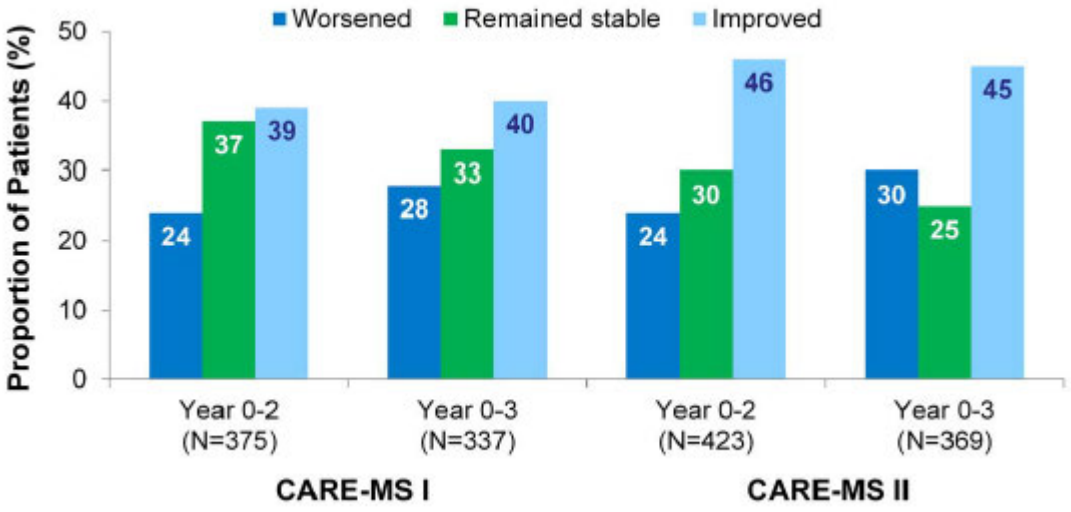
While relapse rate comparisons between the prior studies and the Extension Study are complicated by the different methods used to classify events, the relapse rates observed in the Extension Study for patients who had received alemtuzumab 12 mg in a prior study were similar to the rates observed in the prior studies. Furthermore, early results show that the relapse rates for patients treated with SC IFNβ-1a in the prior studies that crossed over to alemtuzumab 12 mg in the Extension Study were lower in the Extension Study than in the prior studies, suggesting that these patients benefited from alemtuzumab treatment [Fox *et al*. 2013].

The proportion of alemtuzumab-treated patients who were relapse and 6-month SAD free at Year 3 is shown in Table B6.5.5 highlighting the durable benefit of alemtuzumab over 3 years [Fox *et al*. 2013]. Additionally, for alemtuzumab-treated patients from both CARE-MS I and CARE-MS II, mean EDSS remains below pre-alemtuzumab baseline after 3 years follow up. As shown in figure B6.5.3 the majority of these patients reported an improved or stable EDSS change from baseline at Year 3, with little change from Year 2 [Fox *et al*. 2013].

Table B6.5.5 Proportion of alemtuzumab treated patients without disease activity and EDSS change from baseline to Year 3 in the Extension Study

	CARE-MS I (n=376)		CARE-MS II (n=435)	
	At year 2	At year 3	At year 2	At year 3
Relapse free, %	78	67	65	55
6-month SAD free, %	92	88	87	80
Mean change from baseline EDSS (SD)	-0.14 (NR)	-0.10 (0.982)	-0.17 (NR)	0.07 (1.134)

Figure B6.5.3 Mean EDSS change from baseline to Year 3 in the Extension Study



Subgroup Analyses

Rapidly Evolving Severe RRMS

Published data exists for a subset of patients with highly active disease. Evidence that frequent early relapses are predictive of disease accumulation prompted an analysis of the efficacy of alemtuzumab with a subset of patients experiencing more frequent relapses [Wingerchuk, 2010]. This subgroup analysis was carried out for two studies CAMMS223 (Phase II) and CARE-MS II.

For both analyses, highly active disease criteria was defined as:

- ≥2 relapses in the year prior to treatment
- At least 1 gadolinium-enhancing lesion at baseline

This is similar to the definition of RES used in the marketing authorisation for natalizumab and subsequent NICE recommendation without the additional NICE criteria relating to changes in T2 lesion load [NICE, 2007(a)].

Analyses from both trials demonstrated superior efficacy of alemtuzumab compared to SC IFNβ-1a in terms of relapse rate, disability accumulation and EDSS. This is presented in Table B6.5.6.

Table B6.5.6. Efficacy of alemtuzumab in patients with rapidly evolving severe disease

Trial No. (acronym)	NCT0050778 (CAMMS223) [Wingerchuk. 2010]	NCT00548405 (CAMMS324, CARE-MS II) [Krieger *et al*, 2013; Confavreux *et al*, 2012]
Relapse rate	RES alemtuzumab patients (pooled dose	There was a 51% reduction in ARR from

	group) had an 81% lower rate of relapse compared to SC IFNβ-1a patients (p<0.0001). ARR from Baseline to Year 3 for the two alemtuzumab dose groups were similar to each other (0.09, 95% CI: 0.06, 0.15 for both dose groups), and were significantly lower than that for the SC IFNβ-1a group (p<0.005).	Baseline to Year 2 in the alemtuzumab (12mg) RES group (0.33) compared to the SC IFNβ-1a RES subgroup (0.65). There was a 56% reduction in proportion of patients with relapse from Baseline to Year 2 in the alemtuzumab RES group compared to the SC IFNβ-1a group (p=0.0018).
Sustained accumulation /reduction of disability	The estimated proportion of RES alemtuzumab patients (pooled dose group) who were 6-month SAD-free at Year 3 was 91% (95% CI: 84.0%; 95.2%) compared to 73% (95% CI: 58.1%, 83.5%) for SC IFNβ-1a patients. The pooled alemtuzumab group had a 70% lower risk for 6-month SAD than SC IFNβ-1a group [HR: 0.30; 95% CI: 0.13, 0.69; p=0.0045]. Comparisons of each dose group to the SC IFNβ-1a were similar: with the 12mg dose there was a 65% lower risk of 6-month SAD (p=0.036).	There was a 51% reduction difference in the percentage of patients with SAD Years 0-2 in the alemtuzumab RES patient subgroup (8.95%) compared to SC IFNβ-1a RES patients (17.62%) There was a 77% increase the number of patients with SRD in patients treated with alemtuzumab compared to SC IFNβ-1a (22.99% vs. 12.99%).
EDSS	Mean EDSS change from Baseline to Year 3 improved by -0.53 point (95% CI: -0.76, -0.31, p<0.0001) in the pooled alemtuzumab group, and by -0.51 points in the 12mg/day group (95% CI: -0.82,-0.21, p<0.0012) whereas the SC IFNβ-1a group worsened by +0.45 point (95% CI: 0.10, 0.80, p=0.013). RES alemtuzumab patients had a net advantage of mean EDSS improvement by 0.98 point (95% CI: 0.58, 1.39, p<0.0001) in the pooled group and 0.96 points (95%CI: 0.50, 1.42, p<0.0001) for the 12mg/day group compared to RES SC IFNβ-1a patients. Comparisons of each dose group to SC IFNβ-1a were comparable.	Mean EDSS change from Baseline to Year 3 improved by 0.24 point in the alemtuzumab group, whereas SC IFNβ-1a group worsened by -0.18 point.
Activity free status		There was a significant difference in percentage of patient who remained MRI activity-free in the alemtuzumab RES patients (40.0%) compared to the SC IFNβ-1a patients (7.5%), p=0.0007. The difference in patients with no Gd-enhancing lesions was 77.8% and 47.5% respectively (p=0.0006) and the proportion of patients with no new/enlarging T2 lesions was 41.0% and 7.5% respectively (p=0.0005). 24.2% of the alemtuzumab RES population remained MS-disease activity free over 2 years compared to 0% of SC IFNβ-1a patients (p=0.0002)
Safety	Treatment-emergent AEs experienced by RES patients were comparable to those	Treatment-emergent AEs experienced by RES patients were comparable to those observed in

	observed in the overall sample	the overall sample

In conclusion, the effectiveness of alemtuzumab in the rapidly evolving severe cohorts was comparable or greater than that seen in the overall study populations.

In the RES subset of the CAMM223 and CARE-MS II study populations, the superior efficacy of alemtuzumab compared to SC IFNβ-1a was evident in relapse rate, sustained accumulation of disability and mean change from baseline EDSS [Wingerchuk. 2010; Confavreux *et al*, 2012; Krieger *et al*, 2013]. Compared to SC IFNβ-1a, alemtuzumab increased the proportion of patients with a sustained reduction in disability in the CARE-MS II RES cohort [Confavreux *et al*, 2012; Krieger *et al*, 2013].

Further subgroup analyses

In a pooled subgroup analysis conducted to assess the influence of gender, age, geographic region, and other baseline or demographic factors on relapse rate and sustained accumulation of disability, the rate ratios comparing alemtuzumab to SC IFNβ-1a for each of the subgroups all favoured alemtuzumab [Figures B6.5.4 and B6.5.5].

[redacted] Summary of Relapse Rate Ratio up to 2 year subgroup analysis (Pooled CAMMS223, CARE-MS I, CARE-MS II CAMMS3409)

[redacted]

Source Genzyme ISE 2012

[redacted]. Summary of Sustained Accumulation of Disability up to 2 year subgroup analysis (Pooled CAMMS223, CARE-MS I, CARE-MS II CAMMS3409)

[redacted]

Source Genzyme ISE 2012

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).

- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individuall and combined results (such as through the use of forest plots).

There are three studies that can be considered for meta-analysis:

- CAMMS223
- CARE-MS I
- CARE-MS II

The following outcome measures are presented for the relevant studies where similar outcomes measures are available:

- Annualised relapse rate (ARR)
- Proportion of patients relapse free
- Three- and six-month sustained accumulation of disability (SAD)
- All-cause discontinuations
- Discontinuations due to adverse events (DAEs)

This was a random-effects meta-analyses, and employed an empirical Bayes estimator of the random-effects variance. These meta-analyses were conducted in R, using package metaphor version 1.6.

In general, very few signs of heterogeneity were found using informal classical meta-analyses of direct and one-bridge-indirect evidence (see notes following). A manual check of the demographic details of patients included in these trials did not flag any warning signs regarding differences in clinical aspects i.e. age, gender, EDSS at entry, or number of previous relapses (see Table B6.3.3). Of note however and inherent as a result of the trial design, all patients in CARE-MS II had received previous DMTs vs. few or none in CAMMS223 and CARE-MS I respectively. Additionally patients in the CARE-MS II trial had a greater time since first relapse compared to CARE-MS I and CAMMS223 trial participants.

[redacted]

There were very few signs of inconsistency or heterogeneity, resulting in an extremely low estimate of random-effects variance. The estimate was so low that there were occasionally convergence problems in sensitivity analyses, caused by the Markov chain Monte Carlo (MCMC) estimation locking into extremely tiny ($\sim<10^{-8}$) estimates of tau.

[redacted]

There were very few signs of inconsistency or heterogeneity, resulting in a low estimate of random-effects variance.

[redacted]

There were very few signs of inconsistency or heterogeneity, resulting in a low estimate of random-effects variance.

[redacted]

Comparisons of alemtuzumab versus other drugs showed little to no sign of heterogeneity.

[redacted]

Comparisons of alemtuzumab versus other drugs showed little to no sign of heterogeneity.

[redacted]

The estimate of random-effects variation was substantively significant for DAEs and care should be taken with generalising this result. However, power was low to detect any particular signals as many studies had very few events; the overall event rate was less than 10%, and most studies had fewer than 100 patients per arm. Also, as with total discontinuations, DAE rates for drugs are typically dependent on the safety of a product. Other factors, such as pre-specified protocol requirements or product characteristics resulting in different routes of administration, also may contribute to discontinuation rates and are independent of safety.

Results of Direct Meta-Analysis

The results of the meta-analysis demonstrated that alemtuzumab 12 mg was consistently superior to placebo for the analysed efficacy and safety outcomes. Alemtuzumab treated patients were less likely to experience a relapse within one year, a sustained accumulation of disability (at either 3 or 6 months) or discontinue treatment (all cause or as a result of adverse effects) compared to SC IFNβ-1a. The proportion of patients who remained relapse free remains greatest in alemtuzumab treated patients. In all cases, the results are statistically significant in that the confidence intervals do not include 1.

Please note we are not presenting Forest Plots for the meta-analysis data. Please see Forest Plots within the mixed-treatment analysis section 6.7.

Summary of direct evidence (Sensitivity analysis Dataset: ≥2000 Recruitment Year and 100% RRMS Patients- see section 6.7.1)

Table B6.6.1 ARR direct evidence

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	0.31 [0.21, 0.45]
	CARE-MS I	0.46 [0.36, 0.58]
	CARE-MS II	0.5 [0.41, 0.61]
	Direct Meta-Analysis	[redacted]

Table B6.6.2 Proportion relapse-free direct evidence

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	2.5 [1.39, 4.51]
	CARE-MS I	2.43 [1.67, 3.55]
	CARE-MS II	2.18 [1.55, 3.07]
	Direct Meta-Analysis	[redacted]

Table B6.6.3. Three-month sustained accumulation of disability

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	[redacted]
	CARE-MS I	[redacted]
	CARE-MS II	[redacted]
	Direct Meta-Analysis	[redacted]

Table B6.6.4. Six-month sustained accumulation of disability

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	0.25 [0.11, 0.57]
	CARE-MS I	0.7 [0.39, 1.24]
	CARE-MS II	0.58 [0.38, 0.89]
	Direct Meta-Analysis	[redacted]

Table B6.6.5 All-cause discontinuation

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	0.24 [0.12, 0.47]
	CARE-MS I	0.28 [0.14, 0.55]
	CARE-MS II	0.24 [0.14, 0.4]
	Direct Meta-Analysis	[redacted]

Table B6.6.6 Discontinuation due to adverse events

Comparison	Trials	Relative Risk (95% CI)
Alemtuzumab (12 mg) vs. SC IFNβ-1a	CAMMS223	0.14 [0.03, 0.62]
	CARE-MS I	0.22 [0.07, 0.63]
	CARE-MS II	0.41 [0.1, 0.88]
	Direct Meta-Analysis	[redacted]

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

None of the primary studies listed in section 6.2.4 have been excluded from the meta-analysis.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Systematic Literature Search

A systematic literature search was conducted to identify studies which could potentially be used for direct and indirect comparison and is described in detail in Section 6.1. Section 10.2 Appendix 2 details the search algorithms used for EMBASE, MEDLINE, and CENTRAL.

MTC Inclusion Criteria

Several recent studies have suggested that the ARR observed in clinical trials has declined over time. In a 2010 publication by Inusah *et al*., a downward trend in ARR was observed in trials for MS published between 1980 and 2008; in some later trials, ARR was three times lower than in earlier trials. In a review of RCTs in RRMS conducted by Nicholas *et al*., the ARR for placebo was found to decrease by 6.2% per year.
Patient recruitment from the year 2000 generally coincided with the widespread introduction of the McDonald diagnostic criteria in MS clinical trials, whereas prior to this the Poser criteria were used in clinical trials. Compared with the Poser criteria, the McDonald criteria generally identify patients much earlier in the disease course, and with less frequent or severe symptoms; therefore, a change in MS diagnostic criteria may have considerable impact on the baseline disease activity of the patient population under study.

Two clinical experts (Prof Patrick Vermersch neurologist from France and Prof Gary Cutter methodologist from the US) were consulted about the feasibility of performing mixed treatment comparison (MTC) analyses for DMTs in MS based on the available evidence. To account for the evidence of decreased relapse rates over time, the clinical experts recommended excluding studies with patient recruitment before 2000, taking into consideration: [Cutter *et al*. 2013]

- New MS diagnostic criteria (McDonald)
- Earlier treatment following the publication of the CHAMPS study [Galetta, 2001]
- Timeframe for the development of the different DMTs
- For studies where the year(s) of recruitment were not reported, year of publication was used as a proxy.

The ≥80% RRMS threshold was suggested following an Advisory Board meeting after reviewing the distribution of the proportion of RRMS patients in the included trials. Based on this review, the vast majority of trials in this analysis seem to cluster into two groups: greater than or equal to 80% RRMS patients, or considerably <80% RRMS patients. As such, 80% was selected as the 'cut-off' for analysis.

Therefore, trials in the network were restricted to studies with patient recruitment after 2000 and with ≥80% RRMS patients. Sensitivity analyses were run on datasets without these restrictions.

In order to support the validity of this approach further, data from trials conducted prior to 2000 were compared to the data identified in the base case systematic review. This analysis suggests relapses prior to study entry, and within the study placebo arms, ARR and disability accumulation were higher in the studies > 2000 compared to those < 2000. Specifically:

- Relapse rate prior to study entry over two year period: 2.1-2.8 studies >2000 and ≤ 2000 2.5-3.9 (Table B6.7.1 and Additional Appendix 4, Table AA4.7)
- ARR range during study in placebo arms: 0.36-0.99 studies >2000 and ≤ 2000 0.84-1.21 (Table B6.7.1 and Additional Appendix 4, Table AA4.8)
- Three-month disability accumulation in placebo arms: 13%-28% studies >2000 and ≤ 2000 24.6%-52.65% (Table B6.7.1 and Additional Appendix 4, Table AA4.9)

Exclusion Criteria

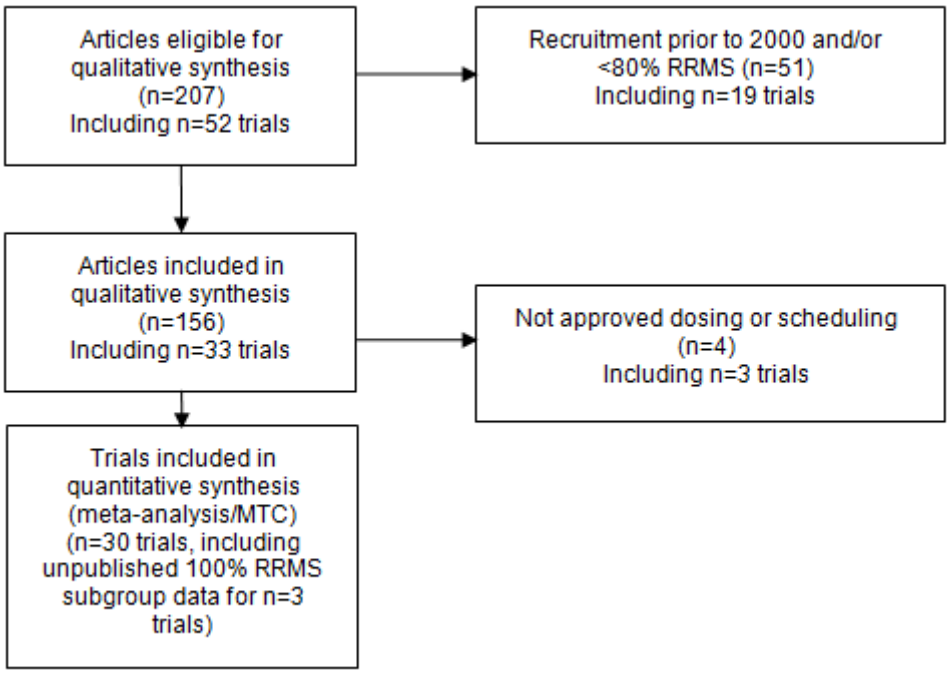
In addition to excluding studies with patient enrolment prior to the year 2000 and with <80% RRMS in the patient population, articles based on expert opinion, commentary, letters, editorials, non-randomised studies, reviews, studies reporting results from more than one RCT, studies with no abstracts, and articles written in a language other than English were excluded from this review. Papers that reported the methods and baseline characteristics, but not the results of an RCT were excluded, as were studies that used RCT data to validate outcome measures or diagnostic criteria. Single-arm studies or studies that did not compare an intervention to one of the selected DMTs or placebo and studies that examined combination therapies were excluded from this report. Also excluded were animal, *in vitro*, foetal, molecular, genetic, pharmacodynamic, or pharmacokinetic studies. Additionally, open-label studies (i.e., trials in which both the patients and the examining physician were not blinded) that were not extensions of blinded RCTs, studies where the number of patients in a specific treatment arm or population could not be determined, studies with fewer than 10 patients in a treatment arm, and studies that continued to recruit patients after study initiation were excluded.

MTC feasibility assessment

A feasibility assessment was performed to determine which trials should be included in the MTC analyses and to account for the evidence of decreased relapse rates over time. As part of the feasibility assessment, clinical and statistical experts in the field of MS were consulted regarding methodology and identified clinical heterogeneity. Two clinical experts (Prof Patrick Vermersch, neurologist from France and Prof Gary Cutter, methodologist from the US) were consulted about the feasibility of performing MTC analyses for DMTs in MS based on the available evidence. Among the trials identified in the SLR, 30 were deemed suitable for MTC analyses. In addition, a sensitivity analysis was considered which included trials from all years, without the restriction of post 2000 publication, however, as discussed this analysis would lead to more studies using older diagnostic criteria (Poser) for MS.

As shown in figure B6.7.1 among the trials identified in the SLR, 30 were deemed suitable for mixed MTC analyses.

Figure B6.7.1 PRISMA diagram



6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The base-case MTC included 30 clinical trials with patient recruitment 2000 and onward, and ≥80% RRMS patient population. Among 21 of these trials, patient recruitment took place after 2000; for the remaining nine trials, recruitment was assumed to be after 2000 on the basis of publication year. Most (25) of the included trials utilised the McDonald diagnostic criteria. See Additional Appendix 5 for clinical trial quality assessment tables.

All the relevant comparators were identified in the MTC in studies post 2000 *with the exception* of Rebif 22µg (SC IFNβ-1a), which is a dose used in UK practice. Six relevant studies were identified pre-2000 including one trial of SC IFNβ-1a 22µg(PRISMS) [Ebers, 1998] and are presented in Additional Appendix 4 (Table AA4.7) as part of a sensitivity analysis which considered all years from 1980 and with a ≥80% RRMS patient population.

As previously discussed it was not appropriate to use the all-years analysis for the base case analysis. Therefore in order to obtain data for SC IFNβ-1a 22µg, the ratios of results between SC IFNβ-1a 44µg and 22µg in the all-years sensitivity analysis were calculated and applied to the SC IFNβ-1a 44µg data in the base case analysis for SAD (3 months) and overall discontinuation, as these data are used in the cost-effectiveness analysis (see Section 7.3). No data were identified for SC IFNβ-1a 22µg for ARR in the all-years analysis

In the laquinimod RMS trial, which was used in the base case for overall discontinuation and discontinuation due to adverse events, one treatment arm (laquinimod 0.1 mg) reported zero events for the discontinuation for adverse events (DAE) outcome and was subsequently removed from that analysis due to lack of ability to estimate an OR vs. placebo (as the estimate would technically be infinite, given the lack of events).

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

See Additional Appendix 5 for MTC quality assessment table

Table B6.7.1 Summary data from the RCTs included in the MTC base case analysis

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years	Male	Baseline EDSS	Previous Relapse Rate	Prev. Treated	Disease Duration, Years*	ARR at End of Trial
							(Mean ± SD)	(%)	(Mean ± SD)		(%)	(Mean ± SD)	
1. CAMMS223 [Coles *et al*. 2008]	Alemtuzumab	12 mg IV annually	112	McDonald	100% RRMS	2002–2004	31.9±8.0	35.7%	1.9±0.7	NR	0%	NR	0.11
	Alemtuzumab	24 mg IV annually	110	McDonald	100% RRMS	2002–2004	32.2±8.8	35.5%	2.0±0.7	NR	0%	NR	0.08
	SC IFNβ-1a	44 µg SC 3 times weekly	111	McDonald	100% RRMS	2002–2004	32.8±8.8	36.0%	1.9±0.8	NR	0%	NR	0.36
2. CARE-MS I [Cohen *et al*. 2012]	SC IFNβ-1a	44 µg SC 3 times weekly	187	McDonald	100% RRMS	2007–2009	33.2±8.5	35.0%	2.0±0.8	1 yr: 1.8	0%	2.0±1.3	0.39
	Alemtuzumab	12 mg IV daily for 5 days at 0 months, daily for 3 days at 12 months	376	McDonald	100% RRMS	2007–2009	33.0±8	35.0%	2.0±0.8	1 yr: 1.8	0%	2.1±1.4	0.18

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
3.CARE-MS II [Coles *et al*. 2012]	Alemtuzumab	12 mg IV daily for 5 days at 0 months, daily for 3 days at 12 months	426	McDonald	100% RRMS	2007–2009	34.8± 8.36	34%	2.7±1.26	1 yr: 1.7	DMT: 100%	4.5±2.68	0.26
	SC IFNβ-1a	44 µg SC 3 times weekly	202	McDonald	100% RRMS	2007–2009	35.8± 8.77	35%	2.7±1.21	1 yr: 1.5	DMT: 100%	4.7±2.86	0.52
4. SELECT [Giovannoni *et al*. 2011]	Daclizumab	300 mg SC injection once every 4 weeks	203	McDonald (Polman)	100% RRMS	NR	35±9	NR	2.6±1.2	1 yr: 1.3	NR	3±NR	0.23
	Daclizumab	150 mg SC injection once every 4 weeks	201	McDonald (Polman)	100% RRMS	NR	35±9	NR	2.8±1.2	1 yr: 1.4	NR	3±NR	0.21
	Placebo		196	McDonald (Polman)	100% RRMS	NR	37±9	NR	2.7±1.2	1 yr: 1.3	NR	2±NR	0.46
5.FREEDOMS [Kappos *et al*. 2010]	Fingolimod	1.25 mg oral daily	429	McDonald	100% RRMS	2006–2007	37.4±8.9	31.2%	2.4±1.4	2 yr: 2.1	DMT history: 39.6%	8.4±6.9	0.16
	Fingolimod	0.5 mg oral daily	425	McDonald	100% RRMS	2006–2007	36.6±8.8	30.4%	2.3±1.3	2 yr: 2.1	DMT history: 42.6%	8.0±6.6	0.18
	Placebo		418	McDonald	100% RRMS	2006–2007	37.2±8.6	28.7%	2.5±1.3	2 yr: 2.2	DMT history: 40.4%	8.1±6.4	0.40

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
6.FREEDOMS II [Calabresi *et al*. 2012]	Fingolimod	1.25 mg once daily	370	NR	100% RRMS	NR	40.9±8.9	24%	2.5±1.3	1 yr: 1.5 2 yr: 2.3	DMT: 77.6%	10.8±8.2	0.20
	Fingolimod	0.5 mg once daily	358	NR	100% RRMS	NR	40.6±8.4	23%	2.4±1.3	1 yr: 1.4 2 yr: 2.2	DMT: 73.7%	10.4±8.0	0.21
	Placebo		355	NR	100% RRMS	NR	40.1±8.4	19%	2.4±1.3	1 yr: 1.5 2 yr: 2.2	DMT: 73.0%	10.6±7.9	0.40
7. FTY720 D2201 Study Group [Kappos *et al*. 2006]	Fingolimod	1.25 mg oral daily	94	McDonald	89% RRMS, 11% SPMS	2003–2004	38.0±NR	24.7%	2.7±NR	2 yr: 1.9	NR	NR	0.35
	Fingolimod	5.0 mg oral daily	94	McDonald	87% RRMS, 13% SPMS	2003–2004	38.3±NR	29.3%	2.5±NR	2 yr: 1.9	NR	NR	0.36
	Placebo		93	McDonald	90% RRMS, 10% SPMS	2003–2004	37.1±NR	33.7%	2.6±NR	2 yr: 1.8	NR	NR	0.77
8. Saida *et al*. 2012 [Saida *et al*. 2012]	Placebo		57	McDonald	100% RRMS	2007–2010	35±8.9	32%	2.1±1.7	1 yr: 1.7 2 yr: 2.8	NR	NR	0.99
	Fingolimod	0.5 mg oral daily	57	McDonald	94.7% RRMS 5.3% SPMS	2007–2010	35±9	30%	2.3±1.9	1 yr: 1.4 2 yr: 2.2	NR	NR	0.50
	Fingolimod	1.25 mg oral daily	57	McDonald	98.2% RRMS 1.8% SPMS	2007–2010	36±9.3	32%	1.8±1.7	1 yr: 1.5 2 yr: 2.3	NR	NR	0.41

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
9. TRANSFORMS [Cohen *et al*. 2010]	Fingolimod	1.25 mg oral daily	426	McDonald/ Polman	100% RRMS	2006–2007	35.8±8.4	31.2%	2.2±1.3	2 yr: 2.2	Any therapy: 58.5%; Any IFN: 49.1%; GA: 15.7%	7.3±6.0	0.20
	Fingolimod	0.5 mg oral daily	431	McDonald/ Polman	100% RRMS	2006–2007	36.7±8.8	34.6%	2.2±1.3	2 yr: 2.3	Any therapy: 55.2%; Any IFN: 50.8%; GA: 13.2%	7.5±6.2	0.16
	IFNβ-1a	30 µg IM weekly	435	McDonald/ Polman	100% RRMS	2006–2007	36.0±8.3	32.2%	2.2±1.3	2 yr: 2.3	Any therapy: 56.3%; Any IFN: 47.6%; GA: 15.4%	7.4±6.3	0.33
10. BG-12 Phase IIb Study [Kappos *et al*. 2008]	BG-12	120 mg oral daily	64	McDonald	100% RRMS	2004–2005	34.8± 10.2	34.4%	2.5±1.1	NR	NR	NR	0.29
	BG-12	120 mg oral 3 times daily	64	McDonald	100% RRMS	2004–2005	36.3±9.5	31.3%	2.5±1.0	NR	NR	NR	0.60
	BG-12	240 mg oral 3 times daily	64	McDonald	100% RRMS	2004–2005	37.3±9.1	33.3%	2.9±1.3	NR	NR	NR	0.28
	Placebo		65	McDonald	100% RRMS	2004–2005	35.6±8.2	44.6%	2.7±1.2	NR	NR	NR	0.41

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years	Male	Baseline EDSS	Previous Relapse Rate	Prev. Treated	Disease Duration, Years*	ARR at End of Trial
							(Mean ± SD)	(%)	(Mean ± SD)		(%)	(Mean ± SD)	
11. CONFIRM [Fox *et al*. 2012]	Placebo		363	McDonald	100% RRMS	NR	36.9±9.2	31%	2.6±1.2	1 yr: 1.4	DMT: 31%	4.8±5.0	0.40
	BG-12	240 mg oral twice daily	359	McDonald	100% RRMS	NR	37.8±9.4	32%	2.6±1.2	1 yr: 1.3	DMT: 28%	4.9±5.1	0.22
	BG-12	240 mg oral 3 times daily	345	McDonald	100% RRMS	NR	37.8±9.4	28%	2.5±1.2	1 yr: 1.4	DMT: 29%	4.6±5.2	0.20
	GA	20 mg SC daily	350	McDonald	100% RRMS	NR	36.7±9.1	29%	2.6±1.2	1 yr: 1.4	DMT: 29%	4.4±4.7	0.29
12. DEFINE [Gold *et al*. 2012]	Placebo		408	McDonald	100% RRMS	NR	38.5± 9.14	25%	2.48±1.24	1 yr: 1.3	55.6%	5.8±5.78	0.36
	BG-12	240 mg oral twice daily	410	McDonald	100% RRMS	NR	38.1± 9.11	28%	2.40±1.29	1 yr: 1.3	54.4%	5.6±5.39	0.17
	BG-12	240 mg oral 3 times daily	416	McDonald	100% RRMS	NR	38.8± 8.85	26%	2.36±1.19	1 yr: 1.3	55.3%	5.1±5.29	0.19
13. FORTE Study Group [Comi *et al*. 2011]	GA	20 mg SC daily	586	McDonald/ Polman	100% RRMS	2006–2007	36.3±9.0	28.2%	2.2±1.2	1yr: 1.5	NR	6.3±6.5	0.33
	GA	40 mg SC daily	569	McDonald/ Polman	100% RRMS	2006–2007	36.3±9.0	28.5%	2.1±1.1	1yr: 1.4	NR	6.5±6.7	0.35

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years	Male	Baseline EDSS	Previous Relapse Rate	Prev. Treated	Disease Duration, Years*	ARR at End of Trial
							(Mean ± SD)	(%)	(Mean ± SD)		(%)	(Mean ± SD)	
14. Dose-Comparison 9006 Study Group [Cohen *et al*. 2007]	GA	20 mg SC daily	44	Poser	100% RRMS	2003–2005	37.1±7.0	29.5%	2.0±1.2	1 yr: 1.5	NR	7.4±6.2	NR
	GA	40 mg SC daily	46	Poser	100% RRMS	2003–2005	37.4±6.5	19.6%	2.1±1.0	1 yr: 1.5	NR	6.7±6.4	NR
15. BEYOND [O'Connor *et al*. 2009]	IFNβ-1b	500 µg SC every other day	899	McDonald	100% RRMS	2003–2005	35.9±NR	30.0%	2.3±NR	1 yr: 1.6	NR	5.4±NR	0.33
	IFNβ-1b	250 µg SC every other day	897	McDonald	100% RRMS	2003–2005	35.8±NR	30.1%	2.4±NR	1 yr: 1.6	NR	5.3±NR	0.36
	GA	20 mg SC daily	448	McDonald	100% RRMS	2003–2005	35.2±NR	31.7%	2.3±NR	1 yr: 1.6	NR	5.1±NR	0.34
16. BECOME [Cadavid *et al*. 2009]	IFNβ-1b	250 µg SC every other day	36	NR	86% RRMS, 14% CIS	NR	36.0±NR	25.0%	NR	1 yr: 1.8	NR	NR	0.37
	GA	20 mg SC daily	39	NR	77% RRMS, 23% CIS	NR	36.0±NR	36.0%	NR	1 yr: 1.9	NR	NR	0.33
17. REGARD [Mikol *et al*. 2008]	IFNβ-1a	44 µg SC 3 times weekly	386	McDonald	100% RRMS	2004	36.7±9.8	31.0%	2.3±1.3	NR	NR	5.9±3.0	0.30
	GA	20 mg SC daily	378	McDonald	100% RRMS	2004	36.8±9.5	28.0%	2.3±1.3	NR	NR	6.5±7.1	0.29

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
18. CombiRx [The CombiRx trial 2012]	IFNβ-1a plus GA	30 µg IM weekly plus 20 mg SC daily	499	Poser/McDonald	100% RRMS	2005–2009	37.1±9.4	25.4%	1.9±1.2	1 yr: 1.7	NR	4.2±5.4	0.12
	IFNβ-1a	30 µg IM weekly	250	Poser/McDonald	100% RRMS	2005–2009	37.6± 10.2	30.8%	2.0±1.2	1 yr: 1.7	NR	4.7±6.4	0.16
	GA	20 mg SC daily	259	Poser/McDonald	100% RRMS	2005–2009	39.0±9.5	28.6%	2.0±1.1	1 yr: 1.6	NR	4.3±5.5	0.11
19. Etemadifar, 2006 [Etemadifar *et al*. 2006]	IFNβ-1a	30 µg IM weekly	30	Poser	100% RRMS	2002–2004	NR	20.0%	1.9±1.1	1 yr: 2.0	NR	2.9±2.3	NR
	IFNβ-1a	44 µg SC 3 times weekly	30	Poser	100% RRMS	2002–2004	NR	23.3%	2.1±1.0	1 yr: 2.4	NR	3.0±2.2	NR
	IFNβ-1b	250 µg SC every other day	30	Poser	100% RRMS	2002–2004	NR	30.0%	1.9±0.7	1 yr: 2.2	NR	3.7±2.3	NR
20. EVIDENCE [Panitch *et al*. 2002]	IFNβ-1a	44 µg SC 3 times weekly	339	Poser	100% RRMS	NR	38.3±NR	25.1%	2.3±NR	2 yr: 2.6	NR	6.5±NR	0.54
	IFNβ-1a	30 µg IM weekly	338	Poser	100% RRMS	NR	37.4±NR	25.4%	2.3±NR	2 yr: 2.6	NR	6.7±NR	0.65
21. BRAVO [Vollmer *et al*. 2011]	Placebo		450	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.37
	Laquinimod	0.6 mg oral daily	434	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.29
	IFNβ-1a	30 µg IM once weekly	447	McDonald	100% RRMS	NR	NR	NR	NR	NR	NR	NR	0.27

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
22. LAQ/5062 [Comi *et al*. 2008]	Laquinimod	0.3 mg oral daily	98	McDonald	100% RRMS	2005	NR	NR	2.3±1.1	1 yr: 1.46	0%	NR	0.76
	Laquinimod	0.6 mg oral daily	106	McDonald	100% RRMS	2005	NR	NR	2.3±1.0	1 yr: 1.51	0%	NR	0.52
	Placebo		102	McDonald	100% RRMS	2005	NR	NR	2.5±1.1	1 yr: 1.37	0%	NR	0.77
23. Laquinimod in Relapsing MS [Polman *et al*. 2005]	Laquinimod	0.1 mg oral daily	68	McDonald	84% RRMS, 16% SPMS	2002	42.4±NR	20.6%	3.2±NR	NR	NR	5.8±NR	NR
	Laquinimod	0.3 mg oral daily	74	McDonald	79% RRMS, 21% SPMS	2002	39.6±NR	29.7%	3.2±NR	NR	NR	5.5±NR	NR
	Placebo		67	McDonald	91% RRMS, 9% SPMS	2002	38.7±NR	26.9%	3.0±NR	NR	NR	5.3±NR	NR
24. ALLEGRO [Comi *et al*. 2012]	Laquinimod	0.6 mg oral daily	550	McDonald	100% RRMS	2007–2008	38.9±9.2	29%	2.6±1.3	1 yr: 1.2 2 yr: 1.9	38.2%	8.7±6.9	0.30
	Placebo		556	McDonald	100% RRMS	2007–2008	38.5±9.1	34%	2.6±1.3	1 yr: 1.3 2 yr: 1.9	39.7%	8.7±6.7	0.39
25. AFFIRM [Polman *et al*. 2006]	Natalizumab	300 mg IV per 4 weeks	627	McDonald	100% RRMS	2001	35.6±8.5	28.4%	2.3±1.2	1 yr: 1.5	NR	NR	0.23
	Placebo		315	McDonald	100% RRMS	2001	36.7±7.8	33.0%	2.3±1.2	1 yr: 1.5	NR	NR	0.73
26. HERMES [Hauser *et al*. 2008]	Rituximab	1,000 mg IV at days 1 and 15	69	McDonald	100% RRMS	NR	39.6±8.7	24.6%	NR	NR	78.3%	9.6±6.4	0.37
	Placebo		35	McDonald	100% RRMS	NR	41.5±8.5	17.1%	NR	NR	77.1%	9.6±7.1	0.72
27. Teriflunomide in Relapsing MS [O'Connor *et al*.	Teriflunomide	7 mg oral daily	61	Poser	88.5% RRMS, 11.5% SPMS	2001–2003	40.1±9.3	24.6%	NR	1 yr: 1.0	83.6	10.3±8.1	0.58

Trial	Treatment Arm	Dose	Number Randomised	MS Diagnosis Criteria	Population	Recru tment Period	Age, Years (Mean ± SD)	Male (%)	Baseline EDSS (Mean ± SD)	Previous Relapse Rate	Prev. Treated (%)	Disease Duration, Years* (Mean ± SD)	ARR at End of Trial
2006]	Teriflunomide	14 mg oral daily	57	Poser	87.7% RRMS, 12.3% SPMS	2001–2003	40.1±9.1	21.1%	NR	1 yr: 1.0	71.9	8.5±7.1	0.55
	Placebo		61	Poser	86.9% RRMS, 13.1% SPMS	2001–2003	39.2±8.7	32.8%	NR	1 yr: 1.0	82	8.6±7.9	0.81
28. TEMSO [O'Connor *et al*. 2011]	Teriflunomide	7 mg oral daily	366	McDonald	91% RRMS, 9% SPMS/ CPMS	2004–2008	37.4±9.0	30.3%	2.7±1.3	2 yr: 2.3	DMT: 27.9%	8.8±6.8	0.37
	Teriflunomide	14 mg oral daily	359	McDonald	92.8% RRMS, 7.2% SPMS/ CPMS	2004–2008	37.8±8.2	29.0%	2.7±1.2	2 yr: 2.2	DMT: 28.4%	8.7±6.7	0.37
	Placebo		363	McDonald	90.6% RRMS, 9.4% SPMS/ CPMS	2004–2008	38.4±9.0	24.2%	2.7±1.3	2 yr: 2.2	DMT: 24.8%	8.6±7.1	0.54
29.TENERE [Vermersch *et al*. 2012; CSR]	Teriflunomide	7 mg oral daily	109	McDonald	[redacted]	2009–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.410
	Teriflunomide	14 mg oral daily	111	McDonald	[redacted]	2009–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.259
	SC IFNβ-1a	44 µg SC 3 times weekly	104	McDonald	[redacted]	2009–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.216
30. TOWER [Sanofi. Clinical Study Report 2012]	Teriflunomide	7 mg oral daily	408	McDonald	[redacted]	2008–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Teriflunomide	14 mg oral daily	372	McDonald	[redacted]	2008–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo		389	McDonald	[redacted]	2008–2011	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

See Additional Appendix 6 for a summary of data used in the MTC analysis and see below.

Table B6.7.2 Summary of the trials used to conduct the indirect comparison – part A

No. Trials	References of trials	Alemtuzumab		Teriflunomide		Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b			Glatiramer Acetate		Natalizumab	Fingolimod		
		12mg	24mg	7mg	14mg				250 µg	500 µg	12mg	20 mg	40 mg		0.5mg	1.25mg	5mg
2	CARE-MS I CARE-MS II	✓						✓									
1	CAMMS223	✓	✓					✓									
3	Phase II Proof of Concept Study TEMSO TOWER			✓	✓	✓											
1	TENERE			✓	✓			✓									
2	Forte Study Group Dose-Comparison 9006 Study Group											✓	✓				
1	Etemadifar						✓	✓	✓								
1	EVIDENCE						✓	✓									
1	BEYOND								✓	✓		✓					
1	BECOME								✓			✓					
1	REGARD							✓				✓					
1	CombiRx*						✓					✓					
1	AFFIRM					✓								✓			

No. Trials	References of trials	Alemtuzumab		Teriflunomide		Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b			Glatiramer Acetate		Natalizumab	Fingolimod		
		12mg	24mg	7mg	14mg				250 µg	500 µg	12mg	20 mg	40 mg		0.5mg	1.25mg	5mg
3	FREEDOMS FREEDOMS II Saida et al					✓									✓	✓	
1	FTY720 D2201 Study Group					✓										✓	✓
1	TRANSFORMS							✓							✓	✓	

Table B6.7.3 Summary of the trials used to conduct the indirect comparison – part B

No. Trials	References of trials	Placebo	IM IFNβ-1a 30µg	SC IFNβ-1a 44µg	IFNB-1b		Glatiramer Acetate		Daclizumab		Laquinimod			Rituximab	BG12			
					250 µg	500 µg	20 mg	40 mg	150mg	300mg	0.1mg	0.3mg	0.6mg		120mg od	120mg tds	240mg bd	240mg tds
1	SELECT	✓							✓	✓								
1	BRAVO	✓	✓										✓					
1	LAQ/5062	✓										✓	✓					
1	Laquinimod in Relapsing MS	✓									✓	✓						
1	ALLEGRO	✓											✓					
1	HERMES	✓												✓				
1	BG-12 Phase IIb	✓													✓	✓		✓
1	CONFIRM	✓					✓										✓	✓
1	DEFINE	✓															✓	✓

Figure B6.7.2 ARR Network (Base Case–Recruitment Year 2000 Onward, at least 80% RRMS)

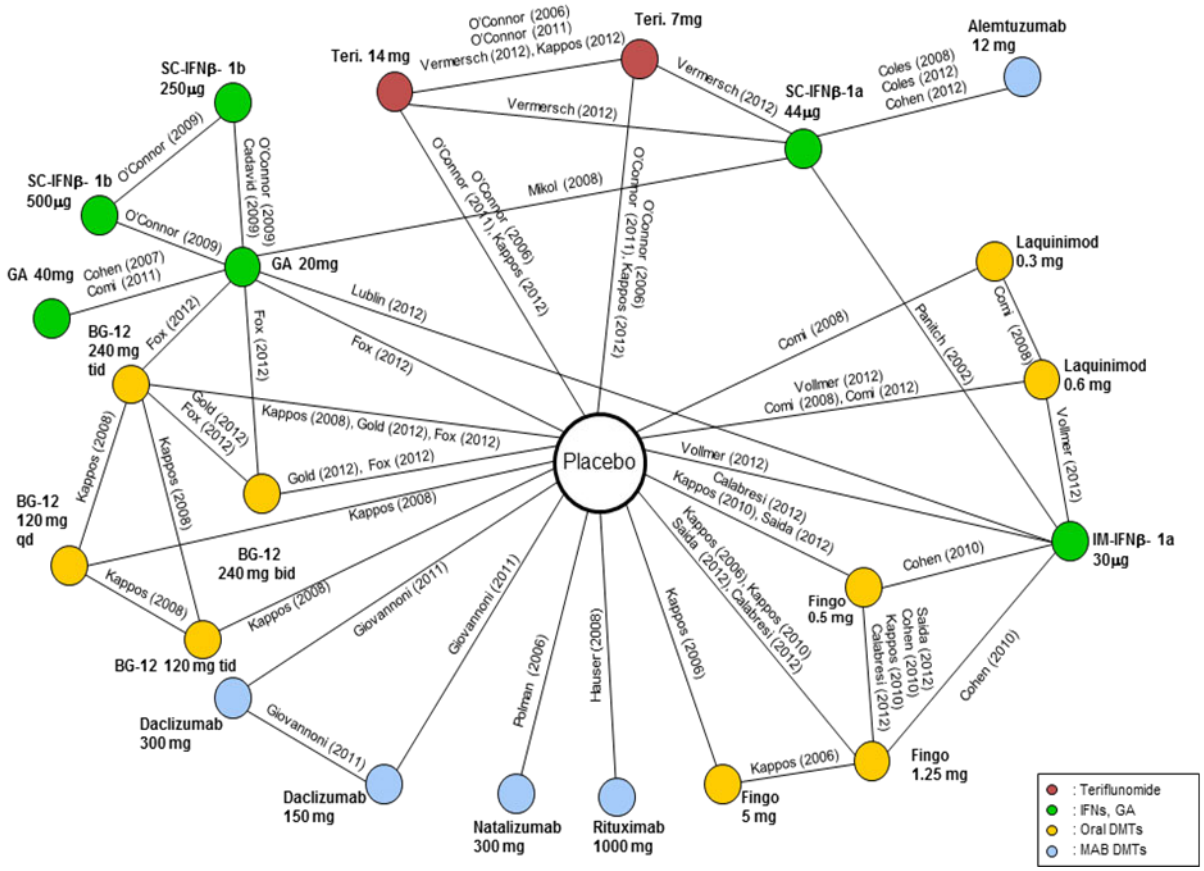


Figure B6.7.3 Relapse-free Network (Base Case –Recruitment Year 2000 Onward, at least 80% RRMS)

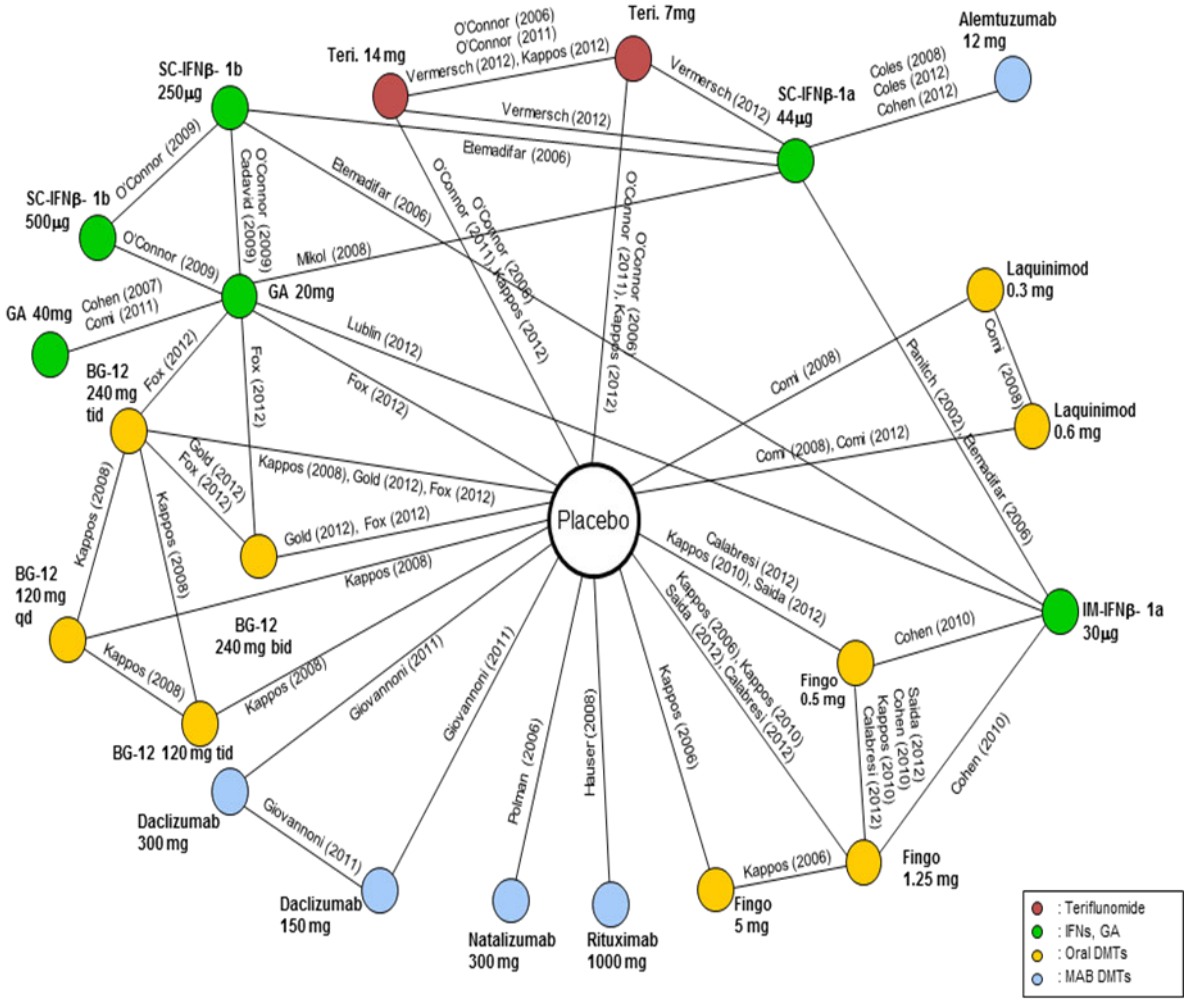


Figure B6.7.4 Three-month SAD Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)

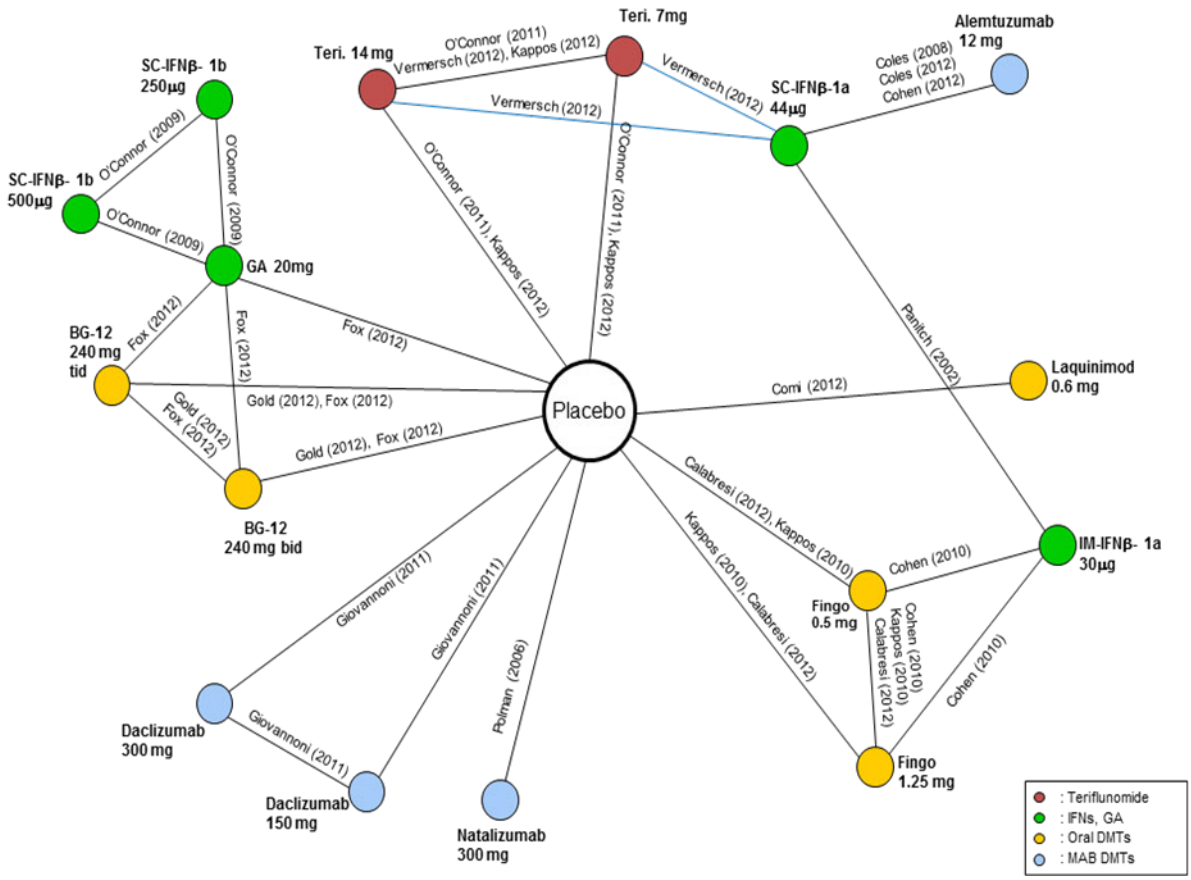


Figure B6.7.5 Six-month SAD network (Base case – Recruitment year 2000 Onward, at least 80% RRMS)

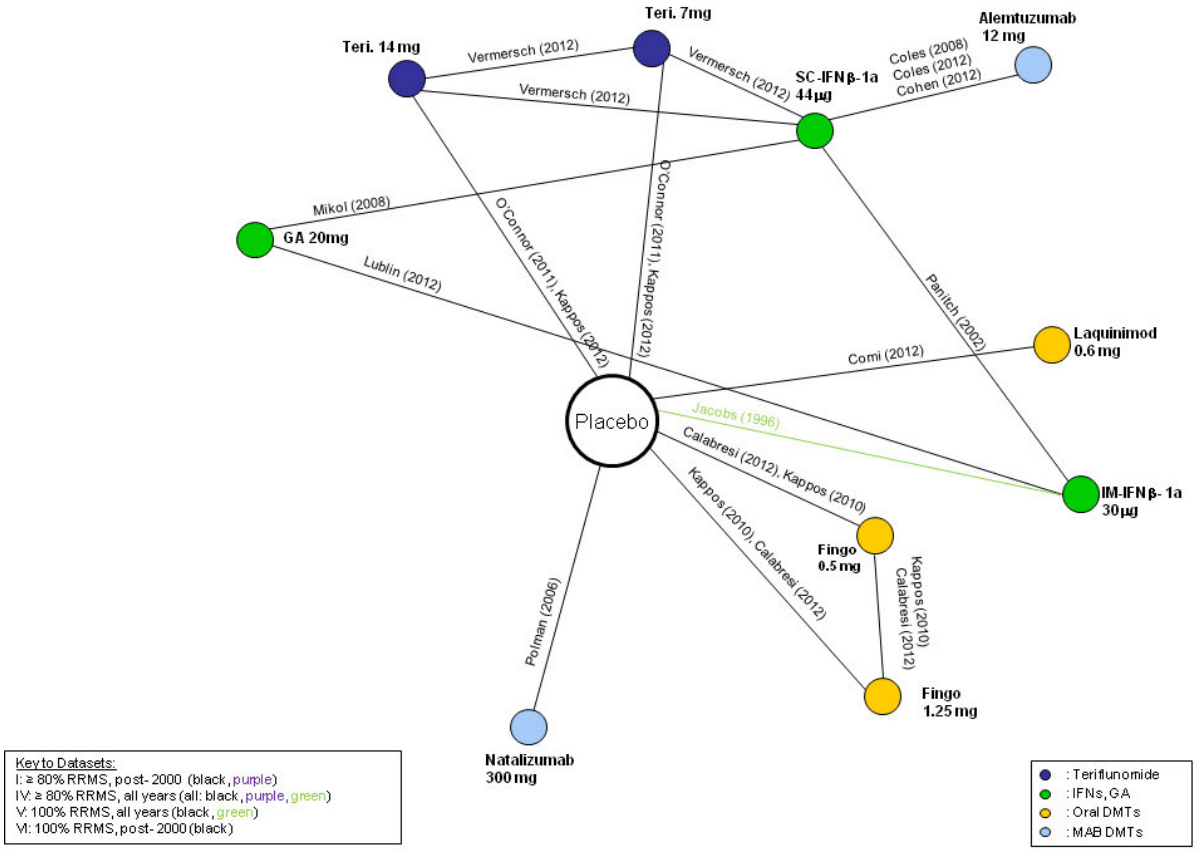


Figure B6.7.6 Overall Discontinuation Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)

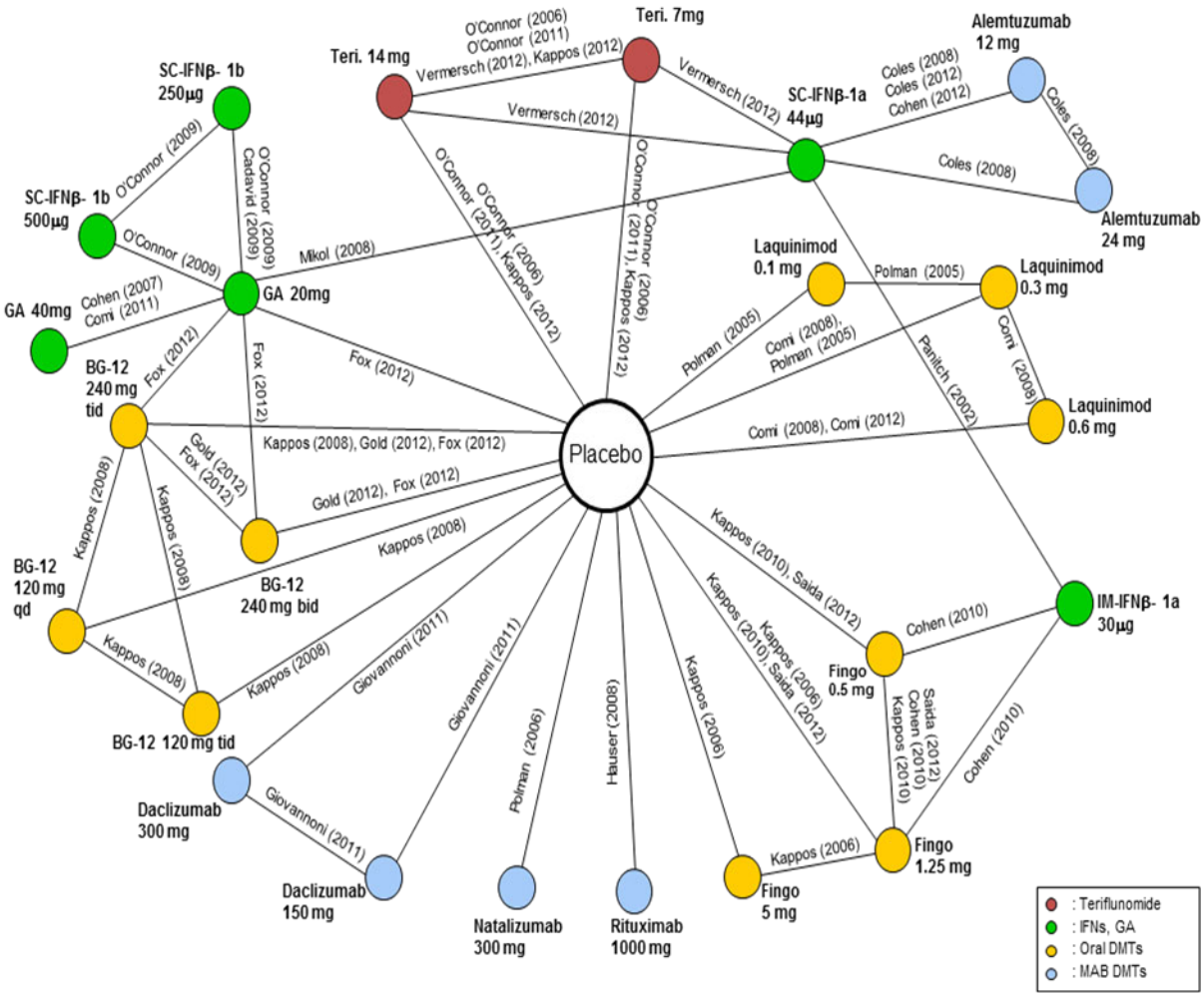
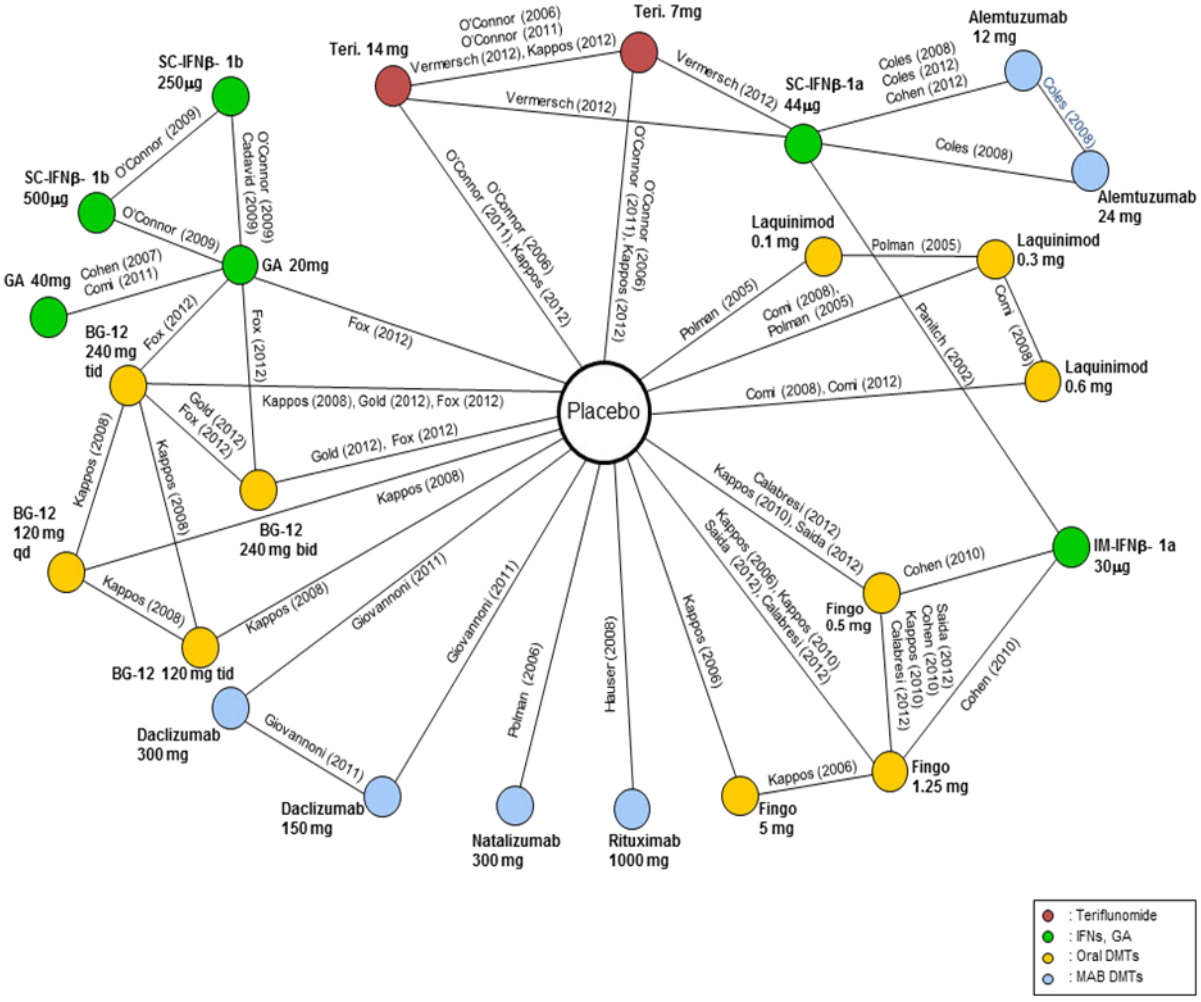


Figure B6.7.7 DAEs Network (Base Case – Recruitment Year 2000 Onward, at least 80% RRMS)



6.7.5 For the selected trials, provide a summary of the data used in the analysis.

Data used in the analyses can be found in Additional Appendix 6.

A sensitivity analysis on trials with 100% RRMS populations is also presented in Additional Appendix 4.

6.7.6 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

See Additional Appendix 8 (MTC Code).

Quantitative analyses were performed on the following outcomes:

Rates Ratio for Annualised Relapse Rate (ARR) (modeling the number of total events in each arm as following a Poisson distribution)

Odds Ratio for remaining relapse-free

Hazard Ratio for three-month SAD

Odds Ratio for total discontinuations

Odds Ratio for discontinuation due to adverse events

MTC

Random-effect MTC analyses were conducted to compare all DMTs under investigation within a single model. MTC analyses employed a vaguely informative normal prior with a uniform standard deviation (SD), the value of which was 1.0 for all outcomes.

Bayesian MTC analyses were conducted assuming the treatment effect came from a random distribution of effects. For Bayesian MTCs, a burn-in of 50,000 iterations was used for all analyses; BGR trace plots suggested this was more than enough of a burn-in to allow estimates to converge. A follow-up of 50,000 iterations was used to create the sample for the posterior, and history plots were reviewed to confirm convergence. In addition, an inspection of the ratio of the measure of convergence error to the SD of the estimates confirmed that the ratio was less than 3.5% for almost all estimates, further suggesting convergence and in keeping with published guidelines. National Institute for Health and Care Excellence (NICE) recommendations provided by the Decision Support Unit suggest that the Monte Carlo error (accounting for both the number of iterations and the extent of auto-correlation) should be ≤5% of the posterior SD for the parameters examined.

All analyses are described in Table B6.7.4 below, including the sensitivity analysis. A sensitivity analysis was included based on ≥80% RRMS and including studies for all years from 1980, rather than from 2000 used in the base case and the results are presented in Additional Appendix 4.

Table B6.7.4 Analyses conducted by outcome

Analysis	Base Case	Sensitivity Analysis	Sensitivity Analysis
Description	**Recruitment ≥2000 and ≥80% RRMS**	**Recruitment ≥2000** and 100% RRMS	Recruitment all years **and ≥80% RRMS**
ARR (rate ratio)	✓	✓	✓
Proportion relapse-free (OR)	✓	✓	
SAD confirmed 3 months (HR)	✓	✓	✓
Total discontinuations (OR)	✓	✓	✓
DAEs (OR)	✓	✓	✓

Note: ✓designates analyses that were conducted.

Abbreviations: ARR = annualised relapse rate; HR = hazard ratio; OR = odds ratio

Subgroup analysis

As required by the decision problem, two subgroup MTC analyses were carried out for the following patient groups:

- RES
- HA

The approach taken to construct the networks for these subgroups and MTC results is presented in section 6.7.7.2.

6.7.7 Please present the results of the analysis.

The results of the MTC analysis demonstrated that alemtuzumab was associated with [redacted] for relapse outcomes. A majority of the relationships were statistically significant, with the exception of [redacted] for ARR; however, alemtuzumab showed a [redacted] over [redacted] for the proportion of patients remaining relapse-free.

For three- and six-month SAD, alemtuzumab was [redacted] to [redacted], with a statistically [redacted] for three-month SAD. Alemtuzumab showed a [redacted] over [redacted] for three-month SAD and was [redacted] for six-month SAD. However, in sensitivity analyses that did not restrict by recruitment year, alemtuzumab showed a [redacted] to [redacted]

Alemtuzumab had [redacted] DAEs and treatment discontinuations for any reason compared with [redacted]. A significant [redacted] in the odds of discontinuation was shown relative to [redacted]. In analyses with no restriction on recruitment year, however, the [redacted] for discontinuations reached [redacted]. For DAEs, the advantage of alemtuzumab was [redacted] in comparisons with [redacted] and [redacted]

Overall, there were very few signs of heterogeneity among outcomes as evaluated by observation of the random-effect variances (sqrt(τ)) for each outcome, with the exception of DAEs.

6.7.7.1 Base case MTC

Results and associated Forest Plots are presented for the base-case MTC of the therapies included in the decision problem. For the “post-2000 100% RRMS” and “all years ≥80% RRMS” sensitivity analysis and additional outcome analysis see, see Additional Appendix 4.

Table B6.7.5. Annualised relapse rate results from the MTC ≥80% RRMS

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 µg	[redacted]	0.68 [0.52, 0.88]
IM IFNβ-1a 30 µg	[redacted]	0.78 [0.67, 0.91]
SC IFNβ-1a 44 µg	[redacted]	0.62 [0.51, 0.76]
GA 20 mg	[redacted]	0.64 [0.53, 0.76]
Fingolimod 0.5 mg	[redacted]	0.46 [0.4, 0.54]
Natalizumab 300 mg	[redacted]	0.31 [0.25, 0.39]

*not statistically significant

[redacted] **Forest Plot: Annualised relapse rate results from the MTC ≥80% RRMS**

[redacted]

Proportion Relapse-Free

Table B6.7.6 Proportion relapse-free results from the MTC ≥80% RRMS

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

*not statistically significant

[redacted]**Forest Plot: Proportion relapse-free results from the MTC**

[redacted]

Three-month SAD

Table B6.7.7_Three-month SAD HRs results from the MTC ≥80% RRMS

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 µg	[redacted]	1.21 [0.68, 2.16]*
IM IFNβ-1a 30 µg	[redacted]	0.91 [0.61, 1.33]*
SC IFNβ-1a 44 µg	[redacted]	0.79 [0.51, 1.24]*
GA 20 mg	[redacted]	0.93 [0.59, 1.45]*
Fingolimod 0.5 mg	[redacted]	0.75 [0.58, 0.96]
Natalizumab 300 mg	[redacted]	0.58 [0.4, 0.84]

*not statistically significant

[redacted] **Forest plot: Three-month sustained accumulation of disability results from the MTC ≥80% RRMS**

[redacted]

Six-month SAD

Table B6.7.8 Six-month SAD HRs results from the MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 µg	NA	NA
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

*not statistically significant

[redacted] **Forest plot: Six-month sustained accumulation of disability results from the MTC**

[redacted]

Total discontinuations

Table B6.7.9. Total discontinuations odds ratio results from the MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	N/A	[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

*not statistically significant

[redacted] **Forest plot: Total discontinuations odds ratio results from the MTC**

[redacted]

Discontinuations due to Adverse Events

Table B6.7.10. Discontinuations due to adverse events odds ratio results from the MTC

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	[redacted]	[redacted]
IFNβ-1b 250 µg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
GA 20 mg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

*not statistically significant

[redacted] **Forest plot: Discontinuations due to adverse events odds ratio results from the MTC**

[redacted]

Data for Rebif® (SC **IFNβ**-1a) 22µg

The ratio between results from the MTC (all-years, ≥80% RRMS) was applied to the base case MTC e.g. the all-cause discontinuation OR of alemtuzumab versus SC IFNβ-1a 22µg from the analysis MTC was [redacted], whilst alemtuzumab versus SC IFNβ-1a 44µg was [redacted]. Therefore, the ratio of SC IFNβ-1a 44µg to 22µg was [redacted] in the MTC. Applying this ratio to the all-cause discontinuation OR of alemtuzumab versus SC IFNβ-1a 44µg from the base case MTC gives an OR for alemtuzumab versus SC IFNβ-1a 22µg of [redacted]

Table B6.7.11 Inferred rates for (SC **IFNβ**-1a) 22µg post-2000

Parameter	All-years MTC Rebif 44µg	All-years MTC Rebif 22µg	Ratio of 44 to 22	Post-2000 MTC Rebif 44µg	Inferred Post-2000 Rebif 22µg value
ARR		N/A			Assume same as Rebif 44µg
Relapse Free	N/A	N/A			
Three-month SAD (comparator vs. placebo)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations (Alem12mg vs. comparator)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations due to AE	N/A	N/A			

6.7.7.2 Subgroup analysis

Compared to the base case MTC results, annualised response rates for alemtuzumab, [redacted] and [redacted] are all [redacted] in the HA sub-group; this is [redacted] in the RES sub-group with the addition of [redacted] to this pool too. Results for [redacted] in HA and similar in RES patients.

Three-month SAD results are [redacted] for alemtuzumab, [redacted] and [redacted] in HA and similarly [redacted] in RES; [redacted] in RES [redacted] Three-month SAD vs. base case.

These results indicate that alemtuzumab remains efficacious in the HA and RES groups of patients.

In response to the decision problem MTCs were also performed to address the efficacy and safety of therapies in HA despite interferon use and RES sub-groups; methodology and results for ARR, 3 month SAD and discontinuations are presented. It was not possible to consider all therapies in these indications (see below).

HA despite interferon use subgroup

This subgroup analysis was carried out to allow comparison to be made between alemtuzumab and fingolimod.

This was necessary because fingolimod's licence is as follows:

- Fingolimod is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

    - Patients 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 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

    - Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

NICE guidance provided a limited recommendation for fingolimod relative to its licence in the following way:

- Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon. In line with the licence this would mean 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. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

Scrutiny of fingolimod data available in the public domain for inclusion in a network analysis identified two sources using the following definitions which could be used as proxy for its' use within NICE guidance:

- 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 (Group C in Devonshire *et al*)

- 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 (Fingolimod EPAR).

Of these two potential sources of available data to make a comparison with fingolimod, the group C data from the Devonshire *et al,* paper [2012] was considered to provide the closest approximation to the use of fingolimod within its recommended use within NICE guidance. There was no statement included in this definition describing the duration of treatment with interferon. According to NICE guidance this should be at least one year.

With this in mind and the fact that this subgroup analysis was focused specifically upon providing a comparison with fingolimod within its licence and NICE recommendation guidance, the following subgroup analysis of the relevant alemtuzumab 12mg studies was carried out (CARE MS I/II and CAMMS 223):

- Patients who received interferon beta during the year before study enrolment and had received it for at least one year 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. Since a count of T2 lesions at baseline was not reported within these alemtuzumab 12mg studies, T2 volume $\geq$0.5 ml was used as proxy for 9 or more T2 lesions. This was in line with the proxy measure of 9 or more T2 lesions used in the assessment of fingolimod by NICE.

In the base case MTC (in addition to data for fingolimod from the subgroup analysis of FREEDOMS in the Devonshire *et al,* paper as outlined above and the subgroup analysis of the alemtuzumab studies), the following data sources were used (Table B6.7.12):

- Teriflunomide vs. placebo comparisons: TEMSO and TOWER, previously treated subgroup analyses
- Teriflunomide vs. Rebif comparison: TENERE (full dataset)

Consideration was given to using the subgroup analysis from TEMSO to populate the network using the following "best fit" proxy for HA despite interferon:

- Patients who received interferon beta during the year and had received it for one year before study enrolment and had at least one relapse in the previous year plus at least one gadolinium-enhancing T1 lesion at baseline. T2 count as with the alemtuzumab studies was not carried out. Unlike the alemtuzumab studies, T2 volume was not measured so that could not be used as a proxy for 9 T2 lesions or more. Patients in the TOWER study did not receive a measurement of gadolinium-enhancing T1 lesion at baseline so TEMSO would have been a preferable study to TOWER to provide data in this form to the network.
- However, this TEMSO data set was small (n=[redacted] and [redacted] for teriflunomide and placebo respectively) and provided very favourable SAD 3mths HR for teriflunomide versus placebo ([redacted] CI, [redacted]). The MTC using this data is provided as sensitivity analysis in Fig 2. It provides more favourable estimates of alemtuzumab HR SAD versus placebo than in the base case HA MTC

The TENERE data set was considered too small to be used either limited to previously treated with an interferon (n=2 in the teriflunomide arm) or to previously treated with a DMT (n=5 in the teriflunomide arm). This was the reason for deciding to populate the network using the full data set from TENERE. This link between teriflunomide and Rebif is necessary to allow a comparison to be made between alemtuzumab 12mg and fingolimod.

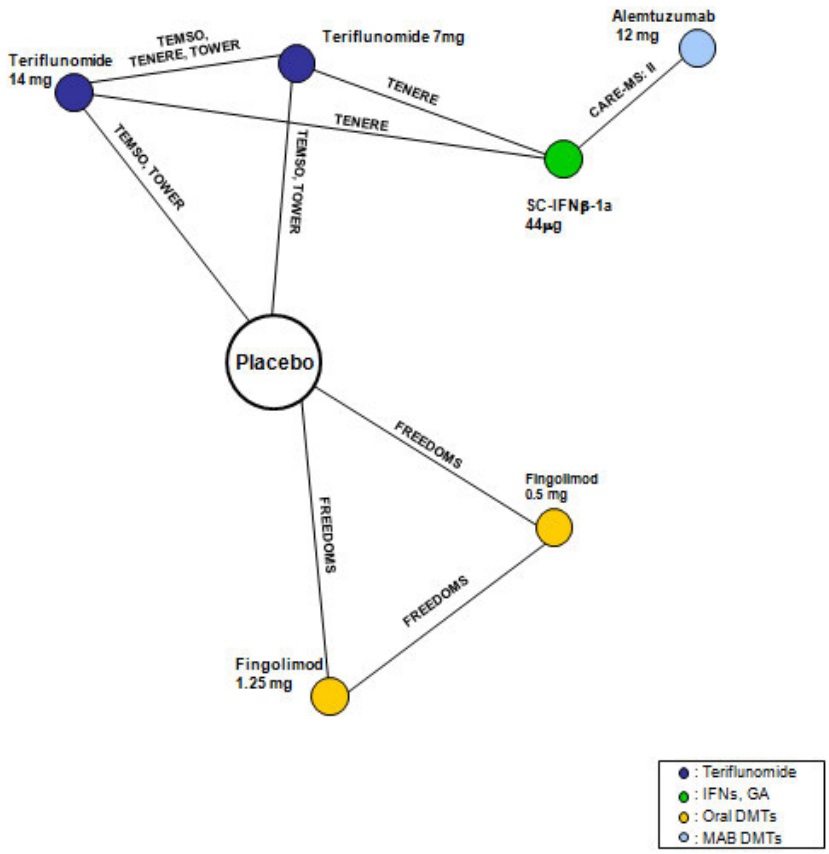
Table B6.7.12. Comparison of definitions of HA by trial included in the HA subgroup MTC

Comparison	Data Source	Subgroup	Data Source
Alemtuzumab 12mg versus Rebif	CARE MS II	Those who received interferon beta during the year before study enrolment and had received it for at least one year and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or T2 volume ≥0.5 ml	Data on file
Fingolimod 0.5 mg vs. placebo	FREEDOMS	Those who have 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	Devonshire et al
Fingolimod 0.5 mg vs. Avonex	TRANSFORMS	Those who have received 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 gadolinium-enhancing lesion on baseline MRI.	Fingolimod EPAR
Teriflunomide 7mg vs. placebo	TEMSO	Previously treated with a DMT	Data on file
Teriflunomide	TEMSO	Previously treated with a DMT	Data on file

14mg vs. placebo			
Teriflunomide 7mg vs. placebo	TOWER	Previously treated with a DMT	Data on file
Teriflunomide 14mg vs. placebo	TOWER	Previously treated with a DMT	Data on file
Teriflunomide 7 mg vs. Rebif	TENERE	Full data set	Data on file
Teriflunomide 14mg vs. Rebif	TENERE	Full data set	Data on file

The MTC network diagram for 3 month SAD in the HA disease despite interferon use subgroup is shown in Figure 6.7.15. The network diagram for 3 month SAD for HA despite interferon use subgroup is presented in additional appendix 7.

Figure B6.7.15 Three-month SAD Network (HA despite interferon use subgroup)



The following outcome measures are shown from the HA MTC analysis:

- 3 month SAD HRs (Table B6.7.13)

- ARR RR (Table B6.7.14)

Table B6.7.13. Three-month SAD, sub-group – analysis: HA despite interferon use

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

Table B6.7.14. Annualised relapse rates, sub-group – analysis: HA despite interferon use

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	[redacted]	[redacted]
IM IFNβ-1a 30 µg	[redacted]	[redacted]
SC IFNβ-1a 44 µg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]

RES subgroup

This subgroup analysis was carried out to allow a comparison to be carried out between alemtuzumab 12mg and natalizumab.

Natalizumab is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following patient groups:

- Adult patients aged 18 years and over 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 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

• Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase

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.

As shown in table B6.7.15, it should be noted that only natalizumab provided data which exactly matched the definition of RES 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.

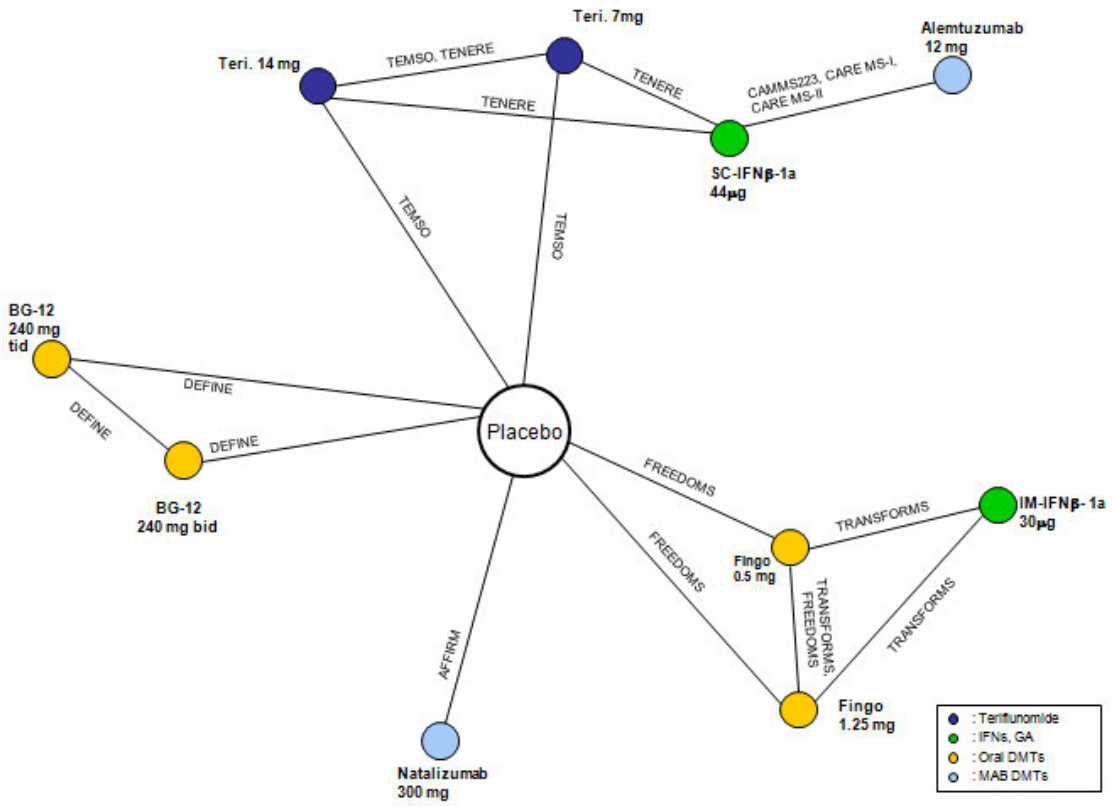
Table B6.7.15. Comparison of definitions of RES by trial included in the RES subgroup MTC

Comparison	Data Source	Subgroup	Data Source
Alemtuzumab 12mg versus Rebif	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
Fingolimod 0.5 mg vs. placebo	FREEDOMS	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI	Data on file
Fingolimod 0.5 mg vs. Avonex	TRANSFORMS	Those experiencing two or more relapses in the previous year, and having at least one lesion on gadolinium (Gd)-enhancing MRI	Fingolimod EPAR
BG 12 BID vs.	DEFINE	Those experiencing two or more relapses in	Barr-Or *et al,* 2012

placebo		the previous year	(data extracted from chart)
BG 12 TID vs. placebo	DEFINE	Those experiencing two or more relapses in the previous year	Barr *et al,* (data extracted from chart)
BG 12 BID vs. GA	CONFIRM	Those experiencing two or more relapses in the previous year	Hutchinson, 2013
BG 12 TID vs. GA	CONFIRM	Those experiencing two or more relapses in the previous year	Hutchinson, 2013
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. Rebif	TENERE	Those experiencing two or more relapses in the previous year	Data on file
Teriflunomide 14mg vs. Rebif	TENERE	Those experiencing two or more relapses in the previous year	Data on file

The MTC network diagram for 3 month SAD in the RES subgroup is shown in Figure B6.7.16. The network diagram for 3 month SAD for the RES subgroup is presented in additional appendix 7.

Figure B6.7.16 Three-month SAD Network (RES subgroup)



The following outcome measures are shown from the RES MTC analysis:

- 3 month SAD HRs (Table B6.7.16)
- ARR RR (Table B6.7.17)

Table B6.7.16. Three-month SAD, sub-group – analysis: RES

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

Table B6.7.17. Annualised relapse rates, sub-group – analysis: RES

	Alemtuzumab 12 mg	Placebo
	Rate ratio [95% CrI]	
Alemtuzumab 12 mg	[redacted]	[redacted]
IM IFNβ-1a 30 μg	[redacted]	[redacted]
SC IFNβ-1a 44 μg	[redacted]	[redacted]
Fingolimod 0.5 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

6.7.8 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

The current analysis in support of alemtuzumab took several steps to reduce heterogeneity, including limiting analyses to trials that enrolled only RRMS patients and recruited during or after the year 2000, conducting separate analyses for three-month and six-month SAD, and carefully evaluating differences in the definitions of other outcomes. Sensitivity analyses were conducted to test these assumptions in the base-case analyses and found no significant differences, indicating a robust base-case analysis.

These results should be interpreted in the context of moderate random-effects variations for some outcomes (DAEs and discontinuations) and indirect comparisons of a high order (connecting through multiple bridges).

Additionally, previous treatment and prior relapse rates were found to potentially contribute to heterogeneity, which could not be controlled for in these analyses.

Heterogeneity was assessed globally by considering the size of the sqrt(tau) from the random-effects MTC, as well as by examining a sequence of pairwise meta-analyses; high values of I^2 (an estimate of the percent of variability due to heterogeneity) indicate heterogeneity for that comparison.
ARR: there were minimal signs of inconsistency or heterogeneity across trials, resulting in an extremely low estimate of random-effects variance (sqrt(τ) = 0.06).

Proportion of patients remaining relapse free: Comparisons of alemtuzumab to other DMTs showed few signs of heterogeneity (sqrt(τ) = 0.17). The only exception to this was the comparison to IM IFNβ-1a 30 µg, which is attributed to heterogeneity in the estimate for SC IFNβ-1a 44 µg versus IM IFNβ-1a 30 µg. Etemadifar *et al*. (2006) found a very high OR in favour of SC IFNβ-1a 44 µg (OR: 5.2), which was inconsistent with direct evidence in EVIDENCE (Panitch *et al*., 2002) and indirect evidence through CombiRx (Lublin *et al*., 2012) (OR: 1.5) and REGARD (Mikol *et al*., 2008) (OR: 1.4) trials. However, this inconsistency did not adversely impact the comparisons to other DMTs of interest.

SAD (3 months): there were very few signs of inconsistency or heterogeneity across trials, resulting in a low estimate of random-effects variance (sqrt(τ) = 0.07).

SAD (6 months): For six-month SAD, the most noteworthy substantive finding of heterogeneity (sqrt(τ) = 0.18) stemmed from the somewhat inconsistent results for the relative effectiveness of SC IFNβ-1a 44 µg versus IM IFNβ-1a 30 µg. The EVIDENCE trial (Panitch *et al*., 2002) estimated six-month SAD to favour SC IFNβ-1a 44 µg (HR: 0.70); however, indirect evidence from CombiRx (Lublin *et al*., 2012) (which showed GA to be worse than IM IFNβ-1a 30 µg) and REGARD (Mikol *et al*., 2008) (which showed GA to be better than SC IFNβ-1a 44 µg) contradict this finding. This inconsistency does not impact comparisons with alemtuzumab to other DMTs, as GA does not perform the role of a common comparator in six-month SAD analyses. Instead, placebo and SC IFNβ-1a 44 µg function as common comparators for these analyses.

Discontinuation: For analyses of treatment discontinuation, there were very few signs of inconsistency or heterogeneity across trials, resulting in a low estimate of random-effects variance (sqrt(τ) = 0.07).

In investigations of heterogeneity of outcomes, there was only one notably large estimate of random-effects variation, which was observed for DAEs (sqrt(τ) = 0.39). While the finding suggests that care should be taken in generalising results for relative effects between treatments, this analysis was limited by low statistical power and few events.

The following areas of clinical heterogeneity were explored (see Table B6.7.1):

- Age was relatively homogenous across studies ranging from 32 years [Coles *et al*. 2008] to 42.4 years [Polman *et al*. 2005].
- Percentage of male patients showed a degree of variation from 17% to 45%.
- Disease duration showed a degree of variation from 2 years to 10.8 years.
- Eight of the 30 studies had a certain proportion of patients without RRMS although in this regard it is noted that the study entry criteria was RRMS ≥80%.
- Of the 15 studies where percentage prior use of DMT was recorded only three were treatment naïve studies. In the remaining 12 studies DMT prior use varied from 11-21% [Vermersch *et al*. 2012] to 77-78% [Hauser *et al*. 2008].
- Baseline EDSS was relatively homogenous across studies with a range of 1.8 to 3.2.
- Relapse rate prior to study entry was relatively homogenous across studies with two year period relapse rate range of 1.7-2.6.
- There was a degree of variation in the ARR during study in placebo arms: 0.36-0.99 across included studies (Table B6.7.4).
- There was a degree of variation in disability accumulation in placebo arms: 13%-29% (Table B6.7.6).

6.7.9 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

No studies were identified within the base case MTC which it was thought appropriate to exclude on the basis of clinical or statistical heterogeneity.

As discussed in Section 6.6.1, to minimise clinical heterogeneity, the base case MTC analysis was conducted on only studies that recruited patients in or after the year 2000. As part of a sensitivity analysis, the impact of excluding studies from the MTC on the basis of the year of recruitment was tested and all studies within the systematic literature review irrespective of year of recruitment were included within an MTC (included in Additional Appendix 4)

Sensitivity analysis: All years, 80% RRMS

The results of this sensitivity analysis MTC are as follows:

Table AA.4.7 in Additional Appendix 4 shows that six studies are added to the base-case MTC as a result of including all studies identified in the literature review irrespective of year of recruitment. This includes three studies of glatiramer acetate versus placebo [Bornstein *et al*. 1987; Johnson *et al*. 1995; Comi *et al*. 2001], one

for IFNβ-1b 250 μg versus placebo [Duquette *et al*. 1993], one for SC IFNβ-1a 44μg (versus SC IFNβ-1a 22μg and placebo) [Ebers *et al,* 1998] and one for IM IFNβ-1a 30μg versus placebo [Jacobs *et al*. 1996].

ARR in Table AA4.8 in Additional Appendix 4 (which when compared to the comparable results in Table B6.7.1 in the base case MTC) shows that for all the included comparators ARR rates appear to be similar. In this regard it is noted that two studies are added to the MTC in the SA compared to the base case of glatiramer acetate versus placebo [Johnson *et al*. 1995; Comi *et al*. 2001], one for IFNβ-1b 250μg versus placebo [Duquette *et al*. 1993] and one for IM IFNβ-1a 30μg versus placebo [Jacobs *et al*. 1996].

HR for 3 month SAD versus placebo is better in the all-years sensitivity analysis MTC (see Table AA4.9, Additional Appendix 4) than in the base case MTC for all comparators (with the exception of the central estimate of natalizumab which remains the same). The most substantial differences are for IFNβ-1b 250μg, SC IFNβ-1a 44μg and for glatiramer acetate. In this regard it is noted that two studies are added to the network MTC in the sensitivity analysis compared to the base case of glatiramer acetate versus placebo, [Johnson *et al*. 1995; Bornstein *et al*. 1987] one for IFNβ-1b 250μg versus placebo [Duquette *et al*. 1993] and one for SC IFNβ-1a 44μg (versus SC IFNβ-1a 22μg and placebo) [Ebers *et al*. 1998] (as shown in Table AA4.7in Additional Appendix 4).

OR for total discontinuation rate versus placebo are worse for all comparators in the all-years MTC (see Table AA4.10, Additional Appendix 4) than in the base case MTC with the exception of natalizumab, where discontinuation rate vs. placebo remained the same. OR for total discontinuations vs. alemtuzumab exhibits less variation, with the exception of IFNβ-1b 250μg, which appears improved in the sensitivity analysis. In this regard it is noted that two studies are added to the network MTC in the all-years sensitivity analysis compared to the base case of glatiramer acetate versus placebo [Johnson *et al*. 1995; Comi *et al*. 2001], one for IFNβ-1b 250μg versus placebo [Duquette *et al*. 1993] , one for SC IFNβ-1a 44μg (versus SC IFNβ-1a 22μg and placebo) [Ebers *et al*. 1998] and one for IM IFNβ-1a 30μg versus placebo [Jacobs *et al*. 1996] (as shown in Table AA4.7in Additional Appendix 4).

This all-year sensitivity analysis MTC analysis needs to be considered in the context of the rationale for having exclusion criteria based on year of recruitment in the base case MTC (as outlined in Section 6.1.1). Namely, changes in diagnostic criteria and in clinical practice leading to the identification of patients much earlier in the disease course, and with less frequent or severe symptoms and a noticeable decline in ARR rates in more recent years, even across patients receiving placebo in clinical trials and definitions of outcomes. In this context the following is noted:

- Relapse rate prior to study entry over two year period: 2.1-2.8 studies >2000 and ≤ 2000 2.5-3.9 (Table B6.7.1 and Additional Appendix 4, Table AA4.7)
- ARR range during study in placebo arms: 0.36-0.99 studies >2000 and ≤ 2000 0.84-1.21 (Table B6.7.1 and Additional Appendix 4, Table AA4.8)
- Three-month disability accumulation in placebo arms: 13%-28% studies >2000 and ≤ 2000 24.6%-52.65% (Table B6.7.1 and Additional Appendix 4, Table AA4.9)

An analysis of the relevant publications was performed to identify heterogeneity in the definition of outcomes. It is noted that whilst this was not identified to be the case for ARR and total discontinuation rate, this was the case for disability accumulation. All the studies included in the base-case MTC used the same measure of disability accumulation which was sustained disability accumulation at 3 months (i.e. a minimum increase in EDSS state of at least one point compared to baseline sustained over two measurements separated by 3 months). Given the fluctuating nature of MS symptoms, such a confirmation that disability accumulation is sustained is of importance. In addition the utilisation of the same measurement of disability accumulation (EDSS) is important to ensure that heterogeneity in outcome measurement in this regard does not occur. In relation to the four studies included in the disability accumulation HR all-years MTC network (see Table AA4.9, Additional Appendix 4) the following is noted.

Three of the studies measured disability accumulation using EDSS: One of glatiramer acetate versus placebo [Johnson *et al*. 1998] (n=251), one for IFNβ-1b 250 μg versus placebo [Duquette *et al*. 1993] (n=147) and one for SC IFNb-1a 44 μg (versus SC IFNb-1a 22 μg and placebo) [Ebers *et al*. 1998] (n=560). Only one of these three studies had a measure of disability which included a repeat measure to confirm sustainability of disability. This was the study of SC IFNb-1a 44 μg (versus SC IFNb-1a 22 μg and placebo) and it used a 3 month definition of sustainability.

One study [Bornstein *et al*. 1987] (n=50) did not use EDSS. This was a study of glatiramer acetate versus placebo. It used the Kurtzke Disability Status Score (DSS). The EDSS is an update of the DSS. The DSS has 10 grades or steps beyond 0 (normal), extending to status 10 (death due to MS). One of the main differences in the EDSS was that it provides, for each step from 1 through 9, two steps that together add up to the same step of the original DSS [Kurtzke, 1983]. The Bornstein study also did not include a repeat measure of sustainability within its definition of disability. The rate of disability accumulation in the placebo arm of this study was substantially higher than in the other three studies included in the all-years sensitivity analysis; 52.65% compared to 28%-29% (see Table AA4.9, Additional Appendix 4) and to those observed in the placebo arms in the base case MTC (13%-28%) (Table B6.7.1).

Sensitivity analysis: ≥2000, 100% RRMS

A further sensitivity analysis was performed to examine to effect of excluding studies where a small but significant proportion of patients may not have been diagnosed with RRMS. Figures AA4.1, AA4.2, AA4.3, AA4.4, AA4.5, AA4.6, A4.7, AA4.8, AA4.9, AA4.10, AA4.11, AA4.12 in Additional Appendix 4 show that eight studies are removed from the base-case MTC as a result of using 100% RRMS as an inclusion criteria (in additional to year ≥2000) (TOWER, TENERE, TEMSO, O'Connor 2006, Polman 2005, Cadavid 2009, Saida 2012, Kappos 2006) .

Tables AA4.1, AA4.3, AA4.4 and AA4.5 in Additional Appendix 4 show that for all the included comparators ARR rates, SAD (both 3- and 6-month) and discontinuation rates are insignificantly affected by the removal of trials where <20% of patients did not have RRMS.

6.7.10 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

See section B6.7.7.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Due to the weight of evidence derived from RCTs a systematic reviews of non-RCT evidence was not undertaken. However, two studies provide supportive evidence for the long-term effects of alemtuzumab treatment, including evidence that:

[redacted]

- The risk of autoimmune disease after alemtuzumab treatment is time limited

Table B6.8.1 Summary of relevant non- RCTs

Trial	Tuohy, *et al*. (Draft manuscript - based on personal correspondence with author, Dr. Alasdair Coles from Addenbrookes Hospital, Cambridge)	Cossburn, *et al*. 2011
Number of patients	[redacted]	248
Study design	[redacted]	Prospective study of clinical and serologic data of patients with MS treated with alemtuzumab. Data was collected from five MS centres in the UK.
Inclusion criteria	[redacted]	MS patients were able to participate in the study if they received their first alemtuzumab treatment in any of the five centres between January 1, 2001, and December 31, 2009, and were not participants in CAMMS 223, CAMMS 323, or CAMMS 324 studies.
Treatment intervention	[redacted]	Alemtuzumab. Prior to 2006, patients received an initiation dose of 24–30 mg IV per day for 5 consecutive days. After 2006, the daily dose was reduced to 12 mg. Routine top-up treatments after 12 months, consisting of three consecutive daily doses of alemtuzumab with concurrent steroid pretreatment, was provided unless contraindicated. Additional courses of alemtuzumab were given as needed after intervals of not less than 12 months, either because of emergent clinical features suggesting recurrence of disease activity or the development of new or enhancing lesions on MRI performed 12 months or more after second treatment.

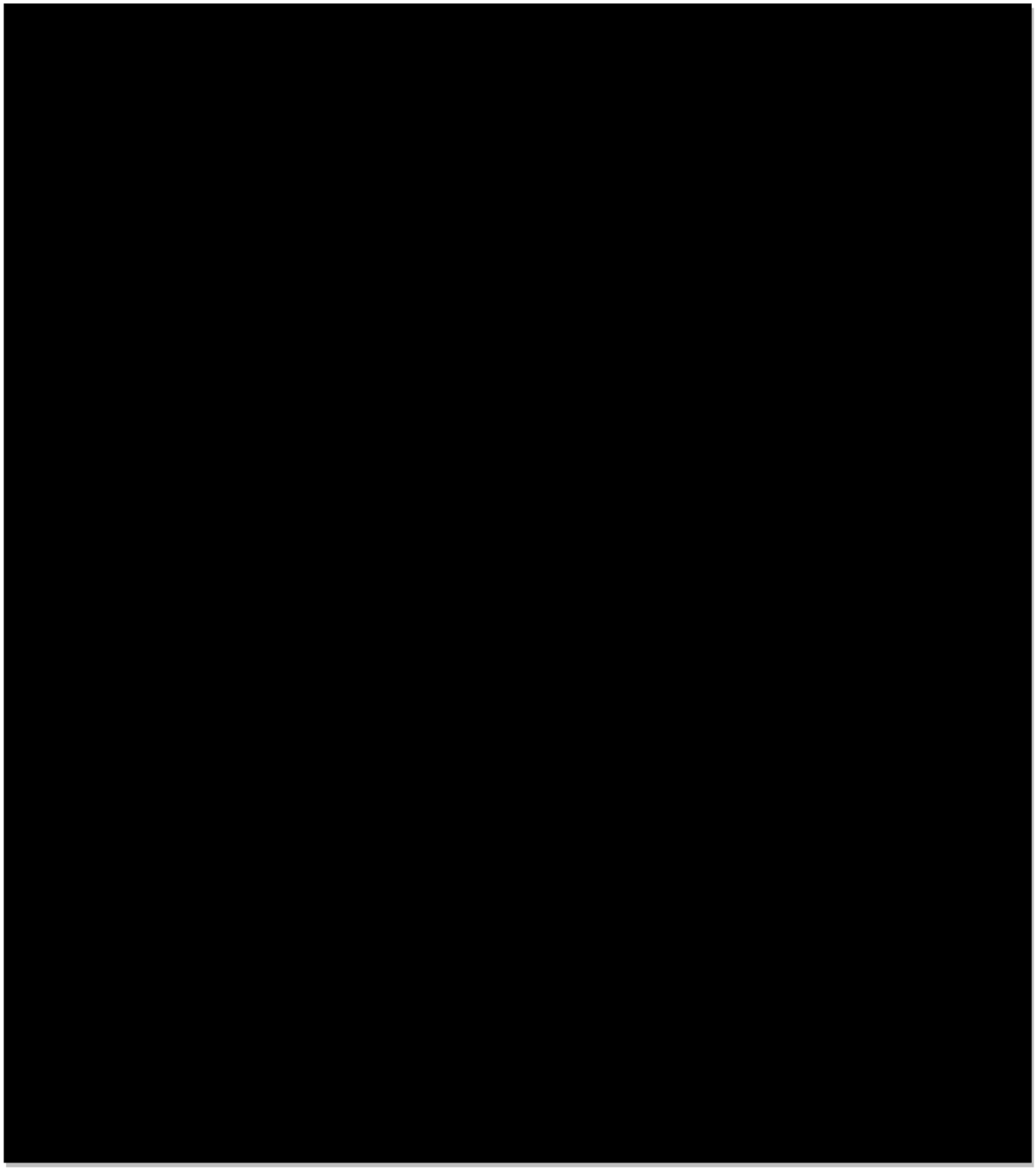
	[redacted]	
Primary trial outcome	[redacted]	The primary outcome measure of the study was the proportion of patients developing new autoimmunity. Development of new autoimmunity was defined as either 1) the presence of a previously undetected autoantibody at unequivocal titers (varying according to type of antibody and local laboratory norms), present on at least 2 occasions separated by at least 3 months; or 2) clinically detectable symptoms, signs, or biochemical disturbance consistent with the diagnosis of an autoimmune condition not present prior to treatment, confirmed by an independent specialist unblinded to alemtuzumab treatment.
Follow-up	[redacted]	Mean duration of follow-up was 41.18 months (SD 24.51), with median follow-up being 34.32 months (range 6.67–107.30).
Baseline Characteristics	Gender: [redacted] Mean age at first treatment: [redacted] Baseline EDSS: [redacted] Pre-treatment annualised relapse rate in two years prior to treatment: [redacted] Disease duration at treatment: [redacted] Prior DMT use: [redacted]	Gender: Female n=171 (69%) Median age: 38years (range 17-65) Baseline EDSS: Median 2.5 (range 0 – 7.5) ARR, median: 2.3 (range 1.1– 4.9) Disease duration, median (years): 3.7 (range 0.3 -7.6) Prior DMT use: 43.1%
Number of treatment courses received	[redacted]	34 patients (14%) received a single course, 139 (56%) received two courses and 75 (30%) received three or more courses of alemtuzumab.

	[redacted]	
Safety	[redacted]	Novel AID developed in 22.2% of patients: • Thyroid AID was most frequent (15.7%). A range of hematologic, renal, and dermatologic AID were also observed as was asymptomatic development of novel autoantibodies. • AID was seen from 2 weeks after initial treatment and was most frequent 12–18 months after first treatment. No new cases of AID were identified 60 months or more after initial treatment and risk of AID was independent of total alemtuzumab dose or interval of dosage.
Efficacy	See below.	Not reported.

Efficacy of alemtuzumab after seven year follow-up [Genzyme DOF (Tuohy *et al)* Draft manuscript].

[redacted] (Figure B6.8.1).

Figure B6.8.1. Follow-up and retreatment of patients after alemtuzumab



The mean annualised relapse rate recorded prospectively over the entire period of follow-up following first treatment was [redacted] assessed retrospectively in the two years prior to treatment.

The mean last-recorded Expanded Disability Status Scale score of [redacted] compared to the mean baseline score of [redacted] Six-month SAD occurred in [redacted]

Table B6.8.2. Disability outcomes of 87 alemtuzumab – treated patients

	Alemtuzumab Cohort (n=87)
Duration of Follow up (months) to last EDSS Median (IQR) Mean (SD)	[redacted]
Baseline EDSS Median (IQR) Mean (SD)	[redacted]
Last recorded EDSS Median (IQR) Mean (SD)	[redacted]

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Selection of trials for reporting of adverse events was via the same process as that described in section 6.1 and 6.2. In addition, an Integrated Summary of Safety from data from the Phase II (CAMMS223) and Phase III (CAMMS323 and CAMMS324) compiled for pharmacovigilance purposes during the trial programme for alemtuzumab was identified.

Adverse event reporting was a mandatory part of all the alemtuzumab studies identified in sections 6.1 and 6.2 (discussed in section 6.3), though safety was not the primary objective.

Data supporting the safety of alemtuzumab for the treatment of patients with RRMS has been collected during alemtuzumab clinical trial program. This included 3 completed, active-controlled, randomised Phase II and Phase III studies (CAMMS223, CARE-MS I, and CARE-MS II) and interim follow–up data from the date of initiation of the Extension Study (CAMMS03409). Safety data is presented here through 31 December 2011 with additional

data from the Safety Update Report (SUR) which provides updated data from the ongoing Extension Study (CAMMS03409) with additional safety data through 26 November 2012.

Safety in the Genzyme-sponsored studies was assessed by evaluation of adverse events, laboratory assessments, physical examinations, and vital signs throughout the studies. Specific safety measures were incorporated into the protocols in the alemtuzumab clinical program in MS to better assess the safety risks associated with alemtuzumab use in MS and potentially minimise the impact of these risks on patients. Risks identified with the use of alemtuzumab in the MS population included infusion associated reactions (IARs), autoimmune disorders (thyroid, ITP, anti-GBM disease), and infections. Safety measures implemented during the clinical development program in MS were informed by the clinical and post-marketing use of alemtuzumab in B-CLL patients, as well as investigator-sponsored pilot studies in MS and the Phase II company-sponsored study in MS. In some cases, specific monitoring elements were based on the observation of particular AEs during the clinical development program (e.g., anti-GBM disease), and therefore, data were not collected from the initiation of the Phase II study. These protocol required procedures and monitoring requirements were robust and generally effective in reducing the severity of IARs and in leading to the prompt detection and treatment of autoimmune disorders, thereby improving overall patient outcomes.

Safety data from the four key studies, CAMMS223, CARE-MS I, CARE-MS II, and the CAMMS03409 Extension Study, were pooled in order to improve the precision of the estimates and to better characterise the incidence of lower frequency AEs. Pooling of alemtuzumab safety data is appropriate because all studies were conducted in patients with RRMS, the alemtuzumab treatment regimen was the same in all studies, and all controlled trials used SC IFNβ-1a as an active control. The results reported in this section include the safety data on all alemtuzumab-treated patients during all available follow-up results.

A summary of the safety overview for CAMMS223, CARE-MS I and CARE-MS II are presented in Additional Appendix 9 (Alemtuzumab Safety Data).

Modelling of the effects of adverse events (see section 7 on cost effectiveness considers the impact of adverse events where incidence is ≥5%. Selected results from the pooled analyses are therefore represented relative to this cut-off. It should be noted that many adverse effects occurring at this level require monitoring or cessation of therapy rather than active treatment of the adverse event. Adverse effects may also incur a disutility.

Cost effectiveness modelling is influenced by monitoring of blood parameters, liver function, management and monitoring of autoimmune events, infusion-associated reactions (a disutility), infections, cytopenias and nephropathies. All are reported below.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

An overview of the AEs reported within 3 years of follow-up in CAMMS223, CARE-MS I, CARE-MS II and CAMMS3409 is provided in Table . The general AE characteristics (frequency, seriousness, severity) observed in the alemtuzumab treatment groups through all available follow up were similar to those in the active-controlled studies. Most patients reported at least 1 AE, the majority of which were mild or moderate in severity. The incidence of grade 3, 4, and 5 AEs were [redacted], respectively. Further, [redacted] of patients discontinued from study treatment or study participation due to an AE, respectively [Genzyme ISS 2012].

Table B6.9.1. Overview of adverse events in all active-controlled studies

	Alemtuzumab 12 mg (N=1216) Cumulative up to and including 31 December 2011		Alemtuzumab 12 mg (N=1217) Cumulative up to and including 26 November 2012	
	Events	n (%)	Events	n (%)
AEs	-	-	-	-
Any Event	[redacted]	[redacted]	[redacted]	[redacted]
Related	[redacted]	[redacted]	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to treatment withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Any Serious Event	[redacted]	[redacted]	[redacted]	[redacted]
Related	[redacted]	[redacted]	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]
SAEs leading to treatment withdrawal	[redacted]	[redacted]	[redacted]	[redacted]
SAEs leading to study discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

SOURCE: (Genzyme ISS 2012) (Table 6-2); (Genzyme SUR March 2013) (Table 5-2)

Note: A patient is counted only once within each System Organ Class (SOC)/Preferred Term (PT)

AE: Adverse event; SAE: Serious adverse event

A full list of all AEs reported at a ≥5% incidence in alemtuzumab-treated patients is shown in Table B6.9.2.

Table B6.9.2. Number (%) of patients with an AE (when incidence ≥5% in any treatment group) by Preferred Term

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=1216) Cumulative up to and including 31 December 2011	Alemtuzumab 12 mg (N=1217) Cumulative up to and including 26 November 2012
Any Event	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Ear and labyrinth disorders	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]
Endocrine disorders	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]
Grave's disease	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=1216) Cumulative up to and including 31 December 2011	Alemtuzumab 12 mg (N=1217) Cumulative up to and including 26 November 2012
Chest discomfort	[redacted]	[redacted]
Influenza like illness	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Gait disturbance	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Oral herpes	[redacted]	[redacted]
Herpes zoster	[redacted]	[redacted]
Gastroenteritis viral	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Pharyngitis	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Fall	[redacted]	[redacted]
Joint sprain	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
CD4 lymphocytes decreased	[redacted]	[redacted]
Protein urine present	[redacted]	[redacted]
Blood urine present	[redacted]	[redacted]
CD8 lymphocytes decreased	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Blood thyroid stimulating hormone decreased	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]
White blood cell urine positive	[redacted]	[redacted]
Body temperature increased	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=1216) Cumulative up to and including 31 December 2011	Alemtuzumab 12 mg (N=1217) Cumulative up to and including 26 November 2012
Muscular weakness	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Neck pain	[redacted]	[redacted]
Musculoskeletal stiffness	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Multiple sclerosis relapse	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]
Migraine	[redacted]	[redacted]
Tremor	[redacted]	[redacted]
Burning sensation	[redacted]	[redacted]
Balance disorder	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Depression	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]
Haematuria	[redacted]	[redacted]
Pollakiuria	[redacted]	[redacted]
Urinary incontinence	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]
Sinus congestion	[redacted]	[redacted]
Wheezing	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Urticaria	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Rash generalized	[redacted]	[redacted]

System Organ Class Preferred Term	Alemtuzumab 12 mg (N=1216) Cumulative up to and including 31 December 2011	Alemtuzumab 12 mg (N=1217) Cumulative up to and including 26 November 2012
Erythema	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Rash pruritic	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Flushing	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

SOURCE: (Genzyme ISS 2012) (Table 6-3); (Genzyme SUR March 2013) (Table 5-3)

Note: MedDRA version 13.1 was used for coding.

Note: Percentages are based on the number of treated patients in the corresponding time period and treatment group. Note: A patient is counted only once within each SOC/PT.

The incidence of AEs for all alemtuzumab 12 mg-treated patients over all available follow up was [redacted] The 3 most frequently affected MedDRA system organ classes were 'Skin and subcutaneous tissue disorders' [redacted] 'Nervous system disorders' [redacted] and 'Infections and infestations' [redacted] The most common AEs were headache [redacted] rash [redacted] pyrexia (30.9%), and MS relapse [redacted] [Genzyme ISS 2012].

Overall the incidence of AEs for alemtuzumab-treated patients was highest in Year 1 (93.6%), with the incidence of AEs decreasing over time to 49.7% in Year 4 (Figure), highlighting that the AEs experienced by alemtuzumab-treated patients become more manageable over time. After [redacted] the numbers of patients with available follow up was small [Genzyme ISS 2012].

Incidence of AEs over time upto Year 4 for alemtuzumab-treated patients

SOURCE: Data adapted from (Genzyme ISS 2012) (Table 6-3)

In contrast to the overall trend, the incidence of increased from for alemtuzumab-treated patients This observed increase in the incidence of was primarily driven by higher incidences of (Genzyme ISS 2012).

The incidence of SAEs was 20.1% through 31 December 2011. The most frequently reported SAEs for the alemtuzumab 12 mg group by MedDRA system organ class were [Genzyme ISS 2012]. A full list of all SAEs reported in ≥2 alemtuzumab-treated patients (any group) over all available follow-up is shown in Additional Appendix 9. The incidence of SAEs did not increase over time to which may indicate that alemtuzumab becomes (Figure B6.9.2). The rate of SAEs by number of courses received was in alemtuzumab-treated group . Furthermore, there did not appear to be an over time [Genzyme ISS 2012].

Figure B6.9.2. Incidence of SAEs over time upto Year 4 for alemtuzumab-treated patients

SOURCE: Data adapted from (Genzyme ISS 2012) (Table 3.3.3.2)

Of all pooled data, 6 deaths were reported in the alemtuzumab12mg group [Genzyme ISS 2012]. The fatal events in 3 alemtuzumab-treated patients were assessed as possible/likely related to treatment by the Investigator:

- 45 y/o female patient in CAMMS223 died from cardiovascular disorder 2 months after receiving the third annual cycle of alemtuzumab 12 mg
- 46 y/o male patient in CAMMS03409 died from sepsis a year and a half after the second annual cycle of alemtuzumab 12 mg.
- 39 y/o male patient in CAMMS223 died from idiopathic thrombocytopenic purpura and a cerebral haemorrhage 7 months after the second annual cycle of alemtuzumab 24 mg.

AEs of interest were those that resulted in treatment or study discontinuation, or were specifically identified prior to the study. Over all available follow-up, of patients treated with alemtuzumab discontinued treatment due to an SAE.

Infusion associated reactions in alemtuzumab-treated patients

IARs were defined as AEs that occurred between the start and stop of any alemtuzumab infusion plus 24 hours. In all alemtuzumab-treated patients, IARs were reported for of patients. A full list of the IARs reported in ≥5% of patients in any treatment group is reported in Additional Appendix 9 [Genzyme ISS 2012].

The most common IARs (≥10% of patients) were [Genzyme ISS 2012].

Serious IARs were reported for [redacted] of patients. [redacted] patients were reported to have IARs leading to dose adjustment in any subsequent cycle [Genzyme ISS 2012].

IARs [redacted] led to permanent discontinuation of treatment; only [redacted] of patients experienced an IAR AE that resulted in treatment discontinuation [Genzyme ISS 2012].

Anaphylactic reactions in alemtuzumab-treated patients

Anaphylactic reactions were defined according to the Sampson Standardised MedDRA Queries (SMQ) criteria and were identified in [redacted] of patients in the alemtuzumab 12 mg group (Genzyme ISS 2012). For the alemtuzumab 12 mg group, the incidence of potential anaphylactic reactions was highest in Cycle 1 (81 patients, [redacted]%) and was lower in subsequent cycles (15 patients [[redacted]%] in Cycle 2, 4 patients [[redacted]%] in Cycle 3, and [redacted] patients in Cycles 4 and 5) [Genzyme ISS 2012;Sampson 2006].

One patient in the alemtuzumab 12 mg group was determined to have an anaphylactic reaction (anaphylactic reaction) in Cycle 1 of the Extension study; their third cycle of treatment overall. The details of the single anaphylactic reaction in the 12 mg-treated patient are as follows (Genzyme ISS 2012):

[redacted]A serious anaphylactoid reaction (Grade 4) was reported in a patient who was treated with alemtuzumab in the Extension Study (CAMMS03409)[redacted]

Autoimmunity in alemtuzumab-treated patients

The annual probability of autoimmune adverse events associated with alemtuzumab (consisting of hyperthyroidism, hypothyroidism, Grave's disease and ITP) in years 2 to 5 in the health economic model (Section B7.3.1) was calculated as the average of the incidence in years 2, 3, 4 and 5 from Pool C safety population. The incidence of autoimmune adverse events plateaued to a rate of approximately [redacted] in the trials after 5 years thus are modelled to only occur up to 5 years. This observation is supported by a UK based observational study of patients on alemtuzumab [Cossburn *et al,* 2011] which reported that novel auto-immune disease developed in 22.2% of patients. In this cohort autoimmune disease was seen from 2 weeks after initial treatment and was most frequent 12–18 months after first treatment. No new cases of autoimmune disease were identified 60 months or more after initial treatment and risk of AID was independent of total alemtuzumab dose or interval of

dosage, consistent with the SmPC requirement to continue monitoring for auto-immune disease for four years after the last dose of alemtuzumab [SmPC 2013].

Thyroid disorders

Autoimmune thyroid abnormalities (particularly Grave's disease) were observed in pilot studies of alemtuzumab in MS patients (Coles 2006; Coles 1999). Therefore, thyroid function was monitored quarterly in the alemtuzumab clinical studies (Genzyme ISS 2012).

Thyroid AEs were observed in an estimated 36.2% of patients during the 4 years after the first course of treatment. The risk of experiencing a first thyroid AE was increased between Months 24 and 42. The highest incidence of thyroid events was observed in [redacted] after the first alemtuzumab treatment course. The majority of events was mild or moderate in severity and included both hyperthyroidism and hypothyroidism at similar rates. Serious thyroid events occurred in [redacted] of all alemtuzumab-treated patients over all available follow-up. Most thyroid events were managed with conventional medical therapy and less than [redacted] required surgical treatment (Genzyme ISS 2012).

The presence of anti- thyroperoxidase antibodies at baseline was associated with higher incidences of thyroid AEs across all treatment groups. However, more than 85% of patients who developed a thyroid disorder were antibody negative prior to treatment. Therefore, the absence of anti-thyroperoxidase antibodies prior to treatment has a low negative predictive value for the occurrence of thyroid disease [Genzyme ISS 2012].

Abnormal thyroid function tests were successful in the early identification of thyroid disorders [Genzyme ISS 2012].

Idiopathic thrombocytopenia purpura (ITP)

Idiopathic thromobocytopaenia is the second most frequent autoimmune AE experienced by alemtuzumab patients after autoimmune thyroid disease.

At an early stage of the alemtuzumab clinical study program, ITP was identified as a risk based on the development of 3 initial cases of ITP in the Phase II study CAMMS223, including the fat index case. Following the identification of these cases, dosing was suspended in the Phase II study per Data Safety Monitoring Board (DSMB) recommendation. Genzyme introduced education and monitoring measures to facilitate the prompt diagnosis and treatment of ITP [Cuker 2011]. The monitoring program included close monitoring for signs of ITP through patient and investigator education, monthly FBCs with platelet counts, and the completion of a monthly symptom monitoring survey. Additionally, a protocol definition of ITP was specified to guide investigators during the conduct of the study. The identification of ITP events was based on the number of treated patients meeting the platelet-based or AE-based definition of ITP in the corresponding treatment group:

- Platelet-based definition: Platelet count ≤100 x 10^9/L on ≥2 occasions over a period of at least 30 days with no platelet counts above the LLN during the 30 day period, or platelet count ≤50 x 10^9/L on ≥2 occasions over any time period with no platelet counts above the lower limits of normal in the period between the 2 platelet counts ≤50 x10^9/L.

- AE-based definition: AEs with preferred term (PT) of autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, or thrombocytopenic purpura.

A total of [redacted] alemtuzumab patients treated with the 12mg dose experienced ITP over all available follow up. The onset of ITP occurred in the majority of alemtuzumab-treated patients after [redacted] The onset of ITP was in Years 1-3 in most cases [Genzyme ISS 2012]. Greater than [redacted] of alemtuzumab and cumulative dose did not appear to increase the risk of ITP. Serious ITP AEs were reported for only [redacted] of patients [Genzyme ISS 2012].

It should be noted that following the introduction of risk minimisation measures all cases of ITP after the index case were identified early through FBC monitoring or via symptom identification by the patient or investigator, thus facilitating prompt diagnosis, and timely intervention in all subsequent cases [Genzyme ISS 2012].

Nephropathies

Alemtuzumab has been associated with glomerular disease in patients with MS, particularly anti-GBM disease. Anti-GBM disease was reported in an MS patient who received alemtuzumab in an Investigator-sponsored study and was identified in one patient in CAMMS223 through quarterly serum creatinine testing [Meyer 2012]. Following these events, Genzyme convened an external expert advisory panel to review the existing monitoring strategy and intensified monitoring was incorporated into the clinical development program. These measures included monthly serum creatinine and urinalysis testing in all alemtuzumab-treated patients (while SC IFNβ-1a -treated patients maintained a quarterly testing schedule). Additionally, questions were added to the monthly symptom monitoring survey (used initially for ITP monitoring) to detect symptoms of anti-GBM disease [Genzyme ISS 2012].

Nephropathies were observed in 0.4% of patients in the alemtuzumab group. Events occurred within 39 months following the last administration of alemtuzumab [Genzyme ISS 2012].

In the alemtuzumab MS clinical program, all cases of glomerular disease were identified through the periodic serum creatinine or urinalysis testing performed as part of the safety monitoring program, thereby allowing early intervention. All cases were promptly treated and responded with preservation of renal function [Genzyme ISS 2012].

Infections in alemtuzumab-treated patients

Over all available follow up, the rate of infections was [redacted]. The most frequently reported infections (≥5% of all patients) were nasopharyngitis, UTI, upper RTI, sinusitis, influenza, oral herpes, bronchitis, and herpes zoster. Results for the alemtuzumab pooled dose group [redacted]; the rate of infections for the alemtuzumab pooled dose group was [redacted] per person-year. [redacted] who discontinued treatment due to an infection [Genzyme ISS 2012].

Over all available follow up, serious infections were reported for [redacted] patients. The incidence of serious infection stayed constant from Year 1 to Year 5. Also the rate of serious infection did not increase with cycle number or cumulative dose and the [redacted] of infections ([redacted] were mild or moderate in severity [Genzyme ISS 2012].

The probabilities of all non autoimmune adverse events (such as infections) in subsequent years in the model were calculated by incidences in years 2 to follow-up in year 9, as weighted averages with the number of patients at risk Table B7.3.17 This is line with the evidence that the rate of serious infections did not appear to be related to cycle numbers.

Cytopenias in alemtuzumab-treated patients

The occurrence of ITP and autoimmune cytopenia were analysed separately in the alemtuzumab clinical trial program. As mentioned, ITP has been reported with the use of alemtuzumab in MS. Other autoimmune cytopenias, such as autoimmune hemolytic anaemia, have also been reported during the clinical trials. Over all available follow-up, cytopenia AEs were reported in [redacted] of patients. The most frequently reported cytopenia AEs (reported for >5% of patients) were [redacted] [Genzyme ISS 2012].It is important to note that such lymphopenias reflect the expected pharmacodynamics of alemtuzumab rather than an autoimmune disorder.

Serious cytopenia AEs were reported in [redacted] of patients. The incidence of serious cytopenia AEs was highest in Years [redacted] and [redacted] ([redacted], and [redacted], and [redacted]). There were no serious cytopenias reported after Year 4 [Genzyme ISS 2012].

Malignancies in all alemtuzumab-treated patients

The risk and type of malignancies associated with alemtuzumab use was examined across the clinical program. Overall, 13/1485 patients reported a total of 15 malignancies in the alemtuzumab pooled dose group over all available follow-up (6 patients treated with alemtuzumab 12 mg, and 7 patients treated with alemtuzumab 24 mg). The most common malignancies reported in more than 1 alemtuzumab-treated patient were thyroid, breast cancer, and basal cell carcinoma. The annualised rate of malignancies overall in the alemtuzumab pooled dose group was [redacted] per person-year. Of the 15 reported events of malignancy, [redacted] were assessed as related by the Investigator [Genzyme ISS 2012].

The overall age-adjusted incidence of cancer in the US is 0.461/100 person-years compared to [redacted] person-years in the alemtuzumab pooled dose group over all available follow up. Thus, the malignancy risk with alemtuzumab is similar to the background incidence in the general population [Genzyme ISS 2012].

Summary of safety update up to and including 26 November 2012

The interim safety data from the Extension study are included in the pooled data for all alemtuzumab-treated patients. AEs occurring in ≥2% of patients from 31 December 2011 up to and including 26 November 2012 are presented in Additional Appendix 9 (Alemtuzumab Safety Data). The cumulative safety data through 26 November 2012 does not change the overall safety profile of alemtuzumab [Genzyme SUR March 2013].

Through the analyses of the active-controlled and long-term experience with alemtuzumab in MS provide a thorough characterization of the safety of alemtuzumab in both treatment naïve and previously treated MS patients. In totality, these data support the safety of alemtuzumab in treatment-naïve and previously treated patients with relapsing forms of MS when administered by IV infusion over 4 hours at a dose of 12 mg for 5 consecutive days at Month 0 (60 mg total dose) and for 3 consecutive days at Month 12 (36 mg total dose) [Genzyme ISS 2012].

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

As outlined above the following key AE are noted for alemtuzumab as reflected in the SmPC:

- Infusion associated reactions
- Automimmune thyroid diseases
- ITP
- Nephropathies
- Infections

The most common AEs associated with alemtuzumab are infusion reactions and infections and which can be managed effectively by the treating clinician. Neither infusion associated reactions nor infections led to treatment discontinuation in the clinical trials.

The risk management programme associated with alemtuzumab and outlined within the SmPC allows the identification of autoimmune disorders early to ensure effective management. Such autoimmune disorders are listed below together with important contextual information from their clinical trial programmes:

- Thyroid disorders – most were managed in the clinical trial programmes with conventional medical therapy and less than 1% required surgical intervention

- Nephropathies - In the alemtuzumab MS clinical program, all cases of glomerular disease were identified through the periodic serum creatinine or urinalysis testing performed as part of the safety monitoring program, thereby allowing early intervention. All cases were promptly treated and responded with preservation of renal function

- ITP - Following the introduction of risk minimisation measures all cases of ITP were identified early through FBC monitoring or via symptom identification by the patient or investigator, thus facilitating prompt diagnosis, and timely intervention in all subsequent cases

Table B9.9.3 and B6.9.4 summarise the EMEA approved, protocol required risk minimisation measures and safety monitoring and prophylactic / concomitant medication administration utilised in the Genzyme-sponsored MS clinical studies.

Table B6.9.3 Protocol Risk Minimisation Measures - Genzyme-Sponsored Clinical Studies of Alemtuzumab in Multiple Sclerosis

Risk	Protocol Risk Minimisation Measure(s)	Protocol Requirement			
		CAMMS 223	CAMMS 323	CAMMS 324	CAMMS 03409
Infusion-Associated Reactions	1. Methylprednisolone pretreatment (1000 mg) on first 3 days of any treatment cycle 2. Antihistamines and/or antipyretics treatment at investigator discretion	Y	Y	Y	Y
Thyroid Disorders	1. Patient and investigator education 2. Thyroid Function Tests at least quarterly for all patients	Y[a]	Y	Y	Y
ITP	1. Patient and investigator education 2. Monthly symptom monitoring survey (offset by 2 weeks from FBC testing) 3. Monthly FBC testing for all patients 4. Protocol –based definition of ITP to guide investigators (based on laboratory and clinical data): • Normal hemoglobin; • Normal white blood cell count though the differential likely reflected lymphopenia as a result of the alemtuzumab treatment; • No splenomegaly; • Normal peripheral smear except for a decrease in platelets without clumping; And either of the following: • A confirmed platelet count ≥50,000/µL but <100,000/µL on at least 2 consecutive occasions over a period of at least 1 month, or • A confirmed platelet count <50,000/µL without clumping documented on at least 2 consecutive occasions over any period of time.	Y[a]	Y	Y	Y
Anti-GBM Disease	1. Monthly serum creatinine for alemtuzumab-treated patients only 2. Monthly urinalysis for alemtuzumab-treated patients	Y[b]	Y[b]	Y[b]	Y

	only 3. Monthly symptom monitoring survey				
Infections	1. Acyclovir prophylaxis beginning on first day of any treatment course continuing for 28 days following the last infusion	N[d]	Y	Y[c]	Y

SOURCE: (Genzyme ISS 2012)

[a] Implemented in Protocol Amendment 3
[b] Quarterly serum creatinine was in place from beginning of Studies CAMMS223, 323, and 324; monthly testing was implemented in Protocol Amendment 10 for CAMMS223, Amendment 3 for CAMMS323, and Amendment 2 for CAMMS324.
[c] Implemented in Protocol Amendment 2
[d] While implemented in Protocol Amendment 10, no patients in Study CAMMS223 received acyclovir prophylaxis
ITP = immune thrombocytopenic purpura; FBC = full blood count; anti-GBM = anti glomerular basement

Table B6.9.4. Summary of protocol-specified safety monitoring and prophylactic/concomitant medication administration

	Protocol		
	CAMMS223	CARE-MS I	CARE-MS II
Premedication			
Methylprednisolone (1000 mg) on first 3 days of any treatment course	Y	Y	Y
Concomitant Medications			
Antihistamines and/or antipyretics (at investigator discretion)	Y	Y	Y
Prophylaxis			
Acyclovir – beginning on 1st day of any treatment course and continuing for 28 days following last infusion	N[a]	Y[b]	Y[c]
Adverse Event Monitoring			
Continuous	Y	Y	Y
Lab Monitoring			
Monthly Testing			
FBC testing	Y[b]	Y	Y
Serum creatinine testing – alemtuzumab patients only	Y[d]	Y[d]	Y[d]
Urinalysis – alemtuzumab patients only	Y[d]	Y[d]	Y[d]
Quarterly Testing			
Thyroid Function Tests (at least quarterly)	Y[b]	Y	Y
Serum creatinine testing	Y	Y	Y
Urinalysis	Y	Y	Y
Blood chemistry	Y	Y	Y
Patient Survey			
Monthly symptom monitoring survey (offset by 2 weeks from FBC testing) – ITP and anti-GBM	Y[b]	Y	Y

SOURCE: (Genzyme Summary of Clinical Safety 2012) (Table 2); FBC: Full blood count; ITP: Immune thrombocytopenia purpura; Anti-GBM: Anti-glomerular basement membrane

[a]While implemented in protocol amendment 10 of Study CAMMS223, no patients in this study received acyclovir prophylaxis.

[b]Implemented in protocol amendment 3.

[c]Implemented in protocol amendment 2 of Study CAMMS324.

[d]Quarterly serum creatinine was in place from beginning of Studies CAMMS223, 323 and 324; monthly testing was implemented in protocol amendment 10 for CAMMS223, amendment 3 for CAMMS323 and amendment 2 for CAMMS324.

Safety of comparators

Direct/indirect comparisons of safety versus the other disease modifying treatments listed in the decision problem (other interferons, glatiramer acetate, natalizumab or fingolimod) are not available. The following summaries below report the risk management strategies and the adverse events observed in the clinical trials for the decision problem comparators.

IFNβ-1b (Betaseron): In controlled clinical trials, the most common adverse reactions (at least 5% more frequent on Betaseron than on placebo) were: Injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia.

IM **IFNβ-1a (Avonex):** The most common adverse reactions (at least 5% more frequent on AVONEX than on placebo) were flu-like symptoms including chills, fever, myalgia, and asthenia.

SC **IFNβ-1a (Rebif):** The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes.

Glatiramer acetate: In controlled studies, most common adverse reactions (≥10% and ≥1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain.

Natalizumab: The most common adverse reactions (incidence ≥10%) in MS were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash; and in CD were headache, upper respiratory tract infections, nausea, and fatigue.

Fingolimod: Most common adverse reactions (incidence ≥10% and > placebo): Headache, influenza, diarrhea, back pain, liver transaminase elevations and cough.

Precautions

Patients receiving any of the various IFN-βs require monitoring for liver toxicity and worsening of pre-existing cardiac disease [Rebif SmPC; Avonex SmPC; Betaferon SmPC]. In addition to liver function tests, routine full and differential blood counts and blood chemistry are recommended. Where the patient has existing thyroid disease, thyroid function tests are necessary [Rebif SmPC].

Patients receiving glatiramer who have pre-existing cardiac disease should also be closely monitored during treatment [Copaxone SmPC].

Patients receiving natalizumab and fingolimod require liver function monitoring; patients receiving the latter also require blood pressure, blood count and ophthalmological monitoring during therapy [Tysabri SmPC; Gilenya SmPC].

Serious adverse events

Natalizumab has been associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML) in JCV (John Cunningham Virus) positive patients, a serious and potentially fatal infection [Tysabri SmPC]. An estimated 47%-68% of MS patients are JCV positive [Ollsen et al 2013]. As of February 2012, reported incidence of PML was 2.1 cases per 1000 patients, ranging from 0.09 per 1,000 or less in lowest risk patients (JC virus-negative) to 11.1 per 1,000 in patients with highest risk [Bloomgren et al, 2012]. Due to this increased risk of developing PML, the benefits and risks of natalizumab treatment should be individually considered by the specialist physician and the patient [Tysabri SmPC].

Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported to occur in all natalizumab treated patients with PML [Tan *et al,* 2011] and is thought to result from the restoration of immune function. This can lead to serious neurological complications and may be fatal. The overall mortality rate in patients that developed PML-IRIS before withdrawal of natalizumab and after withdrawal of natalizumab has been reported at 22% and 29% respectively [Tan *et al,* 2011]. Monitoring for development of IRIS, which has occurred within days to several weeks after plasma exchange in natalizumab treated patients with PML and appropriate treatment of the associated inflammation during recovery from PML should be undertaken [Tysabri SmPC].

Initiation of fingolimod results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete atrioventricular block. All patients should have an ECG and blood pressure measurement performed prior to and six hours after the first dose of fingolimod. All patients should then be monitored for a period of six hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurements. Continuous (real time) ECG monitoring during this six hour period is recommended [Gilenya SmPC]. Patients who develop cardiac abnormalities during the first dose monitoring period may require an overnight hospital stay [Gilenya SmPC].

Adverse events leading to disruption or cessation of treatment

AEs and poor tolerability of medical treatments can reduce adherence to therapy. Results from one IFN-β study report a number of AEs as a reason for treatment interruption of more than 1 month. These include injection site

reactions (occurring in 12% of the patient cohort receiving IM and SC IFN-β), flu-like symptoms (10% of patients receiving IM and SC IFN-β), and depression (9% of patients receiving IM and SC IFN-β) [Tremlett and Oger 2003]. Results indicate that one third of patients taking IFN-β, interrupted treatment for more than 1 month over 5 years of follow-up and more than 9% discontinued treatment within 6 months [Tremlett and Oger 2003].

Neutralising antibodies

In patients treated with interferons or natalizumab, disease exacerbations or infusion related events may indicate the development of neutralising antibodies against these medicines.

The precise incidence of neutralising antibodies in interferon treated patients is as yet uncertain. Clinical data suggest that after 24 to 48 months of treatment with Rebif 22 micrograms, approximately 24% of patients develop persistent serum antibodies to interferon beta-1a and after 24 to 48 months of treatment with Rebif 44 micrograms, approximately 13 to 14% of patients develop persistent serum antibodies to interferon beta-1a. The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (beta-2 microglobulin and neopterin). Although the clinical significance of the induction of antibodies has not been fully elucidated, the development of neutralising antibodies is associated with reduced efficacy on clinical and MRI variables. If a patient responds poorly to therapy with interferon, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.

In natalizumab treated patients, the presence of antibodies should be evaluated and if these remain positive in a confirmatory test after 6 weeks, treatment should be discontinued, as persistent antibodies are associated with a substantial decrease in efficacy of natalizumab and an increased incidence of hypersensitivity reactions.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Key outcomes alemtuzumab vs. interferon**β**-1a (**SC IFNβ**-1a) (please refer to Table B6.5.1 for full outcomes)

In previously untreated active RRMS patients (CAMMS223 and CARE-MS I)

- Alemtuzumab demonstrated significant and clinically meaningful superiority in reducing relapses in both trials
    - In the CAMMS223 trial, alemtuzumab 12 mg reduced the relapse rate by 69% compared with SC IFNβ-1a (p<0.001) over three years. The ARR at 36 months was 0.36 for SC IFNβ-1a and 0.11 for alemtuzumab 12mg [Coles et al. 2008].
    - In the CARE-MS I trial, alemtuzumab 12mg significantly reduced the relapse rate over two years by 55% compared with SC IFNβ-1a (p<0.0001). The estimated ARR over two years was 0.18 for alemtuzumab versus 0.39 for SC IFNβ-1a [Cohen *et al*, 2012]. [redacted] [Genzyme CARE-MS I CSR 2012].
    - In CARE-MS I, in alemtuzumab treated patients, there was a 57% reduction in the risk of relapses treated with corticosteroids compared with SC IFNβ-1a -treated patients (p<0.0001). In addition, only a small number of relapses in either group required hospitalisation, with no significant differences between groups (p=0.34) [Fox 2012].
- Alemtuzumab demonstrated significant and clinically meaningful superiority in reducing risk of 6-month SAD in the CAMMS223 trial
    - In CAMMS223, alemtuzumab 12mg reduced the risk of 6-month SAD by 75% over 3 years compared to SC IFNβ-1a (p<0.001). The percentage of patients experiencing SAD at 3 years was 26.2% in the SC IFNβ-1a group, and 8.5% in the 12 mg group [Coles et al. 2008].
    - This reduction was not observed in CARE-MS I. The percentage of patients experiencing 6-month SAD at 2 years was 11.1% in the SC IFNβ-1a group and 8.0% in the alemtuzumab group. The 11.1% 6-month SAD rate in the SC IFNβ-1a group was much lower than the expected rate of 20%, which was based on the observed rate in study CAMMS223 [Cohen *et al,* 2012].
- 76% and 77.6% of patients remained relapse-free at study end in CAMMS223 and CARE-MS I respectively (vs. 50% and 58.7% for SC IFNβ-1a) [Coles *et al*, 2008, Cohen *et al*, 2012].

- A reduction of T2-hyperintensive lesion volume for alemtuzumab vs. SC IFNβ-1a was observed in the trials. In both trials, the reduction difference between the two groups was not statistically significant.

- In CARE-MS I, alemtuzumab, when compared with SC IFNβ-1a, significantly reduced the risk of developing Gd-enhancing lesions (7% vs. 19%, respectively; p<0.0001) and new or enlarging T2-hyperintense lesions over 2 years (48% vs. 58%; p=0.04) [Cohen at al. 2012].
- Importantly, alemtuzumab -treated patients had significant reductions in the rate of brain atrophy as measured by the brain parenchymal fraction compared with SC IFNβ-1a -treated patients (-0.867% vs. -1.488%, respectively; p<0.0001) [Cohen *et al*, 2012].
- In both trials, alemtuzumab a reduction in disability as demonstrated by a mean improvement from baseline in the EDSS score
  - In CAMMS223, alemtuzumab 12mg demonstrated a mean improvement of 0.32 point from baseline at Year 3 (95% CI, -0.55, -0.10; p=0.006), whereas SC IFNβ-1a treated patients experienced a mean worsening from baseline of 0.38 (95% CI, 0.13, 0.63; p=0.003). This difference was apparent as early as 3 months following the initiation of alemtuzumab treatment. [Coels et al 2008].
  - In the CARE-MS I trial, both study groups experienced a mean reduction in EDSS scores, (both -0.14 points over 2 years) however no significant difference between study groups was observed [Cohen *et al,* 2012].
- Patients treated with alemtuzumab in CARE-MS I were significantly more likely to be clinically disease free compared with those treated with SC IFNβ-1a (74% vs. 56%, respectively; p<0.0001) [Cohen *et al,* 2012].
- In both trials, alemtuzumab demonstrated an increase in quality of life, measured via SF-36 questionnaires, vs. SC IFNβ-1a
  - In CAMS223, the mean mental and physical component scores [redacted] than for the SC IFNβ-1a group [redacted] [Genzyme CAMMS223 CSR, 2010]
  - For CARE-MS I, both treatment arms consistently improved from baseline SF-36 and EQ-5D to Year 2. Improvements seen with alemtuzumab –treated patients exceeded those observed for SC IFNβ-1a -treated patients on SF-36 PCS and EQ-VAS, although these differences were not significant [Selmaj *et al, 2012*].

For previously treated patients (CARE-MS II)

- The ARR over 2 years was 0.26 for alemtuzumab treated patients versus 0.52 for SC IFNβ-1a -treated patients [Coles *et al,* 2012a]. [redacted] [Genzyme CARE-MS II CSR 2012].
    - When looking at ARR, results demonstrated alemtuzumab was superior to SC IFNβ-1a regardless of prior disease modifying therapy [Freedman *et al*, 2013], [redacted] [Genzyme CARE-MS II CSR 2012]
    - A 56% reduction in risk of relapses was observed in patients treated with corticosteroids in the alemtuzumab treatment arm versus the SC IFNβ-1a group (p<0.0001). Alemtuzumab also reduced the risk for relapses that led to hospitalisation vs. SC IFNβ-1a by 55% (0.05 vs. 0.1, respectively) [Twyman, 2013]
- Alemtuzumab significantly reduced the risk of 6-month SAD over two years by 42% compared with SC IFNβ-1a (p=0.0084). The percentage of patients experiencing 6-month SAD at two years was 12.7% in the alemtuzumab group and 21.1% in the SC IFNβ-1a group [Coles *et al,* 2012a]
    - Alemtuzumab demonstrated greater efficacy than SC IFNβ-1a at reducing the risk of SAD regardless of the type of previous treatment [Freedman *et al*, 2013]
- Alemtuzumab significantly increased the proportion of patients who were relapse-free at two years compared with SC IFNβ-1a. At Year 2, 65.4% of patients receiving alemtuzumab remained relapse-free compared with less than half (46.7%) of SC IFNβ-1a -treated patients, which represents a 47% reduction in the risk of relapse over two years (p<0.0001) [Coles *et al,* 2012a]
- Patients treated with alemtuzumab significantly lowered (improved) EDSS scores over two years of follow-up by a mean of 0.17 points, while patients receiving SC IFNβ-1a reported a worsening of EDSS score by 0.24 points (p<0.0001). Moreover, alemtuzumab -treated patients were more likely to improve from baseline in mean EDSS score, indicating a decrease in disability with alemtuzumab treatment, whereas SC IFNβ-1a -treated patients were more likely to experience a worsening from baseline [OR 2.10, p<0.0001) [Giovannoni et al, 2013]. [redacted] [Genzyme CARE-MS II CSR 2012]

- Both the alemtuzumab and SC IFNβ-1a treatment groups showed a median reduction in T2-hyperintense lesion volume from baseline to Year 2 (-1.27% and -1.23%, respectively), however there was no significant difference between treatment groups [Coles *et al*, 2012a]

  - [redacted] [Genzyme CARE-MS II CSR 2012]

- [redacted] [Genzyme CARE-MS II CSR 2012]

- Alemtuzumab -treated patients showed significantly greater improvements from baseline than SC IFNβ-1a patients over 2 years on two of the self-reported measures of HRQL: the FAMS ($p<0.01$ for both Year 1 and Year 2) [Arroyo *et al,* 2013] and the PCS component of the SF-36 ($p<0.01$ for both Year 1 and Year 2) [Selmaj *et al*, 2012]. In both measures, between-group differences mainly reflected greater improvements on scales pertaining to physical functioning as opposed to mental or social functioning [Selmaj *et al*, 2012, Arroyo *et al,* 2013]

- After 2 years, patients treated with alemtuzumab were significantly more likely to be clinically disease free compared with those treated with SC IFNβ-1a (60% vs. 41%, respectively; $p<0.0001$). Alemtuzumab -treated patients were also significantly more likely than SC IFNβ-1a -treated patients to be [redacted] and MRI and clinically disease free (32% vs. 14%) [Genzyme CARE-MS II CSR 2012, Coles *et al*, 2012a]

Key outcomes: long-term efficacy (please refer to Section 6.5.3 for full outcomes)

CAMMS223 (Phase II) extension

- The extension arm of the phase II CAMMS223 study demonstrated long term efficacy for alemtuzumab over 5 years [*Coles et al, 2012c*]. Over 5 years, alemtuzumab lowered the risk of SAD by 72% and the rate of relapse by 69% compared with IFNβ-1a (both $p<0.0001$)

- Most alemtuzumab patients [redacted] did not require a third cycle of alemtuzumab [Genzyme, CAMMS223 CSR]

Phase III extension study (CAMMS03409)

- Interim results from the Extension Study show that patients treated with alemtuzumab in the Phase III studies (CARE-MS I and CARE-MS II) experienced similar ARRs as were observed during the Phase III study period [Fox 2013].

- Early results show that the relapse rates for patients treated with SC IFNβ-1a in the prior studies that crossed over to alemtuzumab in the Extension Study were lower in the Extension Study than in the prior studies, suggesting that these patients benefited from alemtuzumab treatment [Fox 2013]

- The proportion of patients in the extension study from CARE-MS I and CARE-MS II who remained relapse free at Year 3 was 67% and 55% respectively [Fox 2013]

- The proportion of patients in the extension study from CARE-MS I and CARE-MS II who were 6-month SAD free at Year 3 was 88% and 80% respectively [Fox 2013]

Additional long term data

- Results from a prospective UK study also demonstrate the long-term efficacy of alemtuzumab [Genzyme DOF (Tuohy et al) Draft manuscript]

[redacted]

[redacted]

Retreatment with alemtuzumab in long-term studies

In four long-term clinical studies the majority of patients did not receive retreatment with more than two cycles of alemtuzumab.

CAMMS 233 extension:

- Consenting alemtuzumab patients could receive additional doses of alemtuzumab in either a “fixed” (annual) retreatment arm or an “as needed” retreatment arm. In the ‘as needed’ arm, patient must have either experienced at least one protocol-defined relapse within the previous year, or accumulated at least two unique lesions on brain/spinal cord MRIs comprised of any combination of gadolinium-enhancing lesion(s) or new/enlarging MRI T2 lesion(s), within the previous year or since their last on-study MRI.

- In this study [redacted] of patients did not need retreatment with a third cycle of alemtuzumab after five years of follow up.

CARE MS I / II extension:

- During the Extension Study, retreatment criteria were defined as at least one relapse or at least two new emerging or enlarging T2 and/or Gd-enhancing brain or spinal lesions.

- During Year 3, 18% of patients who had enrolled from CARE-MS 1 and 20% of patients who had enrolled from CARE-MS II received alemtuzumab retreatment [Fox et al. 2013].

Two single-arms, prospective UK studies:

- In the study by Cossburn et al. additional courses of alemtuzumab were given as needed after intervals of not less than 12 months, either because of emergent clinical features suggesting recurrence of disease activity or the development of new or enhancing lesions on MRI performed 12 months or more after second treatment. After median follow-up of over seven years, only 30% of patients received three or more courses of alemtuzumab [Cossburn et al. 2011].

- In a second study [Genzyme DOF (Tuohy et al) Draft manuscript], [redacted]

Meta-analysis

- The results of the meta-analysis demonstrated that alemtuzumab 12 mg was [redacted] to SC IFNβ-1a for the analysed efficacy and safety outcomes.

    - In all cases, the results are statistically significant in that the confidence intervals do not include 1.

- This confirms that patients will experience relapses [redacted], have an [redacted] of remaining relapse free and [redacted] to achieve sustained accumulation of disability (at 3 and 6 months)

MTC

- In the base case (>2000 and ≥80% RRMS);
  - Alemtuzumab was associated with [redacted] for relapse outcomes. A majority of the relationships were statistically significant, with the exception of [redacted]; however, alemtuzumab showed [redacted] for the proportion of patients remaining relapse-free.
  - For three- and six-month SAD, alemtuzumab was [redacted], with a statistically significant advantage over [redacted] for three-month SAD. Alemtuzumab showed a [redacted] for three-month SAD and was [redacted] for six-month SAD. However, in sensitivity analyses that did not restrict by recruitment year, alemtuzumab showed a [redacted].

HA despite interferon use and RES subgroup analysis

- The results of the subgroup analysis indicate that alemtuzumab remains efficacious in HA despite interferon use and RES disease
- Alemtuzumab was [redacted] to fingolimod for ARR and 3 month SAD in the subgroup analysis the HA despite interferon use population
  - ARR:
  - Alemtuzumab 12mg vs. fingolimod 0.5mg rate ratio = [redacted]
  - Alemtuzumab 12mg vs. placebo rate ratio = [redacted]
  - Fingolimod 5mg vs. placebo rate ratio = [redacted]

  - 3 month SAD:
  - Alemtuzumab 12mg vs. fingolimod 0.5mg rate ratio = [redacted]
  - Alemtuzumab 12mg vs. placebo rate ratio = [redacted]
  - Fingolimod 5mg vs. placebo rate ratio = [redacted]

- Alemtuzumab was [redacted] to natalizumab for ARR and 3 month SAD in the RES population
  - ARR:
  - Alemtuzumab 12mg vs. natalizumab 300mg rate ratio = [redacted]
  - Alemtuzumab 12mg vs. placebo rate ratio = [redacted]

- Natalizumab 300mg vs. placebo rate ratio = [redacted]

- 3 month SAD:
- Alemtuzumab 12mg vs. natalizumab 300mg rate ratio = [redacted]
- Alemtuzumab 12mg vs. placebo rate ratio = [redacted]
- Natalizumab 300mg vs. placebo rate ratio = [redacted]

Adverse Events

Alemtuzumab has a manageable and predictable safety profile observed in long-term phase II (8.5 years interim analysis, 9 years expected at launch) and phase III extension studies and observational studies.

- Adverse events rates were comparable between alemtuzumab and SC IFNβ-1a
- In CAMMS223, AEs were reported in 100% of patients in both treatment groups at Year 3
- In CARE-MS I, AEs were reported in 92.0% of SC IFNβ-1a -treated patients and 96.0% of alemtuzumab-treated patients at Year 2.
    - In CARE-MS II, AEs were reported in 94.6% of SC IFNβ-1a -treated patients and 98.4% of alemtuzumab-treated patients at Year 2.
- The majority of events for both groups were mild or moderate in severity

Serious adverse events rates were comparable between alemtuzumab and an active comparator

- In CAMMS223, 22.4% of the SC IFNβ-1a -treated patients and 22.2% of the 12mg alemtuzumab-treated patients reported serious adverse events at Year 3.
- In CARE-MS I, [redacted] of the SC IFNβ-1a -treated patients and [redacted] of the alemtuzumab-treated patients reported serious adverse events at Year 2.
- In CARE-MS II, [redacted] of the SC IFNβ-1a -treated patients and [redacted] of the alemtuzumab-treated patients reported serious adverse events at Year 2.

Risks identified with alemtuzumab included IARs, autoimmune disorders (thyroid, ITP, and nephropathies including anti-GBM), and infections

- These AEs were experienced in a low proportion of patients and proactive risk minimisation procedures allowed early detection and management with good outcomes
- In CAMMS223, SAEs related to IARs, infections, thyroid, and ITP were [redacted] respectively, in alemtuzumab-treated patients at Year 5.
- In CARE-MS I, SAEs related to IARs, infections, thyroid, and ITP were [redacted] respectively, in alemtuzumab-treated patients at Year 2.
- In CARE-MS II, SAEs related to IARs, infections, thyroid, and ITP were [redacted] respectively, in alemtuzumab-treated patients at Year 2.
- Proactive risk minimisation procedures allowed early detection and management with good outcomes

Continued safety follow up with alemtuzumab-treated patients has not identified new risks or issues

[redacted]

In a pooled analysis of CAMMS223, CARE-MS I and CARE-MS II results, most patients reported at least 1 AE, the majority of which were mild or moderate in severity. The incidence of grade 3, 4, and 5 AEs were [redacted], [redacted], respectively. The most commune AEs were [redacted]. Over all available follow-up, [redacted] of patients treated with alemtuzumab discontinued treatment due to an AE [Genzyme ISS 2012].

Overall the incidence of AEs for alemtuzumab-treated patients was highest in [redacted] with the incidence of AEs decreasing over time to [redacted], highlighting that the AEs experienced by alemtuzumab-treated patients become more manageable over time. In contrast to the overall trend, the incidence of thyroid AEs increased from [redacted] for alemtuzumab -treated patients ([redacted] [Genzyme ISS 2012].

The incidence of serious AEs was [redacted] up to 31 December 2011. The most frequently reported serious AEs for the alemtuzumab group by MedDRA SOC were [redacted]. The rate of serious AEs by number of courses received was [redacted] across courses in alemtuzumab-treated group [redacted] [Genzyme ISS 2012].

With the exception of thyroid disorders, administration of more than 2 treatment cycles of alemtuzumab did not result in increased frequencies of common AEs or clinically important events which had not already been observed after 1 or 2 treatment cycles. This observation is supported by a prospective analysis of clinical and serologic data from 248 patients with MS treated with alemtuzumab, (median follow-up of 34.3 months [6.7–107.3], a cohort which excluded patients who were enrolled in CAMMS223, CARE-MS I or CARE MS-II [Cossburn *et al,* 2011].

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The clinical development program for alemtuzumab has evaluated the safety and efficacy of alemtuzumab in the treatment of active RRMS in three randomised controlled studies and one ongoing Extension Study. These studies have continued to explore the hypothesis that patients with active, relapsing disease treated at an early stage of disease will have reduced accumulation of disability and a lower rate of relapses and were initiated to investigate whether alemtuzumab improves outcomes for both treatment-naïve RRMS patients as well as for those RRMS patients who relapsed while receiving another treatment for MS.

Strengths

The alemtuzumab phase II and phase III studies represent the one of the most comprehensive clinical trial programmes carried out for an MS therapy and all studies were against an active comparator.

The primary efficacy population across all studies was the intention-to- treat (ITT) population which was all randomised patients, with the safety population being all randomised patients that received at least one dose of study medication.

All three Phase II and III studies had the same co-primary efficacy endpoints: relapse rate and time to 6-month sustained accumulation of disability (6-month SAD [based on changes in EDSS]). Additional efficacy endpoints were evaluated to support the relapse and disability co-primary endpoints and to assess the effect of alemtuzumab on brain lesions as observed on MRI. All are clinically meaningful and were carefully chosen to evaluate different ways in which MS may impact patients. Most notably:

- Relapses are a defining feature of RRMS and reduction in relapse is a key clinical end point when treating RRMS.
- Sustained accumulation of disability (SAD) maintained for at least 6 months (measured using EDSS) remains an outcome of high importance to patients as it most closely conveys how MS incrementally reduces the ability to function ‘normally’ as a result of accumulation of associated disabilities. Reaching an EDSS score of 6 is considered an important clinical milestone as it represents the onset of walking disability and has implications for the suitability of treatment further treatment with DMTs [ABN, 2009].

Alemtuzumab consistently demonstrated superior reduction in annualised relapse rates compared with SC IFN-β 1a, an active comparator, across the Phase II and III clinical development programme.

Long-term extension arms of the Phase II (completed) and Phase III studies (ongoing) have generated follow-up data out as far as nine years; and have demonstrated the durable efficacy of alemtuzumab. In the majority of patients, the effect of alemtuzumab has been shown to last for up to five years without the need for retreatment.

Safety in the Genzyme-sponsored studies was assessed by evaluation of adverse events (AEs), laboratory assessments, physical examinations, and vital signs throughout the studies. Specific safety measures were incorporated into the protocols in the alemtuzumab clinical program in MS to better assess the safety risks associated with alemtuzumab use in MS and potentially minimise the impact of these risks on patients. Risks identified with the use of alemtuzumab in the MS population included:

- IARs
- Autoimmune disorders (thyroid, ITP, nephropathies including anti-GBM disease)
- Infections

Safety measures implemented during the clinical development program in MS were informed by the clinical and post-marketing use of alemtuzumab in B-CLL patients, as well as investigator-sponsored pilot studies in MS and the Phase II company-sponsored study in MS. The risk minimisation methods, protocol-required procedures, monitoring requirements, and prophylactic/concomitant medication administration were robust and generally effective in reducing the severity of IARs and in leading to the prompt detection and treatment of autoimmune disorders, thereby improving overall patient outcomes.

The adverse event profile for alemtuzumab has remained consistent throughout the phase III studies. It should be noted that more patients in the SC IFNβ-1a group discontinued the study drug because of adverse events compared with alemtuzumab [redacted]. The phase II and ongoing Phase III extension studies continue to provide reassurance about the manageable safety profile of alemtuzumab.

Limitations

Clinicians and participants were not blinded to treatment assignment in the Phase II and Phase III clinical trials. A double-blind study design was considered unfeasible for a number of reasons, including a difference in the timing of administration, mode of administration, and distinctive side-effect profiles for alemtuzumab and SC IFNβ-1a. However, all Phase II and Phase III studies were rater-blinded to minimise the potential for bias. Key assessments, including evaluation of relapses, EDSS, MSFC, and MRIs, were performed by personnel who were blinded to the treatment assignment. Blinded raters received training regarding procedures for maintaining the blind study and did not have contact with study patients except when performing the blinded assessments. [Genzyme ISE 2012]

No head to head comparisons with glatiramer acetate, interferons other than SC IFNβ-1a, natalizumab or fingolimod are available for alemtuzumab. Therefore a mixed treatment comparison was performed in order to compare to these treatments.

Limited direct evidence has been reported describing the efficacy of alemtuzumab in highly active (HA) despite an interferon or rapidly evolving severe (RES) disease. Mixed treatment comparison was performed to compare efficacy between alemtuzumab and its comparators in these subgroups. Subgroup analysis was required as it was not possible to exactly match the NICE/regulatory definitions of HA despite interferon use and RES RRMS with the trial populations of CAMMS223 and CARE trials.

- The HA despite interferon use subgroup included patients who received interferon beta during the year before study enrolment and had received it for at least one year and had at least one relapse in the previous year plus at least either one gadolinium-enhancing T1 lesion or T2 volume $\geq$0.5 ml as a proxy for 9 or more T2 lesions at baseline. This was in line with the proxy measure of 9 or more T2 lesions used in the assessment of fingolimod by NICE and is considered justified on pragmatic grounds of data availability and the relationship between the criteria explored [NICE ERG report 2011].
- Only natalizumab provided data which exactly matched the definition of RES within NICE guidance. Alemtuzumab could do this because no data was available to provide "significant increase in T2 lesion load compared to a previous, recent MRI." 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.

Rebif (SC IFNβ-1a) is used in practice at a dose of 22μg for patients who cannot tolerate the higher dose in view of the treating specialist [Rebif SmPC]. It is therefore a limitation of the base-case MTC that primary reference sources are unavailable to include this dose in the base-case treatment networks. This has been compensated for in the results presented in the MTC by applying the ratios of results in the all-years sensitivity analysis to the results for SC IFNβ-1a 44μg in the base case to provide inferred results for SAD and discontinuation rates.

Whilst alemtuzumab demonstrated significant and clinically meaningful superiority over SC IFNβ-1a, there was no significant difference observed between the treatment arms in the risk of 6 month SAD (co-primary endpoint) in CARE-MS I. Whilst the rate of disability accumulation in patients treated with alemtuzumab was nearly identical in the CARE MS-I and CAMMS223 trial (8% vs. 8.5% respectively), it should be noted that the 11.1% 6-month SAD rate in the SC IFNβ-1a group in CARE-MS I was much lower than the expected rate of 20%, based on that observed in CAMMS223 [Cohen et al. 2012]. It has not yet been elucidated as to the reasons for these differences between similar studies.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Population

The scope from NICE defined the population as all RRMS but the EMA has defined use as active RRMS

The evidence base presented is for patients with active RRMS as reflected in the CHMP opinion for alemtuzumab [EMA, CHMP Summary of Opinion, 2013]. Other types of MS, such as primary progressive MS would be outside of the licensed indication.

Based on positive CHMP opinion granted on 27th June 2013, marketing authorisation for alemtuzumab is anticipated in the following indication:

> "Treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features."

In the context of clinical practice in England and Wales, as a minimum requirement for initiation of treatment of alemtuzumab in treatment naïve patients, active disease would be defined as patients meeting the ABN eligibility criteria for initiation with beta interferons and glatiramer acetate which is two or more relapses in the prior two years. Alemtuzumab would also be anticipated to be used in patients who have failed existing therapies such as interferons and glatiramer acetate. We would anticipate that in clinical practice in England and Wales active disease defined by clinical features (e.g. the occurrence of relapse) or imaging features will be used to initiate treatment experienced patients on alemtuzumab. This would include, for example, those circumstances where a neurologist will switch treatment to alemtuzumab in patients who have demonstrated a new brain lesion on MRI whilst receiving beta interferon even in the absence of clinical relapses.

The clinical development program for alemtuzumab has evaluated the safety and efficacy of alemtuzumab in the treatment of active RRMS in three randomised controlled studies and one ongoing Extension Study. These studies have continued to explore the hypothesis that patients with active, relapsing disease treated at an early stage of disease will have reduced accumulation of disability and a lower rate of relapses and were initiated to investigate whether alemtuzumab improves outcomes for both treatment-naïve RRMS patients as well as for those RRMS patients who relapsed while receiving another treatment for MS.

Comparator

The scope from NICE defined comparison of alemtuzumab in all RRMS versus interferons and glatiramer acetate however CHMP positive opinion has indicated the use of alemtuzumab in patients with active RRMS defined by clinical or imaging features.

Direct evidence is presented for alemtuzumab vs. SC IFNβ-1a from the CAMMS223, CARE-MS I, and CARE-MS II trials for both treatment experienced and treatment naive patients. For other interferons and glatiramer acetate, evidence is presented from a mixed treatment comparison (MTC) as head-to-head data are absent. Evidence has also been presented in the MTC for the other comparators natalizumab and fingolimod for the entire RRMS patient population. This is to cover the situation where patients may be switched from natalizumab or fingolimod to alemtuzumab who, although experiencing highly active RRMS at treatment initiation are not necessarily so at the time of switching. A sub-group analysis of the phase II and III trials has been carried out for both the RES and HA despite interferon use RRMS populations to allow comparison with natalizumab and fingolimod in line with the scope.

Rapidly evolving severe (RES) disease is defined in the NICE natalizumab guidance [NICE, 2007(a)] as two or more disabling relapses in one 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. The TEMSO population could be analysed for those patients with RES and at least one gadolinium-enhancing lesion at baseline. The ITT population of the study were patients with at least two relapses within one year before randomisation.

Highly active (HA) disease despite interferon use is defined in the NICE fingolimod guidance [NICE, 2012(a)] as those patients failing to respond to a full and adequate course of beta-interferon defined as at least 1 relapse in the last year and at least nine T2 hyper intense lesions or at least one gadolinium enhancing lesion. The CARE MS-II population could be analysed for those with HA disease, having had interferon therapy for at least 12 months prior to randomisation (with a gap no longer than 12 months between prior therapy and randomisation) with at least one gadolinium-enhancing lesion at baseline. The ITT population of the study had experienced at least one relapse within one year before randomisation.

Subgroups

The following sub-groups have been presented:

- Patients with highly active relapsing-remitting multiple sclerosis despite treatment with an interferon (in line with the fingolimod licence and associated NICE recommendation)
- Patients with rapidly evolving severe relapsing-remitting multiple sclerosis (in line with the natalizumab licence and associated NICE recommendation)

These subgroups are available as a direct comparison against SC IFNβ-1a, and as an indirect comparison against other comparators listed in the decision problem (see discussion in Section B6.10.2 see discussion around the limitations of these analyses).

Outcomes

Evidence is presented for the majority of outcomes listed in the decision problem alongside primary outcomes of the individual trials where these were additional to those identified in the decision problem. Evidence is also presented for resource utilisation with regard to hospitalisation (for relapse or any cause) and emergency medical visits.

Relapses and disability accumulation

The course of MS may be looked upon as the interaction between the two clinical phenomena of relapses and disability accumulation although the contribution of the former to the latter is not clear [Confavreux *et al*. 2006]. Relapses may require admission to hospital, and are associated with a level of disability and incapacity that disrupts working, family and social life. Accumulation of disability clearly presents a challenge to patients and their carers, alongside the very real representation of worsening disease. Relapses can have a significant impact on quality of life [Orme *et al*. 2007].

There are some key elements of MS as a disease process that are of high importance to a patient vs. clinical signs and symptoms. The end points in the alemtuzumab clinical trial program are highly relevant to clinical practice:

- Annualised relapse rate provides a measure of the number of relapses suffered by patients in the studies.
- Time to sustained accumulation of disability is a measure of disability accumulation and uses EDSS, a scale used to measure disability in clinical practice.
- Measuring symptoms of MS such as fatigue is relevant to clinical practice as fatigue has a profound effect on the daily activities of patients with MS.

In the clinical trial programme, alemtuzumab showed a significant reduction in relapse rate vs. SC IFNβ-1a:

- In CAMMS223, alemtuzumab (12mg) reduced the rate of relapse by 69% compared with SC IFNβ-1a ($P<0.001$) [Coles *et al,* 2008].
- In CARE-MS I, alemtuzumab reduced the rate of relapse compared with IFNβ-1a. The yearly rate of relapse was 0.18 compared with 0.39 in the SC IFNβ-1a group.

- In CARE-MS II, alemtuzumab 12 mg reduced the rate of relapse compared with IFNβ-1a. The yearly rate of relapse was 0.26 compared with 0.52 in the SC IFNβ-1a group.

The most accepted tool to measure disability is the Expanded Disability Status Scale (EDSS), which is a 10-point instrument that measures different areas of functional disability in the lower half of the scale and focuses on hard ambulatory disability in the latter half. A score of 6 on the EDSS is considered an important milestone as it represents the onset of walking disability and has implications for the suitability of treatment with disease-modifying treatments (DMTs) [Kurtze, 1983]. Frequent and prolonged relapses with incomplete recovery at onset and a short interval between the initial episode and first relapse are adverse prognostic features but the main determinant of disability is onset of the progressive phase [Compston *et al*. 2002]

As shown in cost effectiveness section 7, the cost effectiveness model is most sensitive to the HR associated with disability accumulation. As stated above, the following results are of relevance in relation to the alemtuzumab clinical trial programme and cost effectiveness:

- In CAMMS223, 54.2% alemtuzumab patients had an improvement in EDSS score from baseline, compared to 33.7% SC IFNβ-1a patients. 41.3% of SC IFNβ-1a patients' EDSS score declined compared to 22.4% of alemtuzumab patients [Coles et al. 2008]. Alemtuzumab reduced the risk of 6-month SAD by 75% over 3 years compared to SC IFNβ-1a (HR 0.25; 95% CI [0.11, 0.57]; p<0.001). At Year 3, 26.2% of patients in the SC IFNβ-1a group had experienced 6-month SAD, compared with 8.5% in the alemtuzumab group [Coles et al. 2008].
- In CARE-MS I, mean EDSS score improved from baseline by 0.14 points in both groups [Cohen *et al*. 2012]. The percentage of patients experiencing 6-month SAD at 2 years was 11.1% in the SC IFNβ-1a group and 8.0% in the alemtuzumab group. The 11.1% 6-month SAD rate in the SC IFNβ-1a group was much lower than the expected rate of 20%, which was based on the observed rate in study CAMMS223 [Genzyme CARE-MS I CSR 2012].
- In CARE-MS II, mean disability improved from baseline by –0.17 EDSS points after alemtuzumab 12 mg (p=0.004) compared with a 0.24 EDSS point deterioration for SC IFNβ-1a (p=0.0064), a net benefit for alemtuzumab of 0.41 EDSS point (p<0.0001) [Coles at al. 2012]. Alemtuzumab significantly reduced the risk of 6-month SAD up to 2 years by 42% compared with SC IFNβ-1a (p=0.0084). The percentage of patients experiencing 6-month SAD at 2 years was 12.7% in the alemtuzumab group and 21.1% in the SC IFNβ-1a group [Genzyme CARE-MS II CSR 2012, Coles 2012]. Alemtuzumab demonstrated greater efficacy than SC IFNβ-1a at reducing the risk of SAD regardless of the type of previous treatment.

Severity of relapse

Increasing severity of relapses has been shown to be associated with higher healthcare costs, and to result in transient increases in disability. Increasing levels of disability likely impacts work and leisure productivity, and lowers quality of life. [Parise, 2013]. Relapse severity has also consistently been identified as the most powerful predictor of incomplete recovery, together with age and polysymptomatic onset, [Leone *et al,* 2007; West *et al,* 2006; Mowry *et al,* 2009; Hirst *et al, 2008]* and is a strong predictor of a poor prognosis [Hirst *et al,* 2010; Scott *et al,* 2010; Ramsaransing *et al,* 2007; Langer-Gould *et al,* 2006]

Consistent with the effect on relapse rate, supportive analyses from CARE-MS I and CARE-MS II showed that alemtuzumab 12 mg led to significantly fewer alemtuzumab-treated patients experiencing severe relapses and fewer relapses that led to steroid treatment or to hospitalisation compared to SC IFNβ-1a.

Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance)

The symptoms of MS experienced by patients are the result of acute neurological dysfunction; this covers a wide array of clinical manifestations encompassing the motor, sensory, visual and autonomic nervous systems [Compston *et al*. 2008; Mallam *et al*. 2009]. Patients commonly experience fatigue, spasticity, bladder dysfunction, pain and cognitive dysfunction. Less common are depression, bowel dysfunction, and paroxysmal symptoms [Crayton *et al*. 2006].

The measurement of MS symptoms is not a routine part of clinical practice, however is clearly important to the patient. During Phase III clinical trials for alemtuzumab, the symptoms of MS were quantified as part of the Functional Assessment of MS questionnaire. The FAMS is a disease specific instrument designed to specifically measure MS-related impacts on HRQL and was assessed at baseline and every 6 months during the study period. Components of the FAMS include six clinically relevant scales: Mobility, Symptoms, Emotional Well-being, General Contentment, Thinking and Fatigue, Family/Social Well-being. FAMS has been validated with MS patients in previous research [Gupta 2012].

Freedom of disease activity

Freedom of disease activity is an outcome for which there is no clearly defined consensus. In the pivotal phase III studies patients were classified as clinically disease free if they did not experience a relapse or six month SAD from baseline and/or MRI disease free if they did not experience a new Gd-enhancing lesion or a new or enlarged T2 hyperintense lesion from baseline. Throughout the clinical trial program for alemtuzumab, treatment with alemtuzumab has consistently led to higher proportions of patients remaining free of relapse vs. SC IFNβ-1a.

Mortality

MS has been associated with an almost threefold increase in the risk for death, with excess mortality rates from other diseases such as cardiovascular disease and infectious and respiratory disease. The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of approximately 10 years [Bronnum-Hansen *et al*. 2004].

There were a total of 8 deaths during the clinical studies, including 7 (0.5%) patients who received alemtuzumab and 1 patient who received SC IFN-β1a. As a result of the reported mortalities, safety programmes are currently underway to detect more serious adverse events, e.g. ITP, ensuring early treatment and management. Alemtuzumab is prescribed within a comprehensive framework of patient education and management providing additional guidance for health care professionals on the treatment of MS and management of any adverse events.

Health related quality of life

Health related quality of life (HRQL) was assessed during the Phase II and III trial program via the Medical Outcome Study (MOS) 36-Item Short-Form Health Survey (SF-36), the Functional Assessment of Multiple Sclerosis (FAMS) and EuroQoL-5D.

- Both treatment [redacted] from baseline SF-36 and EQ-5D upto Year 2 in CARE-MS I. Improvements seen with alemtuzumab–treated patients [redacted] those observed for SC IFNβ-1a-treated patients on SF-36 PCS and EQ-VAS, although these differences were [redacted].
- In CARE-MS II alemtuzumab-treated patients [redacted] from baseline across all measures of HRQL at all timepoints, whereas SC IFNβ-1a-treated patients [redacted] from baseline on any HRQL measure except at Month 12 on the SF-36 MCS. Further, the improvement from baseline was [redacted] or alemtuzumab-treated patients than SC IFNβ-1a-treated patients on all HRQL measures at most timepoints.

These patient-reported improvements in HRQL parallel [redacted] of alemtuzumab compared to SC-IFNβ-1a on other efficacy endpoints, and further support the potential for alemtuzumab to be an important additional treatment option for RRMS patients [Selmaj 2012]

Hospitalisation (as a result of relapses).

Even in the early stages of the disease, cost burden per patient is high, and is known to increase with sustained accumulation of disability due to reduced productivity and increased health care burden. Multiple studies have demonstrated that hospital admissions tend to account for the greatest proportion of direct costs compared with other direct costs such as ambulatory care, testing, drug, or healthcare provider payment costs (Kobelt 2006e;

Kobelt 2006d; Miltenburger 2002; Noyes 2011; Phillips 2004). Direct costs increase gradually in the initial stages, but rapidly at more advanced disability levels (National Multiple Sclerosis Society 2011c).

- In CARE-MS I only a small number of relapses in either group required hospitalisation, with no significant differences between groups (p=0.34) [Fox 2012]
- Notably, in CARE-MS II alemtuzumab reduced the risk for relapses that led to hospitalisation vs. SC IFNβ-1a by 55% (0.05 vs. 0.1, respectively) [Twyman 2013].

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The CHMP approved indication for alemtuzumab is for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features [CHMP, 2013l]. In the context of clinical practice in England and Wales, a minimum criteria of two or more relapses in the prior two years is, based on clinical opinion, likely to be used to initiate treatment naïve patients on alemtuzumab in line with ABN guidance defining active disease as it relates to starting patients on interferons and glatiramer acetate. In patients receiving another DMT a definition of active disease which is based either on a clinical definition of active disease (e.g. the occurrence of relapses) or one based on imaging will be used to switch patients to alemtuzumab.

In the alemtuzumab Phase II and III studies, only patients that had experienced at least two clinical episodes in the two years prior to the study were eligible. In the Phase III studies, patients must also have had at least one episode in year prior, with objective neurological signs. Therefore patients included in the alemtuzumab studies meet the ABN criteria of active disease and are expected to reflect patients treated in clinical practice in this respect.

In clinical practice in England and Wales, alemtuzumab will be prescribed for patients with active RRMS in the following way

- 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 natilizumab or fingolimod (although the definition of highly active for use of alemtuzumab would not need to be as restrictive as that contained within the licences for these two drugs and would be aligned to the more inclusive definition used amongst clinicians in England and Wales treating MS). Feedback from a number of MS specialists experienced in prescribing alemtuzumab in clinical trials or in off label use shows a trend towards using alemtuzumab earlier in the disease process as experience is gained . This includes patients who are treatment naïve or those with less severe disease. This includes patients who have active RRMS which is not highly active.

- There will be use of alemtuzumab in patients who have active RRMS which is not highly active disease. The extent of this use is an area of uncertainty. However, it is a highly important group to consider because the current discussions amongst MS Specialists about use in this group based on experiential use of alemtuzumab within its broad licence over the medium to long term has the potential to lead to a paradigm shift in the treatment of MS and make a substantial impact on patient's clinical outcomes. Of note in this regard is the following:
    - Some clinicians will choose to use alemtuzumab in place of interferons or glatiramer acetate in active RRMS which is not highly active. This will include first lne use. This includes some clinicians who will use the drug in this way immediately. This is in line with increasing confidence amongst MS specialists about the value of using alemtuzumab in the earlier stages of MS as a means of achieving better outcomes [Coles 2006].
    - Alemtuzumab demonstrated superiority, in patients with active RRMS, against an interferon (SC INF-1a) in terms of reducing the sustained accumulation of disability and reducing relapses. Alemtuzumab is the first MS treatment to show improved efficacy on disability accumulation endpoints against an active comparator. This active comparator was sc INF-1a [Coles *et al,* 2008, Coles *et al,* 2012b, Cohen *et al,* 2012].
    - The categorisation of MS into an earlier focal inflammatory phase (equating to EDSS 0-3) leading to a later neurodegenerative phase (beyond EDSS 3) has been postulated within the literature [Leroy et al 2010] with the suggestion that this earlier phase may signify a "therapeutic window of opportunity" in which DMTs should be targeted to maximise long term patient outcomes [Leroy et al 2010; Coles et al 2006;

Gold et al 2010]; earlier use of alemtuzumab would be aligned to this view of how to achieve optimal outcomes.

The broad licence of alemtuzumab supports this compared to the licences of natalizumab and fingolimod which limit them to use in highly active RRMS patients

Clinical studies support the use of alemtuzumab in all of these subgroups:

Subgroup	Evidence
Treatment naive patients	CAMMS223 (Phase 2), CARE-MS I
Treatment experienced patients with active disease	CARE-MS II (See note below)
In patients with highly active disease despite interferon use (in line with the fingolimod licence)	Subgroup analysis
In patients that have RES RRMS	CARE-MS II subgroup analysis

A subgroup analysis for alemtuzumab in the RES (in line with the natalizumab licence and associated NICE guidance) and HAD despite interferon use RRMS population (in line with the fingolimod licence and associated NICE guidance) has been presented in response to the final scope. In addition MTCs were carried out specifically to address efficacy in the RES and HAD despite interferon use populations to demonstrate relative efficacy compared to natalizumab and fingolimod which are restricted to these groups of highly active RRMS patients, respectively (in a way defined by their licences).

DMTs are not normally prescribed unless patients are ambulant (maximum EDSS 6.5) and aged 18 or more years [ABN, 2009]. In the alemtuzumab studies patients had a starting EDSS of 3 or less, or 5 or less in studies of treatment naive and previously treated patients, respectively. It is expected that this is representative of the population that would be treated in clinical practice.

Dose, retreatment

The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses[4] [SPC, 2013]. In clinical studies the majority of patients were treated with the

[4] Initial treatment course of 12 mg/day for five consecutive days (60 mg total dose) and a second treatment course of 12 mg/day for three consecutive days (36 mg total dose) administered 12 months after the initial treatment course.

licensed dose of 12mg (Table B6.10.1). Data from patients treated with the 24mg dose was used in the safety analysis.

Table B6.10.1. Proportion of patients treated with 12mg alemtuzumab in Phase II and 3 clinical studies

	12mg dose	24mg dose
CAMMS223	112	110
CARE-MS I	376	0
CARE-MS II	426	170
Total	914	280

In the extension phase of clinical studies some patients received more than two treatment courses, with [redacted] of patients receiving three or more courses in the Phase II extension in years 3 – 5 [CAMMS223 CSR]. The reason for the high percentage of patients receiving a third dose of alemtuzumab arises from the original trial design which stipulated retreatment at month 24 at the treating physicians discretion if CD4+ T-cell count was >$100x10^6$ cells per litre. In clinical practice a lower proportion of patients are expected to receive more than two courses.

In CARE MS I / II extension in year 3 18%-20% received retreatment [Fox, 2013]. Retreatment rates are anticipated to be low in clinical practice.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic review was conducted to obtain all relevant cost-effectiveness studies in MS. Consequently, the PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review question:

"What modelling techniques have been used previously to conduct economic evaluations for DMTs in the treatment of multiple sclerosis?"

Section 10.10 details the search strategies, databases searched and subsequent results from the database sites searched, resulting in 33 studies being identified as evaluating cost-effectiveness in MS.

Of these cost-effectiveness studies, no studies for alemtuzumab were identified. However, two cost-effectiveness studies from the UK NHS perspective have recently been published for MS DMTs and used in NICE assessments.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Although no cost-effectiveness studies for alemtuzumab were identified, two cost-effectiveness studies have been analysed and quality assessed since they can be used to inform the cost-effectiveness model for alemtuzumab (Table B7.1.1). In addition, the company is aware that the Canadian Agency for Drugs and Technologies in Health (CADTH) are currently undertaking a project to examine the comparative efficacy and safety of drug therapies for RRMS. The draft materials including a list of included studies for the review are no longer in the public domain since the consultation period closed and as such were not included in the review.

The two studies are relevant as they are both from the UK NHS & PSS perspective, with comparators relevant to alemtuzumab and have been assessed by NICE [Chilcott et al. 2003; Gani et al. 2008]. The first identified study by Chilcott et al. was developed by the School of Health and Related Research (ScHARR) to evaluate beta-interferons and glatiramer acetate and was then adapted by Gani et al. to evaluate natalizumab in the treatment of multiple sclerosis.

Key differences identified between the two models were: time horizon, which was 20 years in Chilcott et al. but 30 years in Gani et al.; patient population, which was all RRMS in Chilcott et al. but restricted to highly active (HA) RRMS in Gani et al.; and the method used to model mortality rates. Chilcott et al. derived annual relative risk of all cause mortality for the cohort assuming the same as a normal healthy population, minus the death observed in the London Ontario cohort, but Gani et al. applied an MS mortality multiplier per EDSS to the UK general population mortality rate. Both studies extrapolated the efficacy observed in trials over a much longer time horizon and presumed the treatment effect would persist of the full time horizon of the model. Both studies also followed guidance developed by the Association of British Neurologists (ABN) and switched patients to best supportive care, rather than DMT, at EDSS 7.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) or Philips et al. (2004).

A complete quality assessment of the two identified studies in section B7.1.2 is presented in Section 10.11. The results of the quality assessment were almost identical for both studies. However, Gani et al. reported resource quantities separately from the unit cost and reported incremental analyses clearly, whilst Chilcott et al. did not. Neither study addressed generalisability issues or provided full details of the probabilistic sensitivity analysis (PSA) undertaken. Nevertheless, the design and structure of the model was clear and appears to be appropriate for informing the cost-effectiveness model for alemtuzumab.

Table B7.1.1 Table detailing two studies identified as potential informants of the alemtuzumab cost-effectiveness model

Study	Year	Country	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chilcott et al.	2003	UK	- The model simulates the clinical course of the disease - Health states were defined according to the Kurtzke expanded disability status scale (EDSS) - The clinical course of the disease, costs, and utilities were assessed with and without treatment over 20 years - The model used an annual cycle length - Patients can remain in their current health state, progress one or more states, die, transit to a secondary progressive health state, or stop treatment	- Patients with relapsing remitting multiple sclerosis and secondary progressive multiple sclerosis - A 20 year time horizon is used, with patients starting treatment at 30 years of age	Not available	Not available	Base case RRMS public model over conventional therapy - IM IFNβ-1a £42,041 - SC IFNβ-1a 22μg £60,963 - SC IFNβ-1a 44μg £71,732 - IFNβ-1b £49,664 - Glatiramer acetate £97,636 Base case confidential model over conventional therapy RRMS: IFNβ-1b £35,282 RRMS and SPMS: IFNβ-1b £39,872
Gani et al.	2008	UK	- The model is based on a previous model for RRMS reported by Chilcott et al. which has been reparameterised for HA RRMS patient population - It is a Markov model in which patients are able to progress through a series of disability states, with the states based on the Kurtzke Extended Disability Status Scale (EDSS) - Over time patients may progress to SPMS - Patients are withdrawn from treatment at a given withdrawal rate, and removed from the cohort at a given mortality rate - The time cycle of the model is 1 year - A 30-year time horizon is taken in the analysis, as this reflects the life-long nature of the disease	- The baseline characteristics for the patient group were taken from the patient population in the AFFIRM study (mean age 36 years, mean time since diagnosis 5 years and a mean EDSS score of 2.5)	- Natalizumab 7.4 - INFβ 5.5 - Glatiramer acetate 5.1 - Best supportive care 4.7	- Natalizumab £449,500 - INFβ £445,200 - Glatiramer acetate £444,800 - Best supportive care £427,100	The model suggests that natalizumab is the most cost-effective DMT, with an ICER of £2,300 per QALY when compared with IFNβ, £2,000 per QALY compared with GA and £8,200 per QALY compared with BSC) From a health and social care cost perspective, the ICERs were £18,700, £20,400 and £25,500 per QALY, respectively.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SmPC/IFU and included in the trials.

The patient population considered within the base case economic evaluation is adults with active RRMS defined by clinical or imaging features. This in line with the anticipated license following positive recommendation for alemtuzumab made by the Committee for Medicinal Products for Human Use (CHMP) on 27th June 2013 [EMA 2013]. In the context of UK clinical practice it is anticipated that the initiation of treatment naïve patients on alemtuzumab will follow the ABN guidelines for active disease as it relates to initiation of patients on interferons or glatiramer acetate (two or more relapses in the prior two years) [ABN 2009]. For initiation of treatment experienced patients on alemtuzumab it is anticipated that a definition based on clinical outcomes (e.g. the occurrence of a relapse) or imaging will be used to define active disease.

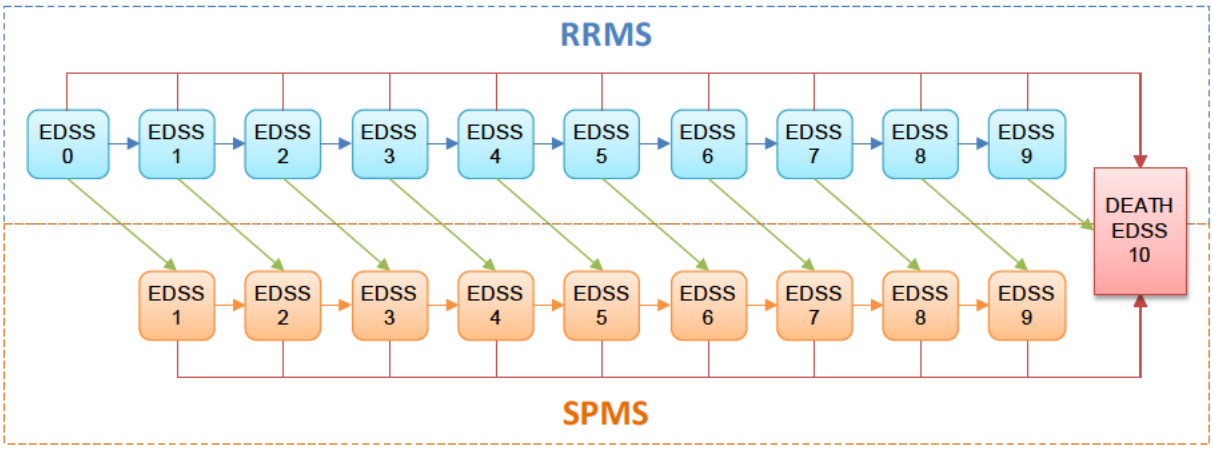
In addition to the licensed indication, the economic evaluation considers two important subgroups within active RRMS, namely HA despite treatment with a beta interferon and RES, which have been highlighted both by clinical experts and NICE as potential subpopulations in which alemtuzumab could be used [Genzyme KOL interview report 2012; NICE Final Scope].

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A multi-state Markov model was developed which considered health states based on disease classification and severity, as shown in Figure B7.2.1. Active RRMS patients enter the model in one of ten health states defined by the Kurtzke Expanded Disability Status Scale (EDSS) [Kurtzke, 1983]. Descriptions of each EDSS state can be found in Section A2.1. In each annual cycle, active RRMS patients may remain in the same EDSS state, progress to a greater EDSS state, convert to SPMS or die. Although the focus of the economic evaluation is on active RRMS, it is essential to model conversion to SPMS since approximately 65% of people with RRMS will develop SPMS within 15 years of diagnosis [NICE Final Scope]. Once a patient converts to SPMS, they may remain in the same EDSS state, progress to a greater EDSS state or die. Death is represented by EDSS 10.

Figure B7.2.1 Schematic of the model



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The structure of the model is based on the previously published ScHARR model, developed for NICE to evaluate the cost-effectiveness of beta-interferons and glatiramer acetate in the treatment of multiple sclerosis [Chilcott et al. 2003]. Adapted versions of the ScHARR model have also been used in previous multiple sclerosis technology appraisals [Biogen 2006; Novartis 2011].

The model structure allows estimation of the full impact of the disease across a lifetime, in terms of both costs and quality of life, from pre-diagnosis at EDSS 0 (normal neurological examination), to EDSS 9 (confined to bed) before reaching EDSS 10 (death). The model structure differs from the original ScHARR model by capturing mortality separately from the transitions through EDSS states to allow for an increasing risk of mortality by age and gender.

Capturing disease classification and progression through EDSS health states within active RRMS and SPMS meant that the costs and quality of life implications could be identified and captured for disability progression, relapses and treatment alternatives. Additionally, results from the systematic review (Section B7.1.2) found that the vast majority of models developed in multiple sclerosis were Markov models. Therefore, it was deemed that a Markov structure was the most appropriative structure to model the cost-effectiveness of alemtuzumab.

In line with the ScHARR model and subsequent versions, it was assumed that when a patient progresses from RRMS to SPMS, their EDSS would increase by 1 (see Figure B7.2.1). This assumption is in line with the definition of SPMS which requires a measurable increase in disability.

7.2.4 Please define what the health states in the model are meant to capture.

The objective of the model was to estimate costs and QALYs of alemtuzumab compared to alternative DMTs for the treatment of active RRMS. The model was developed to capture differences in outcome measures specified in the NICE scope which could affect both costs and QALYs (see Figure B7.2.2):

- There are 20 possible health states in the model: RRMS EDSS 0 to 9, SPMS EDSS 1 to 9 and death (EDSS 10). Transition matrices are used to estimate progression of patients through the disease scale (EDSS) as well as the disease classification in terms of active RRMS and SPMS. Costs and QALYs are calculated based on both EDSS level and disease classification. Consequently, this would capture disability, symptoms of multiple sclerosis, and freedom of disease activity.

- The number of relapses associated with each health state is estimated along with the corresponding costs and impact on quality of life. Severity of relapses is accounted for both in terms of costs and quality of life (see Section B7.2.5).

- Mortality from disease progression is captured in the model and is adjusted for age and gender.

- Costs and disutilities associated with treatment-related adverse events are captured in the model.

Figure B7.2.2 Outcomes in NICE alemtuzumab final scope

Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom of disease activity • mortality • adverse effects of treatment • health-related quality of life

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what

treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Disease progression is captured in terms of both progression of patients through EDSS states, and conversion from RRMS to SPMS. In addition, number of relapses (split by severity) are captured and linked to EDSS states. Two methods were used to measure disease progression in the model. The first approach applied hazard ratios, derived from a mixed treatment comparison, to a natural history dataset. The natural history of the disease was modelled based on real-world longitudinal observational disability progression data obtained from the London Ontario data set and placebo arms of TOWER and TEMSO. The second approach used transition probabilities derived directly from patient level data of the two pivotal alemtuzumab trials (CARE-MS I and CARE-MS II). These two methods are subsequently referred to as "natural history comparison" and "direct comparison" respectively.

EDSS progression and conversion to SPMS

Previous technology appraisals have used the London Ontario dataset for predicting natural history progression without DMT because this was used in the original ScHARR model [Chilcott et al. 2003]. However, recently there have been concerns regarding the use of this old data set, which may not accurately reflect current disability progression rates in multiple sclerosis [NICE 2011 (a)]. Therefore, a systematic review was conducted to identify the most appropriate natural history transition matrix for disability progression for patients receiving no DMT (see Additional Appendix 10). A number of different sources of natural history were identified through the search including the UK Risk Share Scheme [Boggild et al. 2009]. These were assessed and evaluated based on their applicability to the decision problem, availability of use in the model and reliability. As discussed in Additional Appendix 10, from the data available, the London Ontario dataset was found to be most appropriate, robust and clinically plausible. However, a restriction of the London Ontario dataset is that it does not include any patients that regress in EDSS which is known to occur in clinical practice [Jones et al. 2010]. This limitation is due to the elimination of short-term variations in EDSS when the dataset was analysed retrospectively, resulting in no EDSS improvement in the final dataset.

The London Ontario registry analyses provided EDSS transition probabilities for active RRMS patients, all RRMS patients and all SPMS patients as well as conversion probabilities for patients progressing from RRMS to SPMS. Active RRMS was defined as "patients with ≥2 relapse events during the 2-year pre-study period, but <2 relapses in the first pre-study year" in the London Ontario analysis. This definition of active RRMS is in line with the most recent ABN guidelines which states patients with active disease (>2 clinically significant relapses in the previous 2 years) are eligible for beta-interferon or glatiramer acetate [ABN 2009]. The marketing authorisation for alemtuzumab is in active RRMS patients (see Section B1.3 or Section B7.2.1 for full definition). Therefore, active disease is the most relevant population of RRMS for alemtuzumab thus the London Ontario dataset of

active patients is used in the base case analysis. A sensitivity analysis considers EDSS transition probabilities based on all RRMS patients.

Since the London Ontario data did not contain any patients with EDSS 0 in RRMS, transition probabilities from EDSS 0 were derived using the placebo arms of two RCTs for teriflunomide (TEMSO and TOWER). These trials were selected for three reasons: the patient level data were available to Genzyme; the trials were placebo controlled and also had similar 'active' inclusion criteria. Thus it was appropriate to combine these data with the active London Ontario dataset. The TEMSO and TOWER derived transition probabilities from EDSS 0 were combined with probabilities from EDSS 1 to 9 from the London Ontario active RRMS dataset to produce the natural history active RRMS transition matrix. The London Ontario registry was also used to generate transition probabilities between EDSS states for SPMS patients, as well as probabilities of conversion from RRMS to SPMS.

The progression of patients receiving DMTs is estimated by adjusting the natural history transition matrix by the relative effect of treatment versus placebo derived from the MTC (see Section B6.7). In addition to delaying sustained accumulation of disability, DMTs also reduce relapse rates, which are modelled by applying a relative risk for each treatment to the relapse rate of best supportive care patients (see Section B6.7). Furthermore, DMTs reduce the severity of relapses which impacts costs and utilities so this is also captured in the model.

Relapses

Different severities of relapses are considered in the model because relapses which require hospitalisation incur greater costs and impact on quality of life than those which do not lead to hospitalisation. Consequently, relapses are segregated according to:

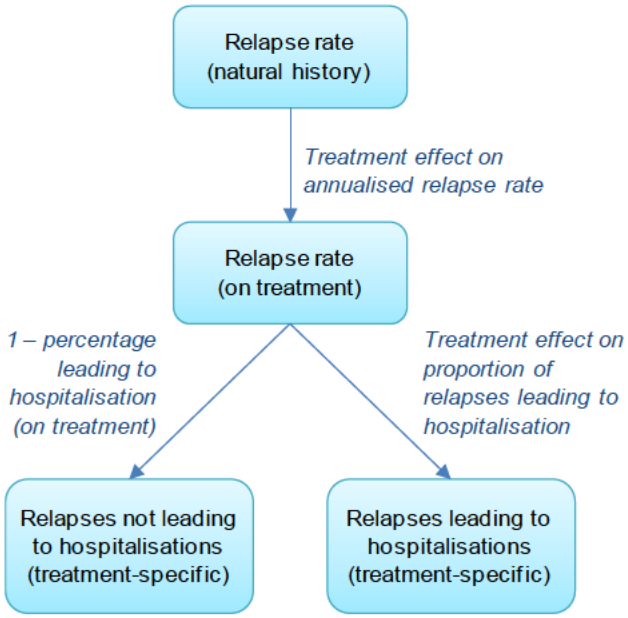
- Relapses leading to hospitalisation
- Relapses not leading to hospitalisation

The approach used to model these different relapse severities is shown in Figure B7.2.3. Two distinct treatment effects on relapses in the model are considered:

1. Treatment effect leading to reduction of relapses (annualised relapse rate reduction), applied onto a natural history rate of relapse

2. Treatment effect leading to a smaller proportion of relapses leading to hospitalisation (relative rate), applied onto the natural history proportion of relapses that lead to hospitalisation

Figure B7.2.3 Application of treatment effect on relapse segregated by hospitalisation status



7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B7.2.1 Key features of analysis

Factor	Chosen values	Justification	Reference
Analytical method	Multi-state Markov model	Long-term chronic condition, clear and reproducible. Considered appropriate by ScHARR in the development of a model to evaluate cost-effectiveness of beta-interferons and glatiramer acetate for NICE.	[Chilcott et al. 2003]
Software	Microsoft Excel	Transparent and widely used software	
Time horizon	Life time (50 years with starting age of 39)	Sufficiently long time to reflect life time differences in costs or outcomes between technologies, as stipulated in reference case	[NICE 2008]
Cycle length	1 year	Previously considered appropriate by ScHARR.	[Chilcott et al. 2003]
Half-cycle correction	Mid-year estimate is an average of: the cohort at the start of each cycle following treatment withdrawal; and at the end of each cycle following mortality, disease progression/ conversion and switch to BSC	As stipulated in reference case	[NICE 2008]
Measure of health effects	Quality adjusted life years (QALYs)	As stipulated in reference case	[NICE 2008]
Discount for utilities and costs	3.5%	As stipulated in reference case	[NICE 2008]
Perspective	NHS & PSS	As stipulated in reference case	[NICE 2008]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The efficacy data from the MTC included data for alemtuzumab at a dose of 12mg. Although a dose of 24mg was evaluated in the Phase II trial and one of the Phase III trials, this is not part of the MAA and has therefore not been included in this economic evaluation.

As detailed in Section B7.2.1, the approved indication for alemtuzumab as outlined in CHMP positive opinion on 27th June is "treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features" [EMA 2013]. In the context of UK clinical practice it is anticipated that the initiation of treatment naïve patients on alemtuzumab will follow the ABN guidelines for active disease as it relates to initiation of patients on interferons or glatiramer acetate (two or more relapses in the prior two years) [ABN 2009]. Patients within the alemtuzumab pivotal trials of CARE-MS I, CARE-MS II and CAMMS 223 all met these criteria. For initiation of treatment experienced patients on alemtuzumab it is anticipated that a definition of active disease based on clinical outcomes (e.g. the occurrence of a relapse) or imaging will be used to define active disease. For these patients the ABN guidance on what constitutes active disease for the initiation of patients on interferons or glatiramer acetate is used as a proxy for this definition of active disease in treatment experienced patients. In line with this, the cost-effectiveness analysis modelled a cohort that received treatment in active RRMS (based on a definition of two or more relapses in the prior two years) who could progress onto SPMS. In the cost-effectiveness model, active RRMS patients are eligible to receive treatment with alemtuzumab up to EDSS 7 but cannot receive treatment above EDSS 7 or whilst in SPMS. This assumption is based on clinical opinion which suggests that alemtuzumab will have no efficacy in these patients and is also aligned with the ABN guidelines for alternative treatments in MS [ABN 2009].

Comparators considered were based on those outlined in the NICE Final Scope (see Figure B7.2.4) and clinical opinion.

Figure B7.2.4 Comparators in NICE alemtuzumab final scope

Comparators	• beta-interferon • glatiramer acetate • natalizumab (for treatment-naïve or previously treated patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)

In clinical practice in England and Wales, alemtuzumab will be prescribed for patients with active RRMS in the following way:

- 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 natilizumab or fingolimod (although the definition of highly active for use of alemtuzumab would not need to be as restrictive as that contained within the licences for these two drugs and would be aligned to the more

inclusive definition used amongst clinicians in England and Wales treating MS). Feedback from a number of MS specialists experienced in prescribing alemtuzumab in clinical trials or in off label use shows a trend towards using alemtuzumab earlier in the disease process as experience is gained . This includes patients who are treatment naïve or those with less severe disease. This includes patients who have active RRMS which is not highly active.

- Some clinicians will choose to use alemtuzumab in earlier disease (including first line use) and in patients with active RRMS and in place of interferons or glatiramer acetate

The company's view is supported by interviews conducted with neurologists in England and Wales to ascertain existing treatment pathways and how this may be impacted by the uptake of alemtuzumab (see Section B7.3.5 for details of interviews). Having reviewed publicly available trial evidence for alemtuzumab, the clinicians stated they would, subject to guidance, expect to use alemtuzumab primarily in RRMS patients after first line interferon or glatiramer acetate use [Genzyme KOL interview report 2013]. This is reflected in the estimation of patient numbers receiving alemtuzumab in Section 8 which states that 78% of those receiving alemtuzumab will be treatment experienced patients. They would also anticipate substantial use in treatment naïve RES patients.

UK clinical opinion suggested natalizumab was the most appropriate comparator for second line positioning and fingolimod was also a relevant comparator. The NICE Final Scope limits the comparison of natalizumab to RES RRMS (which may include treatment experienced patients) and fingolimod to HA despite interferon use RRMS patients that have received prior treatment beta-interferons [NICE Final Scope]. In addition, clinicians remarked that they would also consider using alemtuzumab as a treatment in patients with rapidly evolving disease as a first treatment [Genzyme KOL interview report 2013]. In line with the NICE Final scope and use as identified by clinical opinion, the use of alemtuzumab to treat patients with RES RRMS instead of natalizumab is addressed in a subgroup analysis of these patients (see Section B7.9) and the use of alemtuzumab to treat patients with HA RRMS despite treatment with a beta interferon instead of fingolimod, is also addressed as a subgroup analysis. As shown in the estimation of patient numbers receiving alemtuzumab in Section 8, use of alemtuzumab in the RES and HA disease despite treatment with a beta interferon subgroups is assumed to comprise 73% of overall alemtuzumab use.

As stated above, it is recognised that there are a certain proportion of clinicians who would use alemtuzumab either as a first line or second line treatment in place of interferons or glatiramer acetate in early stage and more moderate MS disease. This is in line with a view advocated by a number of clinicians that the use of alemtuzumab in the earlier inflammatory stage of MS will lead to better outcomes when compared to delaying treatment which consequently increases the probability of patients transitioning from the inflammatory to the neurodegenerative stage of the disease. In the UK, RRMS patients most commonly receive interferons or glatiramer acetate within the DoH Risk Sharing Scheme in earlier stages of the disease [DoH 2002]. Specifically,

these are IM IFNβ-1a, IFNβ-1b, SC IFNβ-1a and glatiramer acetate. There are two doses of SC IFNβ-1a used in clinical practice: 22µg and 44µg. Clinical opinion suggested that as a first line treatment option, a comparison with interferon beta and glatiramer acetate would be most appropriate [Genzyme KOL interview report 2013]. Therefore, these five treatments are included as direct comparators to alemtuzumab in the model, in line with the NICE Final Scope.

The most efficacious treatment of the beta-interferons and glatiramer acetate according to the MTC (see Section B6.7.7), in terms of reduction in sustained accumulation of disability and relapse, was SC IFNβ-1a 44µg. Since the CARE-MS trials provide a direct comparison of alemtuzumab vs. SC IFNβ-1a 44µg, of all the DMTs available on the Risk Sharing Scheme, results from the economic evaluation have focussed on this comparison. This concurs with the EMA regulators perspective that SC IFNβ-1a 44µg was an appropriate comparator in the CARE MS trials.

Whilst interferon and glatiramer acetate use is identified within the scope as a comparator for alemtuzumab in RRMS the percentage of patients receiving alemtuzumab in place of these treatments is estimated to be relatively small: 7% of overall alemtuzumab use (split approximately 50:50 between treatment naïve and treatment experienced patients). Please see Section 8.

There are an estimated 20% of all patients receiving alemtuzumab who are not receiving it in place of interferons or glatiramer acetate (7% of all patients) or to treat RES or HA disease despite treatment with a beta interferon (73% of all patients). These patients fall into the following categories:

- Patients receiving natalizumab who switch to alemtuzumab. Whilst they will have been initiated on natalizumab to treat RES RRMS, many will no longer be experiencing RES symptoms. It is thought possible that natalizumab patients may be switched by clinicians to alemtuzumab; particularly those who are concerned about the risk benefit associated with JCV positive patients on natalizumab for two years (see Section A2.5). This is in line with the natalizumab SPC which notes the following:
    - Use of natalizumab has been associated with an increased risk of PML, an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Due to this increased risk of developing PML, the benefits and risks of natalizumab treatment should be individually reconsidered by the specialist physician and the patient. The risk factors are associated with an increased risk of PML are: the presence of anti-JCV antibodies, treatment duration, especially beyond 2 years and immunosuppressant use prior to receiving natalizumab [Tysabri SmPC].
- Switching patients from natalizumab because high NAB levels provide concern to clinicians about the level of continued efficacy

- Treatment experienced patients who would receive natalizumab outside of NICE guidance and who instead of being initiated on natalizumab will be initiated on alemtuzumab
- Patients receiving fingolimod who switch to alemtuzumab
- Treatment experienced patients who would receive fingolimod outside of NICE guidance and who instead of being initiated on fingolimod will be initiated on alemtuzumab

To address the use of alemtuzumab in the four categories of patients listed directly above both natalizumab and fingolimod have been included as comparators as well as interferons and glatiramer acetate in the active RRMS population. These are two additional comparisons not outlined within the NICE scope. In this regard it is worth noting that the estimated use of alemtuzumab to treat patients who are not experiencing RES RRMS nor have HA RRMS despite treatment with a beta interferon is 27% and will be split in the following way:

- 70% instead of natalizumab
- 25% instead of interferons / glatiramer acetate
- 4% instead of fingolimod

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SmPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.

- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

In the RRMS population, guidelines produced in 2001 from the Association of British Neurologists (ABN) do not recommended the use of DMT in patients that have lost the ability to walk [ABN 2001]. The Department of Health agreed with the ABN criteria to determine eligibility for treatment using beta-interferon and glatiramer acetate for people with MS within the RSS [NICE 2003]. Therefore, the most recent NICE guidance (2003) recommends stopping treatment in patients that have the lost the ability to walk, with or without assistance, which corresponds to an EDSS of 6.5 or greater. The updated 2009 ABN guidelines also recommend treatment in this group of patients [ABN 2009]. Since EDSS states in the model are rounded up to the nearest integer, this stopping rule is implemented as: when a patient progresses to EDSS 7, they switch from a DMT to treatment with BSC only. The RRMS stopping rule of EDSS 7 is applied to all comparators.

In clinical practice, a patient's EDSS level is regularly monitored by a neurologist or MS nurse [Genzyme KOL interview report, 2013]. This is reflected in the model through neurology visits for treatment monitoring, in addition to direct medical and non-medical costs. Therefore, using a stopping rule based on EDSS is accurate, robust, feasible in clinical practice, incurs no additional cost over regular monitoring, and is in line with NICE guidelines.

In line with ABN guidelines for alternative DMTs, clinical opinion suggests there would be no efficacy after EDSS 7 or in SPMS for patients receiving treatment with alemtuzumab and consequently, the costs and benefits of alemtuzumab are modelled to persist only in RRMS and only up EDSS 7 [Genzyme KOL interview report, 2013]. Once an alemtuzumab patient reaches EDSS 7 or converts to SPMS, they cease to receive treatment benefit (in terms of reduction on sustained accumulation of disability and relapses) and effectively receive the same benefits as a best supportive care patient (see Section 7.3). As discussed in Section 7.5.1, it is expected that the majority of patients will only require two courses of treatment and the effect of alemtuzumab will persist over the long-term. No residual efficacy is assumed once a patient reaches EDSS 7 or converts to SPMS, and this is independent of the number of courses a patient has received. In addition, the user may implement a waning of treatment effect for alemtuzumab patients who still receive benefit from treatment (RRMS EDSS ≤6) (see Section B7.3.3). Finally, it is assumed that once an alemtuzumab patient reaches EDSS 7 or converts to SPMS, they cannot be retreated with additional doses, and therefore there are no further acquisition costs for alemtuzumab.

Glatiramer acetate and IM IFNβ-1a are not indicated for use in SPMS [Avonex SmPC; Copaxone SmPC; NICE CG8 (Multiple Sclerosis), 2003]. Since the MAA submitted for alemtuzumab does not include the SPMS population, a SPMS stopping rule was implemented for all comparators at EDSS 0 such that no patients were treated with a DMT upon conversion to SPMS in the base case model. However, sensitivity analyses were

performed to evaluate the impact of modelling SC IFNβ-1a and IFNβ-1b according to their licence in SPMS up to EDSS 7, in line with NICE guidance [NICE, 2003].

Any withdrawal of treatment prior to stopping at EDSS 7 for RRMS patients is captured by treatment-specific discontinuation rates for each comparator in the model. These all-cause discontinuation rates are derived from the MTC (see Section B6.7). Therefore, the continuation rule applied through the model is that a patient can remain on a treatment with alemtuzumab whilst the following conditions are met:

- Patient has RRMS with an EDSS < 7
- Patient does not have SPMS.

Similarly, a patient can remain on a treatment with IM IFNβ-1a or glatiramer acetate whilst the following conditions are met:

- Patient does not discontinue treatment due to events specified in the MTC
- Patient has RRMS with an EDSS < 7
- Patient does not have SPMS.

Finally, a patient can remain on a treatment with SC IFNβ-1a and IFNβ-1b whilst the following conditions are met:

- Patient does not discontinue treatment due to events specified in the MTC
- Patient has an EDSS < 7.

7.3 Clinical parameters and variables

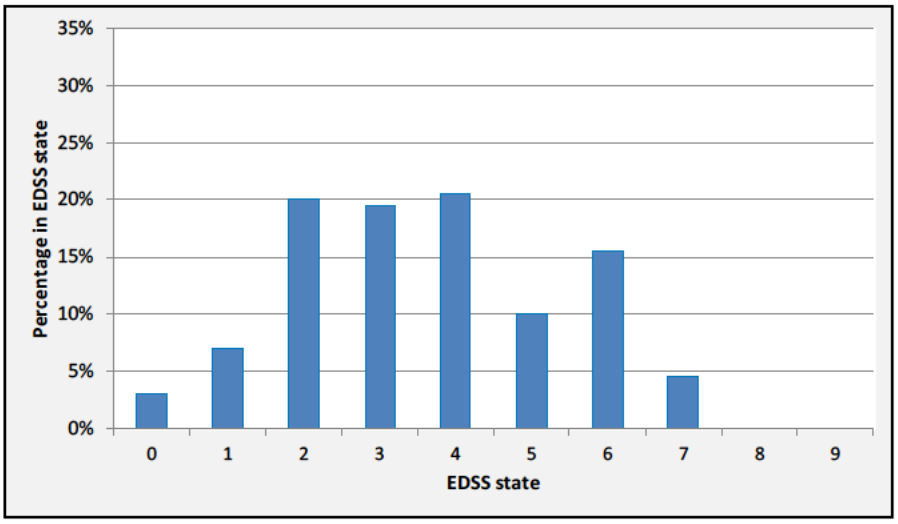
7.3.1 Please demonstrate how the clinical data were implemented into the model.

Patient characteristics

The population entering the model was based on the average demographic profile of RRMS patients in the UK. This was considered representative of the active RRMS population modelled in the cost-effectiveness analysis and defined by the ABN as having two relapses in two years. For the base case, the demographic profile at baseline of RRMS patients was sourced from the UK Risk Sharing Scheme (RSS) [Pickin et al. 2009]. The population of the RSS analysis included 85.8% RRMS patients; for the purposes of using these data to inform baseline characteristics in the model, this was assumed to be a 100% RRMS population. The mean baseline EDSS of SPMS patients was 5.5 whereas the mean baseline for RRMS patients was 3.1 thus assuming the

distribution is 100% RRMS slightly overestimates the severity of the cohort. Additionally, the EDSS distribution for UK patients starting treatment may be overestimating severity because the RSS analysis covered years when treatments were introduced for the first time thus could include patients that were waiting for treatments and had progressed in the interim. However, the UK RSS EDSS distribution has a similar mean EDSS to two key observational UK alemtuzumab datasets [Cossburn et al. 2011; Genzyme DOF (Tuohy et al.) draft manuscript], suggesting it is an appropriate distribution for the economic evaluation of alemtuzumab. The mean age of patients at baseline was 39.3 years. The female to male ratio is 2.98:1. The baseline EDSS distribution is shown in Figure B7.3.1.

Figure B7.3.1 Baseline EDSS distribution used in base case modelling, sourced from UK Risk Sharing Scheme



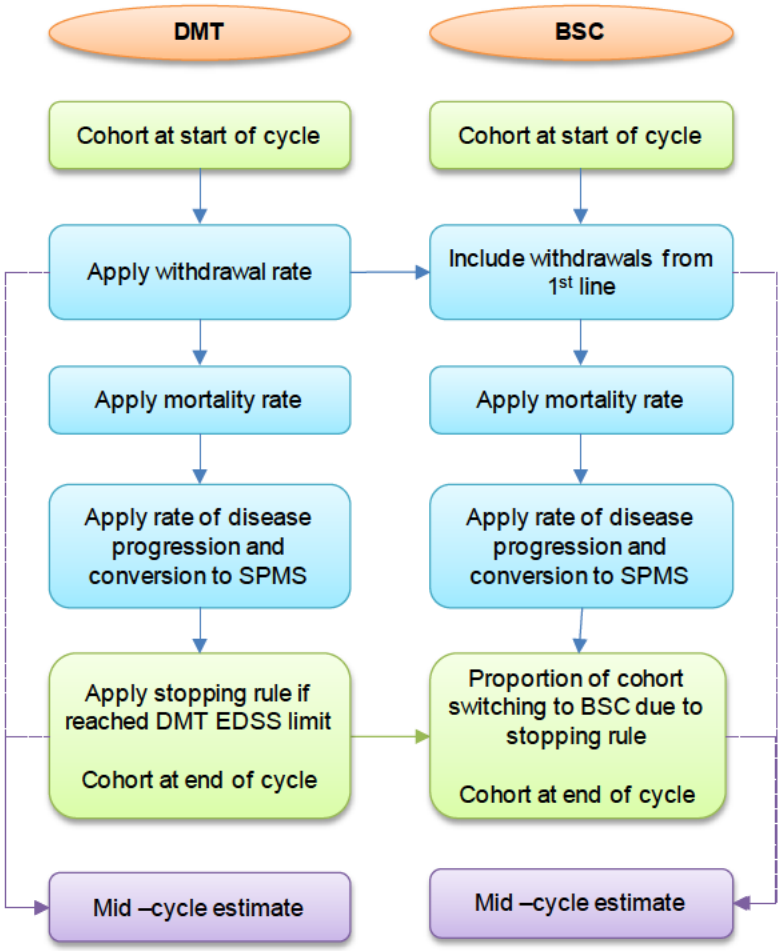
As a sensitivity analysis, the age, gender and EDSS distribution at baseline from the pivotal phase III trials (CARE-MS I AND CARE-MS II) for alemtuzumab were used. The mean age of patients at baseline in the pooled CARE-MS trials was 39.3 years thus comparable to the UK RSS data. The female to male ratio was also the same in the CARE-MS trials as the UK RSS. The EDSS distribution indicated milder patients than the UK RSS (Figure B7.3.2).

[redacted] Baseline EDSS distribution used in modelling alternative scenario, sourced from pivotal alemtuzumab CARE-MS trials

[redacted]

Figure B7.3.3 illustrates how patients transition through the model accounting for withdrawal, mortality, disease progression, conversion to SPMS, and DMT stopping rule (see Section B7.2.8).

Figure B7.3.3 Markov transition matrices for cohort



Withdrawal

Due to the sustained effect of alemtuzumab long after courses of treatment, the impact of withdrawing from treatment was assumed to have no effect and was therefore not modelled explicitly, although the implications of the DMT limit and SPMS conversion are discussed in Section 7.2.8. The majority of patients receive only two courses of alemtuzumab and then continue to receive benefit (see Section B6.5.3). In addition, patients are very unlikely to withdraw due to lack of efficacy as they would be given further doses. It is therefore more appropriate to model patients that do not receive re-treatment (e.g. 3rd or 4th doses) rather model withdrawal directly. Therefore in the model, no patients withdraw from treatment with alemtuzumab. The implications of re-treatment are discussed in Section 7.5.1.

For all comparators, at the start of each cycle, patients may withdraw from treatment. The method used to calculate the probability of treatment withdrawal is based on the 2-year withdrawal probability for teriflunomide combined with results from the base case MTC. This method was applied in the manufacturer submission of teriflunomide submitted by Genzyme to NICE in May 2013. The same method has been used in this evaluation to remain consistent.

Given that the majority of MS trials are 2-years in length, a 2-year weighted average withdrawal probability for teriflunomide was calculated using data from the Phase II and Phase III trials. The 2-year average probability of withdrawal for teriflunomide was combined with the MTC to obtain annual probabilities of withdrawal for all treatments using the following method:

1. First, the 2-year odds for teriflunomide was calculated using:

   Odds (treatment) = Probability / (1-Probability)

   2-year odds (teriflunomide) = [redacted]

2. The inverse odds ratios for teriflunomide versus the comparators from the MTC (Table B7.3.1) were applied to the 2-year odds for teriflunomide to give the 2-year odds for each comparator treatment e.g. natalizumab 2-year odds [redacted]

Table B7.3.1 Mean odds ratios of withdrawal for teriflunomide vs. comparators in the model

Treatment	Teriflunomide versus comparator odds ratio	95% Lower confidence interval	95% Upper confidence interval
IM IFNβ-1a	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 44µg	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 22µg	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]

*Calculated based on sensitivity analysis MTC (all-years, 80% RRMS) applied to base case MTC (post-2000, 80% RRMS) (see Additional Appendix 2)

3. The 2-year odds for each comparator treatment were then converted back to 2-year probabilities using:

   Probability = Odds / (1+Odds)

4. The 2-year probabilities were converted to absolute annual withdrawal rates using:

   $r = - [\ln(1-p)] / t$

   where p equals the probability/risk, r is the rate, and time t = 2.

5. Finally, annual rates were converted to annual probabilities using:

   $p = 1 – \exp(-r)$

The resulting annual rates of withdrawal used in the model are reported in Table B7.3.2. The model assumes that the annual probability of withdrawal for each treatment will not persist over the 50-year time horizon. This assumption was made on the basis that a patient suffering adverse events is less likely to withdraw from treatment due to adverse events if they have tolerated them for two years. Similar assumptions have been made in other economic evaluations of RRMS treatments [NICE 2007(b)]. After two years it is assumed that the probability of withdrawal will be 50% of those calculated for all treatments. Sensitivity analyses considered persistence of withdrawal as well as a steeper 75% decline in the probability of withdrawal for all treatments.

Table B7.3.2 Annual all-cause rates of withdrawal rates used in the model

Treatment	2-year odds	Source	2-year risks	All-cause annual withdrawal probability	95% confidence interval of all-cause annual withdrawal probability
IM IFNβ-1a	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IFNβ-1b	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 44µg	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 22µg	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC with ratio applied from all-years, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]

Mortality

After determining withdrawals, patient mortality may occur. A relative increase in mortality per EDSS state was sourced and applied to all-cause mortality rates for the general population in the UK. A systematic review of mortality by EDSS revealed no additional literature to inform mortality predictions compared to the methods used

in previous submissions (TA 127 and TA 254) (see Additional Appendix 11). Therefore, the same approach considered in the aforementioned submissions was taken for this analysis.

This method uses mortality multipliers by MS disease severity from Pokorski et al. [Pokorski et al. 1997]. It is assumed that there is no excess mortality risk for patients in EDSS 0. Cubic regression analysis was applied to these mortality multipliers to obtain a mortality adjustment for each individual EDSS state [Novartis 2011]. The final mortality multipliers associated with individual EDSS states are listed in B7.3.3.

Table B7.3.3 Mortality multipliers by EDSS score

EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
1	1.432	1.600	1.637	1.674	1.842	2.273	3.097	4.447	6.454

The assumption was made that mortality per EDSS would not differ for SPMS patients. As per the definition of a progressive MS patient, a SPMS patient is more likely to experience increased disability at a quicker rate than an RRMS patient thus indirectly increasing mortality risk.

All-cause mortality rates were obtained from Interim life tables for England and Wales from 2008-2010 [Office for National Statistics 2011]. A weighted average all-cause mortality rate was calculated based upon the female to male ratio of MS patients (2.98:1) [Pickin et al. 2009].

The mortality multipliers reported in Table B7.3.4 are applied to the all-cause weighted average mortality rates to derive the risk of mortality of RRMS and SPMS patients in different EDSS states. Finally, mortality rates were converted in annual probabilities of mortality by EDSS, the results of which are presented in Additional Appendix 12. The probability of mortality per cycle is dependent on the starting age of the cohort such that at cycle 20, the probability of mortality in a cohort with average starting age 39 will correspond to the all-cause mortality probability of a patient aged 59.

Sustained accumulation of disability

As discussed in Section B7.2.5, two methods of modelling sustained accumulation of disability were used in the cost-effectiveness analysis. The method used in the base case model was to apply 3-month sustained accumulation of disability hazard ratios obtained from the MTC to a natural history matrix. This method allows flexibility to be adapted to all comparators. The second method that was tested in sensitivity analysis was to utilise data obtained in the clinical trials of alemtuzumab to obtain direct treatment-specific transition matrices for RRMS.

The active London Ontario dataset was found to be the most appropriate natural history data for active RRMS and SPMS patients receiving no DMT, as discussed in Section B7.2.5. Since no data for EDSS 0 were available,

these transition probabilities were obtained from the placebo arms the recent of teriflunomide trials: TOWER and TEMSO.

The statistical approach used to derive the transition matrix was to model EDSS states as homogeneous continuous-time Markov process with a transition matrix *Q*. For example, a transition matrix for a disease with three progression states and one absorbing state (e.g. Death) is:

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

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

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

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

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

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

The complete natural history data for the active RRMS and SPMS populations used in the model, representative of best supportive care, are shown in Tables B7.3.4 and B7.3.5 respectively.

The probabilities of progression at later EDSS states reflect the nature of the disease and the EDSS. The level of neurological damage required to go from walking with a stick (EDSS 6) to being confined to a wheelchair (EDSS 7) is a significant change and thus a person is less likely to transition in EDSS each year once they have passed EDSS 6.

Table B7.3.4 Natural history transition matrix of active RRMS patients. Transition probabilities from EDSS 0 sourced from TOWER and TEMSO placebo arms. Transition probabilities from EDSS 1 to 9 are sourced from London Ontario

		year i+1									
	EDSS	0	1	2	3	4	5	6	7	8	9
year i	0										
	1										
	2										
	3										
	4										
	5										
	6										
	7										

	8										
	9										

Table B7.3.5 Natural history transition probabilities of SPMS patients sourced from London Ontario

		year i+1									
	EDSS	0	1	2	3	4	5	6	7	8	9
year i	0										
	1										
	2										
	3										
	4										
	5										
	6										
	7										
	8										
	9										

The probability of converting from RRMS to SPMS is calculated from hazard rates, derived using time to event data and survival analysis. The hazard rate for conversion from EDSS 1 to SPMS is calculated assuming an exponential survival function (i.e. a constant hazard of converting from EDSS 1 to SPMS over time). The exponential survival function has the form of:

$$S(t) = exp(-\lambda t)$$

The hazard rate λ for an exponential distribution can be estimated from the median time of conversion to SPMS, reported to be 15 years from disease onset from London Ontario [Scalfari et al. 2010]. The annual hazard rate of conversion for patients in EDSS 1 is therefore:

$$\lambda = \ln(2)/15 = 0.0462$$

The hazard rate of conversion for the other EDSS states can be calculated from the hazard rate of conversion from EDSS 1 by using a Cox proportional hazards model analysis. The Cox proportional hazards model using EDSS as a continuous variable is reported by analysis of the London Ontario data as:

$$H(t) = H(t)_{EDSS1} \exp(\beta X) = \lambda \exp(\beta X)$$

Where H(t) is the hazard rate of conversion for any EDSS state, $H(t)_{EDDS1}$ the hazard rate of conversion for EDSS 1, and β the coefficient of the relationship between EDSS and the hazard ratio of sustained accumulation of disability between the base case EDSS 1 and all other EDSS states. The analysis from London Ontario reports β = [redacted]. This above equation for H(t) is then used to derive the hazard rates of conversion from EDSS 1 to each successive stage to EDSS 8 (Table B7.3.6). Data for EDSS 9 was not available from the London Ontario dataset so a 100% conversion rate for RRMS patients in EDSS 9 was assumed. All estimated hazard rates were subsequently converted into probabilities using the standard formula of $p = 1 – \exp\{-rt\}$.

Table B7.3.6 Annual probability of conversion to SPMS from RRMS by EDSS score

EDSS	Calculation	Hazard rate	Calculation	Probability
0				0
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9				[redacted]

The probabilities are reflective of the characteristics of SPMS disease. In practice, very few patients enter SPMS with low EDSS scores. SPMS follows RRMS and usually starts around EDSS scores of 4-5. The probabilities used in the model show a low likelihood of converting to SPMS for a patient with an EDSS of less than 4 and are therefore reflective of clinical practice.

The natural history matrix is calculated using the active RRMS and SPMS natural history data with the probability of conversion from RRMS to SPMS (Table B7.3.7).

The natural history transition matrix from RRMS to RRMS states is upper triangular, such that a patient does not regress in EDSS, only progresses in EDSS or remain in their existing EDSS. This is also true for the transitions from SPMS to SPMS states. Due to the clinical nature of progressive MS, the probability of transitioning from an SPMS state to an RRMS state is 0.

Since the non-regressive nature of the London Ontario dataset is a significant limitation, data collected from the CARE-MS trials were also incorporated into the model which showed patients receiving alemtuzumab and SC IFNβ-1a regressed in EDSS. Further details of the treatment transition matrices derived directly from the trials are provided in Section B7.3.2.

Table B7.3.7 Natural history transition matrix per EDSS health state and classification based on active RRMS and SPMS transitions from the London Ontario dataset and TOWER, TEMSO

		RRMS											SPMS										
	From \ To	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
RRMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Relapses rates

EDSS state-dependent relapse rates split by MS classification were included in the model. Due to a lack of relapse data available from the London Ontario dataset or alternative registries, relapse rates were sourced from alternative literature sources, which included two studies: Patzold et al. and Held et al. [Patzold et al. 1982; Held et al. 2005].

There are advantages and disadvantages to choosing either Patzold et al. or Held et al. as a source for annualised relapse rate by years since diagnosis (Table B7.3.8). The relapse rates calculated using Held et al. has been used in the base case since these are more recent. The relapse rates calculated from Patzold et al. as per previous submissions (TA 127 and TA 254) is considered in a sensitivity analysis.

Table B7.3.8 Summary of sources for natural relapse rates

Study	Description	Strengths	Limitations
Held et al. 2005	Retrospective analysis of 821 patients of the placebo arms of the Sylvia Lawry Centre for Multiple Sclerosis database	• Fairly recent data • Large number of patients	• Relapses are not clearly defined and requires adjustment
Patzold et al. 1982	Long-term prospective analysis of 102 MS patients	• Directly in line with our requirement for relapse rate per years since diagnosis.	• The data analysed dates from 1976 to 1980 • Smaller number of patients

The relapse rates by MS classification and EDSS state and were calculated in a two step process:

Step 1: Mean annual relapse rates by years since diagnosis were derived

Held et al. conducted a multivariable Poisson regression analysis assessing the effect of disease duration and the number of relapses in the previous 24 months on the annual relapse rate. Weighted average relapse rates for 5, 10, 15 and 20 years after diagnosis were estimated using a weighted mean of annual relapse rates for patients who experienced 0, 1, 2, or 3 relapses in the previous 24 months. The regression coefficient of a gain in years since diagnosis was applied to the weighted average relapse rates to give an estimated annual relapse rate per year since diagnosis (Table B7.3.9).

Table B7.3.9 Weighted average of relapse rate per year since diagnosis derived by Held et al [Held et al. 2005]

Years since diagnosis	Weighted average
5	0.932878581

10	0.857517053
15	0.787476126
20	0.725102319

Patzold et al. conducted a regression analysis to investigate the relationship between mean annual relapse rate and the number of years since diagnosis. This regression equation was used to derive the annual relapse rates for each year since diagnosis (Table B7.3.10).

Table B7.3.10 Annual relapse rate per year since diagnosis derived from [Patzold et al. 1982]

Years since diagnosis	Annual relapse rate
1	1.613
2	1.258
3	1.051
4	0.903
5	0.789
6-7	0.656
8-9	0.518
10-11	0.410
12-13	0.320
14-15	0.244
16+	0.136

Step 2: The UK MS survey provides patient level data of the number of patients in each EDSS state by the number of years since diagnosis (Table B7.3.11). The relapses rates per year since diagnosis, derived from Held or Patzold, were applied to the number of patients from the UK MS Survey to give the number of relapses per EDSS per year since diagnosis. For each EDSS, a weighted average was taken of the relapses per year since diagnosis to give the relapse rate per EDSS. Due to the small number of patients in EDSS states 6.5 - 9, numbers were summed together to produce on rate applicable to EDSS states 7, 8 and 9. The final relapse rates by EDSS and MS classification are presented in Table B7.3.12.

Table B7.3.11 UK MS Survey patient numbers per PDDS / EDSS state by year since diagnosis [Orme et al. 2007]

			Years since diagnosis										
	Adapted PDDS scale	EDSS equivalent scale	1	2	3	4	5	6-7	8-9	10-11	12-13	14-15	16+

RRMS	0	0	2	2	1	2	6	6	3	2	0	1	3
	1	1	11	16	18	11	16	22	15	10	3	10	18
	2	2	11	16	7	17	14	13	19	19	9	5	22
	3	3	6	4	4	5	7	9	4	1	5	6	6
	4	4	6	15	7	12	13	24	8	13	6	2	17
	5	5	2	5	12	9	13	18	11	10	4	7	23
	6	6	2	3	3	5	2	6	11	2	2	6	20
	7	6.5	1	0	2	0	3	3	4	1	2	2	9
	8	7	1	0	0	0	0	0	1	1	1	0	3
	9	8	0	0	0	0	1	2	1	0	0	0	1
	10	9	1	0	0	0	0	0	0	0	0	0	1
SPMS	2	2	0	0	0	1	2	2	0	0	0	0	5
	3	3	2	0	1	1	0	4	0	1	1	0	1
	4	4	1	2	3	3	0	6	6	2	6	1	7
	5	5	6	6	5	6	7	14	17	15	10	11	35
	6	6	3	5	8	14	11	20	23	21	17	14	74
	7	6.5	2	1	3	4	5	18	16	11	19	12	78
	8	7	0	1	0	0	3	8	10	9	7	8	63
	9	8	0	0	0	0	3	5	4	7	4	5	46
	10	9	0	0	0	0	0	1	2	1	2	0	2

Table B7.3.12 Relapse rates by EDSS score and MS classification

EDSS scale	Relapse Rate			
	Base case		Sensitivity analysis	
	RRMS	SPMS	RRMS	SPMS
0	0.905	0.000	0.725	0.000
1	0.905	0.000	0.743	0.000
2	0.895	0.851	0.690	0.448
3	0.899	0.910	0.723	0.788
4	0.900	0.872	0.707	0.567
5	0.881	0.860	0.599	0.517
6	0.859	0.847	0.509	0.445
7	0.856	0.818	0.504	0.312
8	0.856	0.818	0.504	0.312
9	0.856	0.818	0.504	0.312

Source used in derivation	[Held et al. 2005; Orme et al. 2007]	[Patzold et al. 1982; Orme et al. 2007]

Treatment effect on relapse rate

To evaluate the effect of treatment with DMT on relapse rate, the ARR derived from the MTC (see Section B6.7 and Table B7.3.13) was applied to the natural relapse rate (Table B7.3.12). As discussed in Section B6.7, ARR data were not available from the PRISMS trial for SC IFNβ-1a 22µg so it has been assumed equal to SC IFNβ-1a 44µg. This is a conservative assumption since the higher dose of SC IFNβ-1a reduces relapses more than the lower dose so in fact the ARR for SC IFNβ-1a 22µg would be higher [PRISMS 1998].

Table B7.3.13 Relative risk of relapse compared to placebo sourced from mixed-treatment comparisons

Treatment	Source	Relative ARR	95% CI Lower	95% CI Higher
Alemtuzumab	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IM IFNβ-1a	Base case MTC: Post-2000, 80% RRMS MTC	0.78	0.67	0.91
IFNβ-1b	Base case MTC: Post-2000, 80% RRMS MTC	0.68	0.52	0.88
SC IFNβ-1a 44µg	Base case MTC: Post-2000, 80% RRMS MTC	0.62	0.51	0.76
SC IFNβ-1a 22µg	No results available from base case MTC so assumed ARR equal to SC IFNβ-1a 44µg	0.62*	0.51*	0.76*
Glatiramer acetate	Base case MTC: Post-2000, 80% RRMS MTC	0.64	0.53	0.76
Fingolimod	Base case MTC: Post-2000, 80% RRMS MTC	0.46	0.40	0.54
Natalizumab	Base case MTC: Post-2000, 80% RRMS MTC	0.31	0.25	0.39

* assumed efficacy of 22µg equals 44µg

Treatment effect on Relapse severity

As discussed in Section B7.2.5, the model distinguishes between relapses which lead to hospitalisation and those that do not. The source of natural history data of the proportion of relapses leading to hospitalisation was based on the results of a systematic literature review (Section 7.5.3) which found a recent study of an Irish population in which 20% of relapses lead to hospitalisation [Dee et al. 2012]. The proportion from Dee et al. is representative of the UK population.

There is limited published literature regarding the treatment effect of reducing the proportion of relapses which lead to hospitalisation, and consequently this was not included as an outcome for the MTC. Table B7.3.14 summarises the sourced literature and any assumptions used in the cost-effectiveness model. Relative risks of relapses leading to hospitalisation are applied to the proportion of patients not receiving a DMT who would be hospitalised following a relapse [Dee et al. 2012].

Table B7.3.14 Relative effects of treatments on relapses leading to hospitalisation

Treatment	Relative effects on proportion leading to hospitalisation	Risk of hospitalisation per relapse / Source	Assumptions
Alemtuzumab	0.225	CARE-MS II (Annualised rate of relapse leading to hospitalisation: alemtuzumab 0.05, SC IFNβ-1a 0.11) [Twyman et al. 2013] =0.05/0.11*0.495 (RR alemtuzumab vs. SC IFNβ-1a * RR SC IFNβ-1a vs. placebo)	SC IFNβ-1a 44µg treatment effect assumed to equate to IM IFNβ-1a
IM IFNβ-1a	0.495	TRANSFORMS IM IFNβ-1a (179 relapses, 36 hospitalised) 20.1%; FREEDOMS placebo (359 relapses, 146 hospitalised) 40.7%. Risk vs. placebo -50.5% [Haas et al. 2011]	FREEDOMS (fingolimod vs. placebo) and TRANSFORMS (fingolimod vs. IM IFNβ-1a) used to derive risk of IM IFNβ-1a vs. placebo
IFNβ-1b	0.495	-	Assumed same as IM IFNβ-1a
SC IFNβ-1a 44µg	0.495	-	Assumed same as IM IFNβ-1a
SC IFNβ-1a 22µg	0.495	-	Assumed same as IM IFNβ-1a
Glatiramer acetate	0.495	-	Assumed same as IM IFNβ-1a
Fingolimod	0.600	TRANSFORMS fingolimod 0.5mg (89 relapses, 11 hospitalised) 12.4%; FREEDOMS fingolimod 0.5mg (172 relapses, 63 hospitalised) 36.6%; FREEDOMS placebo (359 relapses, 146 hospitalised) 40.7% Risk vs. placebo -40% [Haas et al. 2011]	Weighted average of Fingolimod risk of hospitalisation from FREEDOMS and TRANSFORMS relative to placebo arm of FREEDOMS only
Natalizumab	0.600	-	Assumed same as fingolimod

Adverse events

To ensure differences in adverse events between treatment and placebo were adequately captured, the criteria for the inclusion of treatment-related adverse events within the model were:

- A difference of ≥4% in the probability of occurrence, compared to placebo. Where comparisons with placebo data were not available, adverse events with an incidence of more than 5% in the treatment arm were included. These conservative arbitrary thresholds were set to identify the most common adverse events that occur with DMTs.

- Included within section 4.4 of SmPC detailing special warnings and precautions for use. This criterion was set to identify the most severe adverse events, which significantly impact the cost and quality of life associated with treatments despite occurrence being less probable.

The sources of data for each DMT were placebo controlled studies that had been included in the sensitivity analysis MTC (All-years, 80% RRMS – see Additional Appendix 2). The frequencies of adverse events were adjusted for length of trial to give annual probability of occurrence. Unless the publications detailed otherwise, adverse events were assumed to occur equally in year 1 and subsequent years. There are placebo-controlled studies published for each of the compactors but no placebo-controlled studies have taken place with alemtuzumab.

Probabilities of adverse events for alemtuzumab were derived from incidence data from Pool C of the ISS (see Section B6.9). Adverse events with incidence ≥5% were assessed for inclusion (see Table B7.3.15).

Table B7.3.15 Adverse events of alemtuzumab included in cost-effectiveness model

Adverse event (Pool C) [Genzyme ISS 2012]	Included within model (Yes/No)	Justification
Lymphopenia	Y	Captured within cytopenias
Tachycardia	Y	Captured within infusion-associated reaction
Hyperthroidism	Y	Captured within autoimmune thyroid-related event
Hypothyroidism	Y	Captured within autoimmune thyroid-related event
Grave's disease	Y	Captured within autoimmune thyroid-related event
Vision blurred	Y	Captured within infusion-associated reaction
Nausea	Y	Captured within infusion-associated reaction
Diarrhoea	Y	Captured within infusion-associated reaction
Vomiting	Y	
Dyspepsia	Y	Captured within infusion-associated reaction
Abdominal pain	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Constipation	N	Negligible cost/utility

Nasopharingitis	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Urinary tract infection	Y	
Upper respiratory tract infection	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Sinusitis	N	Negligible cost/utility
Influenza	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Oral herpes	N	Negligible cost/utility
Bronchitis	Y	
Herpes Zoster	Y	
Back pain	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Pain in extremity	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Arthralgia	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Muscular weakness	N	Believed to be a symptom of multiple sclerosis rather than treatment-related
Muscle spasms	N	Believed to be a symptom of multiple sclerosis rather than treatment-related
Mylagia	Y	Captured within infusion-associated reaction
Headache	Y	Captured within infusion-associated reaction
Paraesthesia	Y	Captured within infusion-associated reaction
Dizziness	Y	Captured within infusion-associated reaction
Hypoaesthesia	Y	Captured within infusion-associated reaction
Dysgeusia	Y	Captured within infusion-associated reaction
Insomnia	Y	Captured within infusion-associated reaction
Depression	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Anxiety	N	Similar results were observed in the placebo arms of TRANSFORMS/AFFIRM/TEMSO
Proteinuria	N	Negligible cost/utility
Oropharyngael pain	N	Negligible cost/utility
Cough	N	Negligible cost/utility
Dyspnoea	Y	Captured within infusion-associated reaction
Pyrexia	Y	Captured within infusion-associated reaction
Chills	Y	Captured within infusion-associated reaction
Fatigue	Y	Captured within infusion-associated reaction

Chest discomfort	Y	Captured within infusion-associated reaction
Pain	Y	Captured within infusion-associated reaction
Asthenia	N	Negligible cost/utility
Influenza-like illness	Y	Captured within infusion-associated reaction
Odema Periperal	N	Negligible cost/utility
Rash	Y	Captured within infusion-associated reaction
Urticaria	Y	Captured within infusion-associated reaction
Pruritus	Y	Captured within infusion-associated reaction
Rash generalised	Y	Captured within infusion-associated reaction
Erythema	Y	Captured within infusion-associated reaction
Flushing	Y	Captured within infusion-associated reaction

Infusion related adverse events associated with alemtuzumab in the model are linked directly to the proportion of patients receiving dosage. In the base case this was [redacted] for years 1, 2, 3, 4-5, 6-50, respectively (see Section B7.5.1 for retreatment assumptions).

The annual probability of autoimmune adverse events associated with alemtuzumab (consisting of hyperthyroidism, hypothyroidism, Grave's disease and ITP) in years 2 to 5 in the model was calculated as the average of the incidence in years 2, 3, 4 and 5 from Pool C safety population [see Additional Appendix 9]. The incidence of autoimmune adverse events plateau'd to a rate of approximately [redacted] in the trials after 5 years thus are modelled to only occur up to 5 years. This observation is supported by a UK based observational study of patients on alemtuzumab [Cossburn et al. 2011] which reported that novel auto-immune disease developed in [redacted] of patients. In this cohort autoimmune disease was seen from 2 weeks after initial treatment and was most frequent 12–18 months after first treatment. No new cases of autoimmune disease were identified 60 months or more after initial treatment and risk of AID was independent of total alemtuzumab dose or interval of dosage, consistent with the SmPC requirement to continue monitoring for auto-immune disease for four years after the last dose of alemtuzumab [SmPC, 2013].

Although ITP occurred in only [redacted] patients within the pooled trial data, there was a particularly wide range of severity [Genzyme ISS 2012]. For this reason, ITP was sub-divided into 5 severities which were also associated with different treatment regimes in the trials (Table B7.3.16). The costs and utilities associated with ITP are based on a weighting of these five severities (see Sections B7.4.8 and B7.5.1).

Table B7.3.16 Breakdown of ITP severity from Pool C [Genzyme ISS 2012]

ITP treatment regime	Breakdown of ITP severity

Steroids only	[redacted]
Steroids, IVIG	[redacted]
Steroids, tranexamic acid, platelets, rituximab and IVIG	[redacted]
Steroids, platelets and rituximab	[redacted]
Treatment with steroids, platelets and IVIG	[redacted]

The probability of adverse events is shown in Table B7.3.17. There were 5 cases of nephropathies reported in the clinical trials but since the time points were unspecified, these have been assumed to occur in the first year only. Unless specified otherwise, the probability of AE occurrence in subsequent years were calculated by the total number of incidences within the 9-year follow up, divided by the number of patients at risk within that 9-year follow up from Pool C [Genzyme ISS 2012]. Unless specified otherwise, adverse events for alemtuzumab were assumed to be independent of the number of courses taken since there is no evidence to suggest a causal link between the number of courses and other adverse events. In line with the assumption that the treatment effect of alemtuzumab persists up to EDSS 7 in RRMS regardless of dosage, it has also been assumed that adverse events associated with alemtuzumab may persists up to EDSS 7 in RRMS. Once patients reach EDSS 7 or SPMS, they are assumed to receive no adverse events for alemtuzumab.

Table B7.3.17 Adverse events probabilities used in the model

	Probability (first year)	Probability (subsequent years)	Source
Alemtuzumab			Pool C: all available follow-up – Phase II and Phase III studies with extensions [Genzyme ISS 2012]
Infusion-related AE	[redacted]	[redacted]	
Autoimmune thyroid-related event	[redacted]	[redacted]	
Urinary tract infection	[redacted]	[redacted]	
Bronchitis	[redacted]	[redacted]	
Herpes Zoster	[redacted]	[redacted]	
Idiopathic thrombocytopenic purpura	[redacted]	[redacted]	
Nephropathies	[redacted]	[redacted]	
Cytopenias	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	
IM IFNβ-1a			[Jacobs et al. 1996]
Headache	33.54%	33.54%	
Influenza-like symptoms	30.38%	30.38%	
IFNβ-1b			[IFNβ MS study group 1995]
Influenza-like symptoms	18.00%	7.00%	
Injection site reaction	80.00%	47.00%	
SC IFNβ-1a 44µg			[PRISMS 1998] [Ebers 1999]
Headache	54.17%	54.17%	

Injection site reaction	43.93%	43.93%	[SPECTRIMS 2001]
Influenza-like symptoms	65.00%	65.00%	
SC IFNβ-1a 22µg			
Headache	52.00%	52.00%	
Injection site reaction	44.71%	44.71%	
Influenza-like symptoms	44.42%	44.42%	
Glatiramer acetate			[Johnson et al. 1995]
Injection site reaction	45.00%	45.00%	
Immediate post injection systemic reactions	7.60%	7.60%	
Fingolimod			[Novartis, fingolimod manufacturer submission, 2011]
Atrioventricular block, first degree	0.12%	0.12%	
Atrioventricular block, second degree	0.12%	0.12%	
Severe infection	1.17%	1.17%	
Macular oedema	0.23%	0.23%	
Natalizumab			[Biogen natalizumab manufacturer submission, 2006]
PML	0.02%	0.14%	
Anaphylactic and anaphylactoid reactions	0.72%	0.08%	
Urinary tract infection	2.00%	2.00%	
Headache	19.00%	19.00%	[Polman et al. 2006]
Fatigue	13.50%	13.50%	
Arthralgia	9.50%	9.50%	

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

As outlined in Section B7.2.5, two methods are used to calculate transition probabilities in the model.

Natural history method

Section B7.3.1 details how the natural history transition matrix (Table B7.3.8) was calculated. The relative effects of treatment on sustained accumulation of disability compared to placebo (r) obtained from the MTC (see Section B6.7 and Table B7.3.18) were used to generate treatment transition matrices.

Table B7.3.18 Relative effects of treatments on 3-month sustained accumulation of disability

Treatment	Source	Hazard ratio versus placebo	95% Lower Confidence Interval	95% Upper Confidence Interval

Alemtuzumab	Base case MTC: Post-2000, 80% RRMS MTC	[redacted]	[redacted]	[redacted]
IM IFNβ-1a	Base case MTC: Post-2000, 80% RRMS MTC	0.91	0.61	1.33
IFNβ-1b	Base case MTC: Post-2000, 80% RRMS MTC	1.21	0.68	2.16
SC IFNβ-1a 44µg	Base case MTC: Post-2000, 80% RRMS MTC	0.79	0.51	1.24
SC IFNβ-1a 22µg	Ratio of 22 µg : 44 µg from SA all-years, 80% RRMS MTC applied to base case MTC: Post-2000, 80% RRMS MTC with	[redacted]	[redacted]	[redacted]
Glatiramer acetate	Base case MTC: Post-2000, 80% RRMS MTC	0.93	0.59	1.45
Fingolimod	Base case MTC: Post-2000, 80% RRMS MTC	0.75	0.58	0.96
Natalizumab	Base case MTC: Post-2000, 80% RRMS MTC	0.58	0.40	0.84

*Calculated based on sensitivity analysis MTC applied to base case MTC (see Additional Appendix 2)

Treatment transition probabilities, p_t, for patients receiving each DMT were calculated by applying the relative effect of treatment, r, to the underlying natural history transition probabilities, p_n, where progression had occurred (e.g. from EDSS 1 to EDSS 2).

$$p_t = 1 – exp(-(-(ln(1 - p_n))r)).$$

In line with the original ScHARR model, it was assumed that the treatment effect on conversion from RRMS to SPMS is reduced such that the treatment transition probabilities are calculated as:

$$p_t = 1 – exp(-(-(ln(1 - pn))*0.5*(1+r))).$$

The probability of a patient staying in the same EDSS state was calculated as 1 minus the probability of transitioning to a greater EDSS or converting to SPMS. The resulting transition matrix for patients receiving alemtuzumab that was used in the base case analysis is given in Table B7.3.20. The transition matrices for the comparators (fingolimod, natalizumab, SC IFNβ-1a 44 µg) are in Additional Appendix 13.

Using the natural history method, applying very high hazard ratios of treatment effect may result in negative transition probabilities of staying in the same EDSS. This is important when considering the PSA results, where 95% confidence intervals are very wide. Applying a 3-month SAD treatment effect hazard ratio greater than 1.39 to the natural history transition matrix results in a negative transition probability for the transition from EDSS 0 to

EDSS 0 i.e. a negative probability of remaining in the same EDSS state. The issue to negative transition probabilities was identified by the ERG Group during the NICE appraisal of fingolimod [NICE, 2011(b)].

The solution applied in the cost-effectiveness model was if the probability of staying the same EDSS was negative, the probability distribution was adjusted such that the probability of staying the same EDSS became zero. This method assumes that if the hazard ratio is very high, i.e. worse than placebo, then the probability of remaining in the same EDSS is 0. Retaining the distribution of progressing from that state, the negative transition probability was redistributed over the probabilities of increasing in EDSS. An example of the application of this solution is given in Table B7.3.19.

Table B 7.3.19 Example of adjustment of transition probabilities to account for negative probabilities of staying in EDSS states for high hazard ratios where negative probability is N

EDSS state	0	1	2	3	4	5	6	7+	Check total
Unadjusted transition probabilities from EDSS 0									
Distribution of probabilities for progressing									
Adjustment									
Adjusted probabilities used in model									

Table B7.3.20 Alemtuzumab transition matrix for EDSS health states and MS classification

		RRMS											SPMS										
	From \ To	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
RRMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SPMS	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Direct comparison method

The alternative method of analysis is using data derived directly from the CARE-MS trials and extensions. The limitation of this analysis is that the trials were conducted only with alemtuzumab and SC IFNβ-1a 44µg so only comparisons of alemtuzumab against SC IFNβ-1a 44µg can be performed using this data. Therefore, to ensure consistency in approach for the comparisons considered and analyses undertaken, the natural history method was chosen for the base case and the direct comparison method was chosen as a sensitivity analysis.

CARE-MS I consisted of treatment-naive patients whilst CARE-MS II contained previously treated patients. The two trials and their extensions have been pooled to create the direct transition matrices for all RRMS patients treated with alemtuzumab and SC IFNβ-1a 44µg. The pooled CARE-MS treatment transition matrices for alemtuzumab and SC IFNβ-1a 44µg are shown in Table B7.3.21 and B7.3.22 respectively.

The transition matrices for the direct analysis were estimated from treatment arms in the alemtuzumab phase III trials, and reflect patients' sustained accumulation of disability as observed whilst receiving alemtuzumab or SC IFNβ-1a 44µg treatment during the trials.

Both CARE-MS trials included patients with relatively low disease severity, as shown by the lower EDSS distribution compared to the RSS EDSS distribution. Therefore, the CARE-MS trials contained a relatively mild cohort with very few patients converting to SPMS over the trial duration. Consequently, few RRMS patients converted to SPMS so the direct transition matrices are only for RRMS patients. The impact that this has is that no patients convert to SPMS, meaning that as long as they remain in EDSS 7 or lower, they are eligible to receive treatment with alemtuzumab and SC IFNβ-1a 44µg over the 50-year duration of the model. This is a significant limitation of the analysis since patients are unlikely to remain on one treatment throughout their lifetime.

The alemtuzumab and SC IFNβ-1a 44µg matrices were derived using the Multi-State Markov (MSM) package built-into the statistical software R (http://www.r-project.org/). The MSM package was used to derive transition matrices through maximum likelihood estimation. In order to combine the matrices and values for both data sets a scaling factor was used to allow the inclusion of values within the combined matrix (rows are required to sum to one in order to ensure that patients are not lost or gained between transitions). The transition probabilities were scaled by equal proportions to force the rows to sum to one.

The MSM method estimates the progression rates between disability states. It uses longitudinal individual patient data from patients with degenerative conditions. Each observation is treated independently using degeneration over a period of time to predict progression. The model makes the following assumptions:

- Transition rates are similar across studies

- The probability of transition from one state to another is constant and independent of the time spent within the state. However, the model approximates the observed mean time spent in each state

Since the extension of CARE-MS II included patients with varying treatment history (patients who had received SC IFNβ-1a 44µg previously during Phase II and III trials) only those patients who had been on alemtuzumab treatment in either CARE-MS I or CARE-MS II, and continued on with treatment post-study were included in the estimation of the transition matrices.

Data on sustained accumulation of disability were not available for the higher EDSS states from the patient level data including transitions to EDSS 9 and transitions from EDSS 8 and 9. Therefore, these data were completed with natural history progression data from London Ontario. This may be considered as a conservative assumption since London Ontario data represents disability progression of patients not on treatment, and alemtuzumab has been observed to have generally lower accumulation of disability progression versus SC IFNβ-1a 44µg; a loss of treatment effect in high EDSS states will consequently penalize alemtuzumab more than SC IFNβ-1a 44µg.

London Ontario data was applied when the number of transitions observed from an EDSS state to any other state from the alemtuzumab trials was fewer than 15. The probability of remaining in the same EDSS state was adjusted so that the probabilities from each EDSS state summed to one.

Table B7.3.21 RRMS transition matrix for alemtuzumab derived using direct trial data (Pooled CARE-MS I and CARE-MS II)

EDSS		*year i+1*										
		0	1	2	3	4	5	6	7	8	9	10
year i	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table B7.3.22 RRMS transition matrix for SC IFNβ-1a 44µg derived using direct trial data (Pooled CARE-MS I and CARE-MS II)

EDSS		*year i+1*										
		0	1	2	3	4	5	6	7	8	9	10
year i	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A comparison between the RRMS transition matrices using the two methods is given in Table B7.3.23.

Table B7.3.23 Comparison between results of natural history method and direct comparison method

Natural history method	Direct comparison method
• Upper triangular matrix, allowing only progression, not regression	• Allows modelling patents that regress in EDSS, which occurs in clinical practice
• Probability of alemtuzumab RRMS patient progressing from: o EDSS 0 is [redacted] o EDSS 1 is [redacted] o EDSS 2 is [redacted] o EDSS 3 is [redacted] o EDSS 4 is [redacted] o EDSS 5 is [redacted] o EDSS 6 is [redacted] o EDSS 7 is [redacted] o EDSS 8 is [redacted]	• Probability of alemtuzumab RRMS progressing from: o EDSS 0 is [redacted] o EDSS 1 is [redacted] o EDSS 2 is [redacted] o EDSS 3 is [redacted] o EDSS 4 is [redacted] o EDSS 5 is [redacted] o EDSS 6 is [redacted] o EDSS 7 is [redacted] o EDSS 8 is [redacted]
• Probability of progressing is fairly stable across all RRMS EDSS states	• Probability of progressing generally decreases as EDSS increases
• Allows for conversion to SPMS	• Does not allow for conversion to SPMS

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

MS has a high degree of variability in the final outcome from one patient to another suggesting there is a possibility that transition probabilities could vary over the duration of the disease [Confavreux et al. 2003]. Since the progression probabilities from the active London Ontario dataset are collected between 1972 and 1984 with 345 patients, it is anticipated that the 12-year time period sufficiently captures patient variability. In addition, the systematic review of natural history did not yield any data to support transition probabilities varying over time (see Additional Appendix 10).

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The efficacy outcome from the CARE-MS trials included time to sustained accumulation of disability, measured by the EDSS. As higher EDSS states have an increased mortality risk, slowing accumulation disease progression will result in a reduced mortality risk. See Section B7.2.5 for details of mortality sources and calculations.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical values in the model were estimated based on expert opinion. However, experts did assess the appropriateness of clinical assumptions within the model and appropriateness of comparators and populations. Ten experts were approached from a range of locations across England and Wales. Five experts, from Cambridge, Newcastle, London, Birmingham and Cardiff participated in telephone interviews. These experts had a combined MS patient population of approximately 8,700. Prior to interviews, the experts were provided with the mapped treatment pathway (Figure A2.5) and publicly available CARE-MS literature for alemtuzumab [Coles et al. 2012 (b); Cohen et al. (2012)].

The experts were asked to describe the typical treatment pathway of a RRMS patient. The experts provided appropriate comparisons for the various populations (RRMS, RES, HA) and confirmed the treatment guidelines adhered to, including stopping rules (see Section B7.2.8) [Genzyme KOL interview report, 2013]. Experts were also asked to describe the baseline characteristics of an average patient at treatment initiation to validate the baseline characteristics of the cohort entering the model. The experts agreed with the male to female ratio but believed the patients were younger (approximately 32) and generally had milder disease than the modelled cohort (EDSS < 3). Consequently, the patient baseline characteristics in terms of age and EDSS distribution have been tested in sensitivity analyses.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B7.3.24 Summary of variables applied in the base case economic model and explored in sensitivity analysis (SA)

Variable / [treatment if applicable]		Value	CI (distribution)	Reference to section in submission
Age at baseline		UK RSS: 37.9 years (SA) CARE-MS: [redacted]	Deterministic only	Patient characteristics 7.3.1
Female to male ratio		UK RSS: 2.52 : 1 (SA) CARE-MS: [redacted]	Deterministic only	Patient characteristics 7.3.1
Baseline EDSS distribution		UK RSS 0: 3% 1: 7% 2: 20% 3: 19.5% 4: 20.5% 5: 10% 6: 15.5% 7: 4.5% (SA) CARE-MS [redacted]	Deterministic only	Patient characteristics 7.3.1
3-month sustained accumulation of disability hazard ratio versus placebo	Alemtuzumab	[redacted]	[redacted](gamma)	7.3.2
	IM IFNβ-1a	0.91	0.61 to 1.33 (gamma)	
	IFNβ-1b	1.21	0.68 to 2.16 (gamma)	
	SC IFNβ-1a 44µg	0.79	0.51 to 1.24 (gamma)	
	SC IFNβ-1a 22µg	[redacted]	[redacted](gamma)	
	Glatiramer acetate	0.93	0.59 to 1.45 (gamma)	
	Fingolimod	0.75	0.58 to 0.96 (gamma)	
	Natalizumab	0.58	0.40 to 0.84 (gamma)	
Relative risk of relapse	Alemtuzumab	[redacted]	[redacted](gamma)	Relapse rates 7.3.1
	IM IFNβ-1a	0.78	0.67 to 0.91 (gamma)	
	IFNβ-1b	0.68	0.52 to 0.88 (gamma)	

	SC IFNβ-1a 44µg	0.62	0.51 to 0.76 (gamma)	
	SC IFNβ-1a 22µg	0.62	0.51 to 0.76 (gamma)	
	Glatiramer acetate	0.64	0.53 to 0.76 (gamma)	
	Fingolimod	0.46	0.40 to 0.54 (gamma)	
	Natalizumab	0.31	0.25 to 0.39 (gamma)	
All-case withdrawal probability	IM IFNβ-1a	[redacted]	[redacted] (gamma)	Discontinuations 7.3.1
	IFNβ-1b	[redacted]	[redacted] (gamma)	
	SC IFNβ-1a 44µg	[redacted]	[redacted] (gamma)	
	SC IFNβ-1a 22µg	[redacted]	[redacted] (gamma)	
	Glatiramer acetate	[redacted]	[redacted] (gamma)	
	Fingolimod	[redacted]	[redacted] (gamma)	
	Natalizumab	[redacted]	[redacted] (gamma)	
Relative risk of relapse leading to hospitalisation	Alemtuzumab	0.22	Gamma assuming standard error is 10% of mean	Treatment effect on Relapse severity 7.3.1
	Natalizumab, fingolimod	0.60		
	IFNβ, glatiramer acetate	0.49		
Probability of progression in RRMS (natural history transitions)		EDSS 0: TOWER + TEMSO EDSS 1-9: London Ontario (active RRMS)	Deterministic only	Sustained accumulation of disability 7.3.1
Probability of progression in SPMS (natural history transitions)		London Ontario	Deterministic only	Sustained accumulation of disability 7.3.1
Probability of conversion from RRMS to SPMS (natural history transitions)		London Ontario	Deterministic only	Sustained accumulation of disability 7.3.1
Natural history relapse rate		Held et al. 2005 (SA) Patzold et al. 1982	Normal assuming standard error is 10% of mean	Relapse rates 7.3.1
Natural history proportion of relapses leading to hospitalisation		Dee et al. 2012: 20%	Gamma assuming standard error is 10% of mean	Relapses leading to hospitalisation 7.3.1

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the

intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Both cost and outcomes are extrapolated beyond the period of the Phase II / III clinical trials of alemtuzumab 12mg and its comparators. Key variables within the model that are extrapolated beyond the clinical trial endpoints are:

- SAD HRs for alemtuzumab, beta-interferons, glatiramer acetate, fingolimod and natalizumab
- ARR HRs for alemtuzumab, beta-interferons, glatiramer acetate, fingolimod and natalizumab
- Withdrawal rates for beta-interferons, glatiramer acetate, fingolimod and natalizumab
- Alemtuzumab retreatment

These assumptions are addressed and justified in detail for this question.

Extrapolation of treatment effect for alemtuzumab, beta- interferons, glatiramer acetate, fingolimod and natalizumab

As discussed in Sections B7.3.1 and B7.3.2, the HRs for withdrawal, SAD and ARR are based on the base case MTC. The studies used to derive HRs in the network MTC were up to 3 years in length (see Table B6.7.6):

- Alemtuzumab studies – two studies for 2 years (CARE-MS I and II) and one for 3 years (CAMMS 223)
- Beta-interferons / glatiramer acetate studies – 8 studies (11 months to 3 years)
- Fingolimod – 3 studies (12 to 24 months)
- Natalizumab – 1 study (12 months)

A systematic literature search was undertaken to ascertain whether the HRs assumed in the MTC (from studies with follow up periods of 11-36 month period) could be assumed to apply beyond the period of the studies (see Additional Appendix 14). Only two studies were identified which had two or more arms with relevant comparators beyond the period of the studies in the MTC. These were as follows:

- Alemtuzumab versus SC IFNβ-1a 44µg up to 5 years [Coles et al. 2012 (a)]
- IFNβ-1b versus placebo – up to 16 years [Ebers et al. 2010]

A MTC for these two longer term studies could not be conducted since no common treatment link was available. However, it is possible to consider what information each study provides with regards to HRs at the time point of the base case MTC (2-3 years) and time points beyond. Due to the fact that SC IFNβ-1a 44µg, fingolimod and alemtuzumab, natalizumab are considered as the primary comparators in the model, the key data that has been

used to assess long term efficacy assumptions in the model is the CAMMS 223 extension study [Genzyme CAMMS 223 CSR]:

- 3 month SAD HRs for alemtuzumab 12mg versus SC IFNβ-1a 44µg at 2 years of [redacted], at 3 years of [redacted] and at 5 years of [redacted] (see Section 6.5.3)
- 6 month SAD HRs for alemtuzumab 12mg versus SC IFNβ-1a 44µg at 2 years of [redacted] at 3 years of [redacted] and at 5 years of [redacted] (see Section 6.5.3).
- ARR HRs for alemtuzumab 12mg versus SC IFNβ-1a 44µg at 2 years of [redacted] at 3 years of [redacted] and at 5 years of [redacted] (see Section 6.5.3).

The model allows waning of treatment effect based on the base case MTC results for the following: year 1, year 2, year 3, year 4, year 5, years 6-9 and year 10 and beyond. These intervals were chosen to align with the retreatment assumptions and where data from the CAMMS 223 study exists. The SAD HR and ARR were assumed to be a proportion of the full treatment effect (100%) for these years.

100% treatment effect is applied to years 1 and 2 for alemtuzumab since this is the shortest period of the alemtuzumab clinical trials included in the MTC (CARE-MS I and II both 2 years, CAMMS 223 3 years).

If a percentage of clinical trial effect were to be applied to years 3 to 5 based on the 3 month SAD HRs from the CAMMS 223 extension study this would be:

[redacted] of the full treatment effect based on 2-5 years HR comparison [redacted]

- or [redacted] of the full treatment effect based on 3-5 years HR comparison [redacted]

If a percentage of clinical trial effect were to be applied to years 3 to 5 based on the 6 month SAD HRs from the CAMMS 223 extension study this would be:

- [redacted] of the full treatment effect based on 2-5 years HR comparison [redacted]
- or [redacted] of the full treatment effect based on 3-5 years HR comparison [redacted]

As outlined, no comparative data was identified that provided valuable information on HR for any comparators in the model other than alemtuzumab 12mg and SC IFNβ-1a 44µg. A decision was therefore made in this context to apply 100% treatment effect to the time period 3-5 years in the model. The basis of this decision was:

- Any narrowing of effect between alemtuzumab 12mg and SC IFNβ-1a 44µg in the CAMMS 223 extension study is relatively small with relative efficacy levels related to slowing SAD ranging from [redacted] of that seen in the 2-3 period when followed up to 5 years

- CAMMS 223 extension, 2 year, 3 year, 4 year and 5 year ARR RR versus SC IFNβ-1a 44µg is [redacted] respectively
- No relevant data on maintenance or waning of treatment effect exists for other comparators and assuming 100% treatment effect for alemtuzumab 12mg in years 3-5 has been matched with the same assumptions for all other comparators for the base case recognising that this assumption is best tested through scenario sensitivity analysis

Given the absence of any relevant data for alemtuzumab 12mg or its comparators beyond year 5, 100% treatment effect has been assumed in this time period recognising that this assumption, in the absence of data, is best tested through scenario sensitivity analysis (see Section B7.6).

Potential reasons why it is thought that no other relevant additional information other than the CAMMS 223 extension study exists to extrapolate MTC derived efficacy levels are:

- Although as outlined above data exists for IFNβ-1b versus placebo up to 16 years, in broad terms it is thought to support the view that IFNβ-1b at all time points was doing no better than placebo which has limited value in deciding how to apply a reduction in MTC derived efficacy beyond a 2 year period. Confirmed progression of disability for IFNβ-1b versus placebo at 3 years was 28% versus 28%, at 4 years 47% versus 46% and at 16 years the percentage reaching EDSS 6 was 45.8% versus 38.8% [IFNBMSSG 1995]
- A number of single arm studies with long term data were identified. It would seem that these provide limited information on how HRs for sustained accumulation of disability and relapses vary with time since they allow no comparison with placebo or active comparators to consider how relative efficacy varies.
    - Fingolimod 0.5mg 3 month SAD at year 2 of 18% and at year 4 26% [Kappos et al. 2010]; 6 month SAD of 24% at year 3 [Comi et al. 2010], 29%-40% at year 5 [Montalban et al. 2011] and 30-47% at year 7 [Antel et al. 2012]
    - SC IFNβ-1a 22µg and SC IFNβ-1a 44µg which demonstrated the percentage with 1 point increase in EDSS scores from baseline at 3 years of 39% and 35% respectively [Freedman et al. 2005]
- A number of single arm studies were identified which provide information on mean / median changes in EDSS scores from baseline. This data is considered to be of limited value because of the absence of a comparator to allow changes in relative efficacy over time to be assessed and also because of conceptual problems in using mean EDSS change as a proxy to determine what is happening with percentage SAD HRs.

- A mean increase in EDSS scores compared to baseline of 0.96 ITT for patients initiated on glatiramer acetate over a 15-year period [Ford et al. 2010]
- A mean increase in EDSS scores compared to baseline of 0.309 for patients on IM IFNβ-1a 30µg over a 4-year period [Ford et al. 2010]
- Additionally, as described above, a study was identified comparing IFNβ-1b and placebo. A median increase in EDSS scores for patients on IFNβ-1b versus placebo of 2.5 versus 3.0 respectively over a 16-year period was reported [Ebers et al. 2010]

However the value of using changes in mean / median changes in EDSS as a proxy for SAD rates is conceptually problematic. This is because:

- Unlike % SAD it is not considered an appropriate efficacy measure. Existing EMA guidelines on the assessment of MS treatments and also in the revised draft guidelines, it is stated "the mean change in EDSS score from the baseline is not an appropriate efficacy parameter. Acceptable efficacy parameters endpoints are the time to reach progression or the proportion of individuals who have shown progression at a pre-specified time" [EMA 2006, EMA 2012]

- The problems of using mean / median EDSS changes as a proxy for SAD rates in the model are further demonstrated by comparing the mean increases in EDSS from baseline demonstrated in the 3 interferon / glatiramer acetate studies over time outlined above (0.309 to 2.5) and the reduction in EDSS compared to baseline observed in the long term alemtuzumab studies:
    - Mean decrease in EDSS score of [redacted] compared to baseline in CAMMS 223 extension study at year 5 [Genzyme CAMMS 223 CSR]
    - Median EDSS score decreased by [redacted] compared to baseline in Cambridge observational study over a median follow up period of 7.1 years [Tuohy et al. draft manuscript]
    - CARE MS I and II extension studies showed a similar decrease in mean EDSS scores from baseline of [redacted] and [redacted] respectively [Fox, 2013]
    - The fact that mean / median EDSS scores can be improved from baseline even though there are a certain proportion of patients whose EDSS scores are worse than baseline (as measured by percentage SAD rates) is because there are a certain proportion of patients whose EDSS scores improve compared to baseline. Changes in mean /median EDSS scores from baseline are capturing both worsening of EDSS scores and improvements (and patients staying the same) compared to baseline and this makes it difficult to use them as proxy for a measure (% SAD) which captures only the proportion of patients whose EDSS scores worsen.

Long term assumptions about retreatment rates with alemtuzumab are considered on page 301 (Section 7.5.1)

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table B7.3.25 Assumptions with justifications, used in the cost-effectiveness model

Assumption	Justification
Model structure	
The model does not include transitions or progression to EDSS state 10 (i.e. MS related death) directly into the transition matrices. Rather, it uses the mortality multiplier by MS state to account for the increased mortality in higher EDSS states.	Pokorski et al. provided evidence that the risk of mortality increases as MS progresses [Pokorski et al. 1997]. To account for the increased mortality risk with disease state as well as the increased mortality risk with age, mortality is captured separately from the transition matrices.
Progression from RRMS to SPMS results in an increase in EDSS by 1.	This is in line with the original ScHARR model. A conversion from relapsing-remitting to progressive disease is an indication of an increase in disability that will likely result in an increase on the EDSS scale of 1, in the one year period of conversion.
Patients are monitored continuously whilst in RRMS and for four years following conversion from SPMS.	Patients are required to receive treatment for four years following their last dose of alemtuzumab [Alemtuzumab SmPC]. Since patients were not individually tracked in the model, it was not possible to track patients for a period of four years following last dose so a conservative assumption was made to track all patients in RRMS (thus still on treatment).
Patients are eligible to experience autoimmune related adverse events for five years following their last dose of alemtuzumab and therefore incur the subsequent costs and disutilities for the first five years.	The incidence of autoimmune adverse events plateau'd in the trials after 5 years [Cossburn et al. 2011] so the same assumption has been made in the economic model.
Half cycle correction	
A cohorts disease status and relapse events at each cycle are from mid-year estimates.	Avoids over- or under-estimation of disease status and severity in the model.
Costs and utilities are applied to a mid-year estimate of the cohort distribution.	Avoids over- or under-estimation of cost and QALYs from the model.
At any point of time all patients must exist in one of the health states which are a combination of disease state and EDSS score.	Mid-year estimates provide a snapshot of the cohort in terms of disease state and EDSS for one cycle. A patient cannot be 'transitioning' between states; they switch directly from being in one state to another.
No patient is exposed to treatment effects, withdrawals, mortality, and progression risks more than once in any individual annual cycle.	Mid-year estimates are taken from the cohort at the start of the cycle, once patients have withdrawn from DMT to BSC (see Figure B7.3.3). Mortality and treatment effect on sustained accumulation of disability takes place between this start and end of the cycle.
Treatment effect	
The results of the mixed treatment comparison that was limited to inclusion of studies with ≥80% RRMS populations are representative of treatment effects in an	The MTC with 100% RRMS inclusion criteria excluded a number of key studies. See Section B6.7.9 and additional appendix 2 for full details regarding the criteria chosen for the MTC.

RRMS population.	
Sustained accumulation of disability and relapses are modelled independently, with independent treatment effects being applied to each.	Some treatments may be more effective in reducing relapses than slowing disease progression, or vice versa. Modelling the two outcomes separately shows the impact that the different costs and QALYs associated with a reduction is sustained accumulation of disability and number of relapses have on the cost-effectiveness of treatments.
All comparator treatments have no sustained treatment effect, only instantaneous, i.e. once a patient stops administering treatment they do not receive any treatment effect the following year as they switch to best supportive care.	There is no evidence to suggest that once a patient has discontinued treatment they should have any sustained benefit.
The effect of alemtuzumab is sustained even in years where a patient does not receive a dose	An additional analysis focusing on patients who received exactly 2 treatment courses of alemtuzumab 12mg during the original 36-month study period (N=161) has been performed. The results suggest that the effects of alemtuzumab on relapse rate and 6-month SAD are able to be maintained up to at least 5 years (4 years after last treatment) (see Section 6.5.3). In addition, there is evidence supporting a sustained treatment effect of up to 7 years in a study where the majority of patients received only two cycles of alemtuzumab [Tuohy et al. draft manuscript]. Thus, in the base case, a sustained treatment effect is modelled over the full time horizon. The sensitivity of the model to assumptions around extrapolation of treatment effect is explored in scenario analyses (see Section B7.6).
In the base case, the treatment effect is assumed to be constant and not degrade over time.	There is no evidence beyond 12 years to indicate that the effect of alemtuzumab wanes over time thus the base case is 100% efficacy over the time horizon of the model (see Section B7.3.3 and 7.3.7). As discussed in Section B7.3.7, a systematic review evaluated the long-term efficacy of comparator treatments and found efficacy persisted up to approximately 5 years. However, it is optimistic to assume the treatment effect will persist over the full 50 years of the model. Therefore, to test the sensitivity of the model to waning treatment effect, scenario analyses have been performed based on results of the systematic review for long term efficacy.
Treatment effect is reduced by 50% whilst patients convert from RRMS to SPMS.	This assumption is implemented in the calculation of treatment transition matrices. It was an assumption made within the original ScHARR model [Chilcott et al. 2003]. There is user flexibility around this assumption.
Withdrawal	
Patient withdrawals are assumed to happen at the start of the year; therefore treatment costs and effects are taken for the cycle of switching to best supportive care.	To avoid double-counting, patient withdrawals occur at the start of the year, before mortality and disease progression. As seen in Figure B7.3.3, mid-year estimates are taken following withdrawal.
Patients can withdraw from a comparator treatment in any year; in the base case the probability of withdrawal is reduced by 50% after year 2.	All-cause annual withdrawal rates of comparator treatments have been derived from 2-year odds ratio for teriflunomide (used in teriflunomide STA) thus a full withdrawal rate has been used for years 1 and 2. As discussed in Section B7.3.7, it is anticipated that

	following two years on treatment, a patient is likely to be more tolerant to adverse events and thus the all-cause discontinuation would decrease. The sensitivity of the model to this scenario has been tested in one-way sensitivity analysis.
Relapse classification	
Relapses can be classified into relapse with and without hospitalisation, with associated rates, costs and disutility weights.	The costs associated with relapses leading to hospitalisation are significantly higher than the costs of relapses not leading to hospitalisation. To assess the impact of a treatment on reduction of relapse costs and utilities, it is essential to measure these two relapse severities separately.
The proportion of relapses leading to hospitalisation is the same for: all beta-interferons and glatiramer acetate; and fingolimod and natalizumab.	The proportion of relapses which lead to hospitalisation is not well measured in MS trial data. Therefore, they are few sources of evidence. One source reports the proportion for IM IFNβ-1a, which is then assumed to represent the proportion for SC IFNβ-1a, IFNβ-1b and glatiramer acetate. The proportion for fingolimod is used to represent natalizumab also.
Cycle length and time horizon	
The model adopts one-year cycles, over a maximum 50-year time horizon.	Following the NICE reference case, a 50-year lifetime horizon is used to measure the full impact of treatments on costs and QALYs [NICE 2008]. Although shorter time horizons have been used in previous MS submissions, the 50-year time horizon was used in the appraisal of fingolimod and was deemed to better represent the lifetime perspective for the patients in the model [NICE 2011(b); Biogen 2006]. A patients EDSS is measured at least once every 6 months [Genzyme KOL interview report 2013], but a one year time horizon is used as this is believed to accurately capture disease progression.

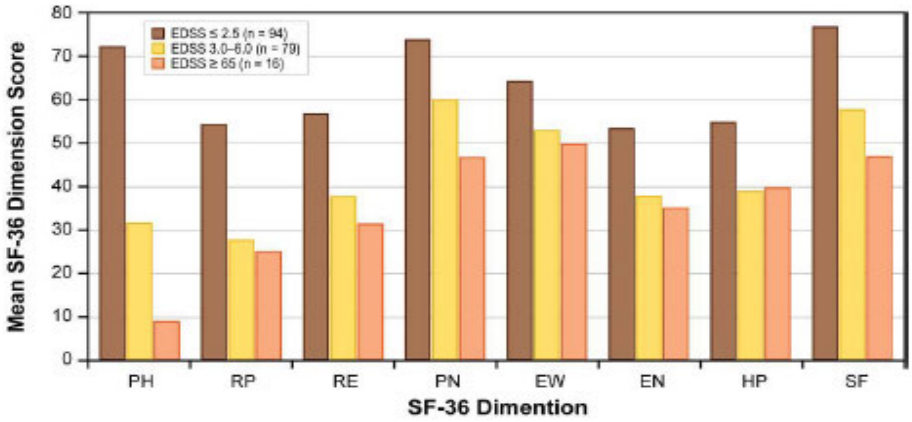
7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

MS has a significant negative impact on the health-related quality of life (HRQL) of patients [Aronson 1997]. It has been shown that disability progression (as measured by EDSS) significantly impacts HRQL [Gray et al. 2009; Kobelt et al. 2006]. As detailed in Section B7.4.6, in later stages of the disease, a patient's quality of life is worse than death [Orme et al. 2007]. These studies have shown a strong negative correlation between increases in EDSS and decreases in HRQL as measured by the EQ-5D or condition specific instruments (Figure B7.4.1). Consequently, this has been captured as the primary driver of quality of life differences in the cost-effectiveness model (see Section B7.4.6).

Figure B7.4.1 Health-related quality of life and disability levels [Novartis 2011]



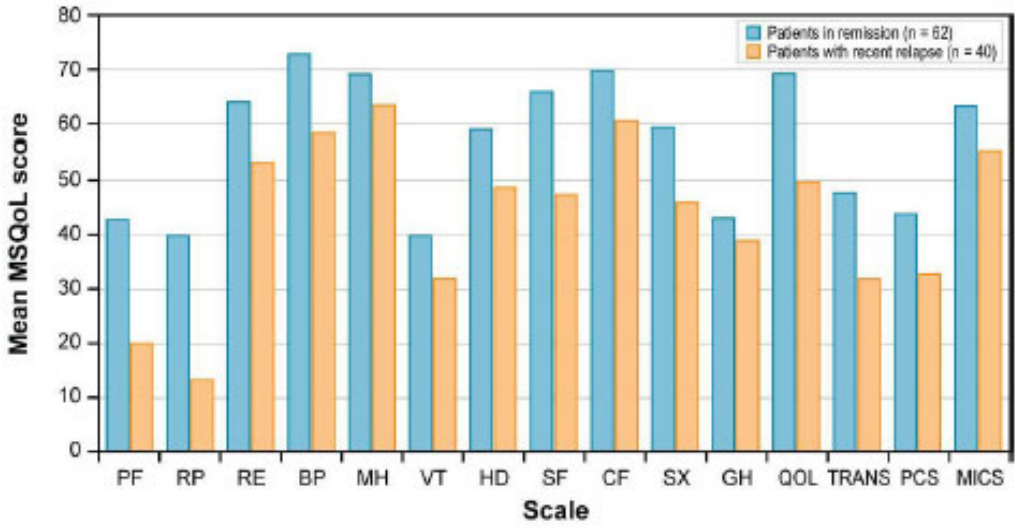
EDSS, Expanded Disability Status Scale; HP, Health Perceptions; HRQL, health-related quality of life; EN, Energy; EW, Emotional Well-Being; PH, Physical Health; PN, Pain; RE, Emotional Role Limitations; RP, Physical Role Limitations; SF, Social Function.

* A higher score indicates increasing disability. The SF-36 Health Survey measures HRQL, with higher scores indicating better HRQL.

Source: Miller et al., 2006.

In addition, relapses also have an impact on HRQL (Figure B7.4.2) and have also therefore been captured within the cost-effectiveness model (see Section B7.4.6). Relapses may result in hospitalisation and be associated with a level of disability that disrupts work, social and family life [Stolp-Smith et al. 1998; Yorkston et al. 2003; McCabe et al. 2005; De Judicibus et al. 2007].

Figure B7.4.2 Health-related quality of life and relapses [Novartis, 2011]

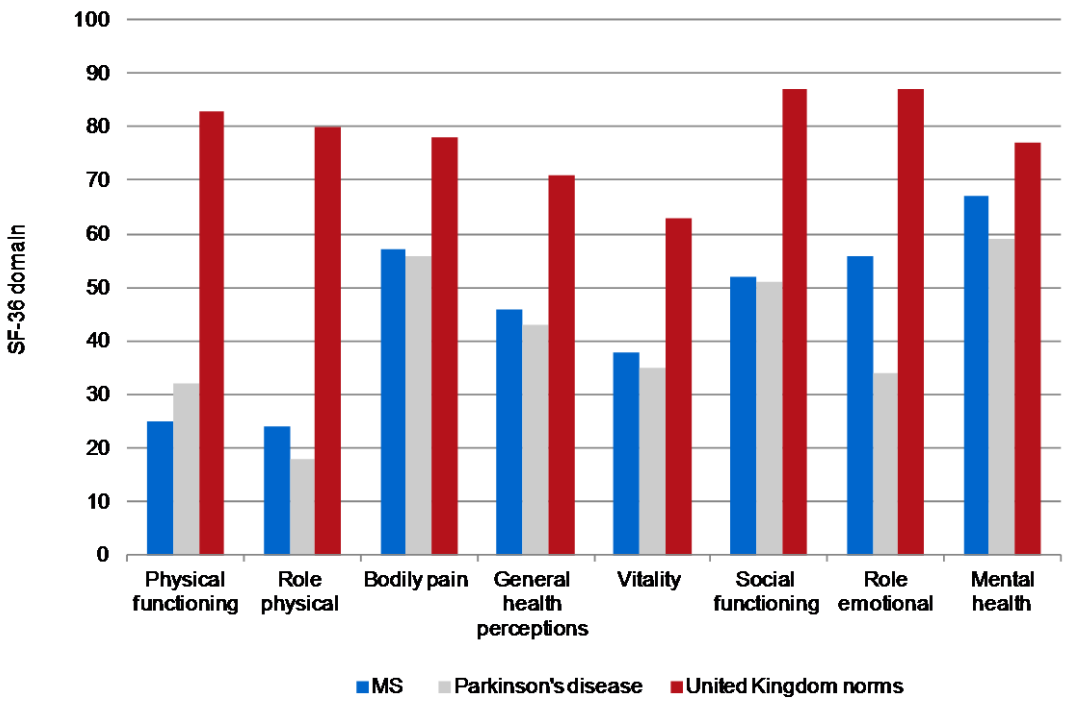


BP, Bodily pain; CF, Cognitive function; GH, General health; HD, Health distress; MH, Mental Health; MICS, Mental health composite score; PCS, Physical health composite score; PF, Physical function; QOL, Overall quality of life; RE, Role emotional; RP, Role physical; VT, Energy/vitality; SF, Social function; SX, Sexual function; TRANS, Change in health.

As well as impacting on day to day life roles, MS can diminish HRQL by interfering with the ability to work which in turn causes economic burdens. Symptoms that affect HRQL may include impaired mobility, fatigue, weakness, depression, pain, spasticity, cognitive impairment, sexual dysfunction, bowel and bladder dysfunction, vision and hearing problems, seizures, and swallowing and breathing difficulties [Zwibel et al. 2011]. Even in its early stages, these symptoms can undermine patients' confidence and restrict professional and personal activities. Symptoms can result in depression and isolation, further magnifying the consequences of reduced economic activity [Ford et al. 2001]. The symptoms of MS increase as a patient progresses though the EDSS thus incurring lower quality of life. Treatments which slow sustained accumulation of disability will therefore prolong the mobility of patients, improving quality of life.

Studies evaluating the impact of MS on HRQL using generic scales consistently show substantial negative effects from the disease, particularly in physical functioning. There are also significant effects on social and mental functioning. In the UK, MS patients were found to have worse health than the UK general population for all eight domains measured by the Short Form-36 (SF-36) (Figure B7.4.1) [Riazi et al. 2003]. As seen in Figure B7.4.3 when compared with patients with Parkinson's disease, MS patients had significantly lower mean scores for physical function (difference 11 points; $P<0.001$) but higher scores for the mental health dimension (difference 6 points; $P<0.05$) [Riazi et al. 2003].

Figure B7.4.3 Short Form-36 (SF-36) scores in MS patients compared with patients with Parkinson's disease and UK norms [Riazi et al. 2003]



7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As a progressive disease, disability from MS increases substantially over time. Ultimately, significant changes in HRQL are observed as EDSS increases due to disease progression (Section B7.4.1). Relapses contribute to HRQL deterioration but are usually only observed over the course of the relapse [Orme et al. 2007; Novartis 2011]. Conversion to SPMS also results in an additional HRQL loss [Orme et al. 2007]. Other factors such as time since diagnosis may impact HRQL [Orme et al. 2007] but these are less pronounced.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section B6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.

- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The following quality of life data was collected in the pivotal trials:

- CAMMS 223: Patients were asked to fill out SF-36 questionnaires every 6 months through 3 years.
- CARE-MS I: The SF-36 was administered at baseline and months 12 and 24, or at early discontinuation. The FAMS and the EQ-5D were administered at baseline and every 6 months thereafter until month 24 or at early discontinuation.
- CARE-MS II: The SF-36 was administered at baseline and months 12 and 24, or at early discontinuation. The FAMS and the EQ-5D were administered at baseline and every 6 months thereafter until month 24 or at early discontinuation.

The SF-36 questionnaire consists of 36 items grouped into 8 subscales or domains designed to assess generic health-related quality of life in healthy and ill adult populations. The physical component score reports the domains of physical functioning, role-physical, bodily pain, and general health; and the mental component score reports the domains of mental health, role-emotional, social functioning, and vitality.

The FAMS is a patient-reported, MS-specific, HRQL questionnaire. The FAMS contains 58 items on 7 clinically relevant scales including mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being and additional concerns.

The health dimensions sampled in the EQ-5D are mobility, self-care, usual activities (role limitations), pain/discomfort, and anxiety/depression. The EQ-5D covers five domains of HRQL (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), with three levels of answers (no, some, and severe problems).

HRQL results from CARE-MS trials are presented in Sections B6.5.1 and Figure B7.4.4. However, these data were not available at the time of submission for implementation into the model.

[redacted] **Observed EQ-5D Utility Score in CARE-MS trials**

[redacted]

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

EQ-5D data were sourced from the literature and thus mapping was not required.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic review was conducted to obtain all relevant HRQL studies in MS. The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review questions:

- *"What is the utility of patients and carers with MS?"*
- *"What is the disutility of patients who experience a relapse after treatment for multiple sclerosis?"*
- *"What is the disutility of patients who experience an adverse event after treatment for multiple sclerosis?"*

Section 10.12 details the search strategies, databases searched and subsequent results from the database sites searched, resulting in 10 studies that met inclusion/exclusion criteria and as such were identified as evaluating quality of life in MS.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Of the 10 studies included in the full review, 2 were implemented in the model and are summarised in Table B7.4.1 below.

Table B7.4.1 Summary of identified quality of life studies implemented in the model

Orme et al. 2007	
Population in which health effects were measured	Subjects were people with MS in the UK identified by a database managed by a UK charity (the MS Trust).
Information on recruitment	A postal questionnaire was sent to 12,968 people in a database managed by the MS Trust as an insert to the February 2005 edition of the UK MS Trust quarterly newsletter "Open Door".
Interventions and comparators	Respondents were asked whether they were currently taking MS treatment and if so whether it was glatiramer acetate, or beta-interferon. Results were not presented.
Sample size	2,048 patients
Response rates	The number of questionnaires returned was 2,708 (20.9%) and 2,048 (15.8%) were suitable for analysis.
Description of health states	A cross-sectional study of people with MS.
Adverse events	Not collected.
Appropriateness of health states given condition and treatment pathway	Appropriate.
Method of elicitation	EQ-5D.
Method of valuation	Questionnaires were completed by the patient or a carer on behalf of the patient.
Mapping	N/A
Uncertainty around values	See confidence intervals below
Consistency with reference case	Consistent with reference case.
Results with confidence intervals	Three quarters of respondents are female and the mean age of the sample is 51.4 years. First symptoms are reported at 32 years. The type of MS reported is slightly biased toward SPMS and RRMS disease, although all three types are well represented. More than three quarters of the population report moderate or severe disease (EDSS 4 or greater) and 29% of the sample reported a relapse in the preceding 3 months. Coefficients from regression analysis for utility derived from EQ-5D:

Parameter	Coefficient	95% CI
Reference case	0.870	(0.782, 0.958)
EDSS 1–1.5	−0.071	(−0.165, 0.023)
EDSS 2–2.5	−0.165	(−0.259, −0.072)
EDSS 3–3.5	−0.296	(−0.398, −0.195)

	EDSS 4–4.5	−0.260	(−0.3□4, −0.167)
	EDSS 5–5.5	−0.352	(−0.444, −0.260)
	EDSS 6	−0.412	(−0.505, −0.319)
	EDSS 6.5	−0.408	(−0.502, −0.314)
	EDSS 7–7.5	−0.573	(−0.670□ −0.477)
	EDSS 8–8.5	−0.919	(−1.017, −0.820)
	EDSS 9–9.5	−1.065	(−1.2□0, −0.919)
	People with MS who have suffered a recent relapse also have a significant utility decrement (−0.071); 95% CI (−0.096, −0.046).		
Appropriateness of the study for cost-effectiveness analysis	Appropriate.		
Gani et al. 2008			
Population in which health effects were measured	The model was parameterised with data from a UK Multiple Sclerosis (MS) Survey 2005 and data from the AFFIRM study, a 2-year multicentre, randomized, double-blind, placebo-controlled trial of natalizumab in RRMS patients. Additional data were sourced from literature.		
Information on recruitment	The AFFIRM study involved 942 patients who were randomly assigned to receive either natalizumab (at a dose of 300 mg; n = 627) or placebo (n = 315), both by intravenous infusion every 4 weeks, and was the largest published placebo-controlled RRMS trial to date. Data from the UK MS Medical Resource Utilisation Survey was conducted in 2005 and involved data collected from 2,048 MS patients across the UK.		
Interventions and comparators	Natalizumab compared with IFNβ, glatiramer acetate and best supportive care.		
Sample size	942 patients from the AFFIRM study, 2,048 patients from the UK MS survey plus additional data sourced from literature.		
Response rates	The number of questionnaires returned was 2,708 (20.9%) and 2,048 (15.8%) were suitable for analysis.		
Description of health states	Patients with RRMS and SPMS.		
Adverse events	Applied the disutility rates of 0.156 for interferon-treated patients and 0.066 for GA-treated patients for each year included in the model.		
Appropriateness of health states given condition and treatment pathway	Appropriate.		
Method of elicitation	EQ-5D.		
Method of valuation	Results from the UK MS survey and literature.		
Mapping	N/A		

Uncertainty around values	Not given.
Consistency with reference case	Consistent with reference case.
Results with confidence intervals	The average length of a relapse is estimated to be 46 days. Carer disutility was extracted: **Table II.** Utilities of caregivers by Kurtzke Extended Disability Status Scale (EDSS) score[20] EDSS score — Average caregivers disutility per patient 0.0 — 0.00 1.0 — 0.00 1.5–2.0 — 0.00 2.5–3.0 — 0.01 3.5–4.0 — 0.01 4.5–5.0 — 0.02 5.5–6.0 — 0.03 6.5–7.0 — 0.05 7.5–8.0 — 0.11 8.5–9.5 — 0.14
Appropriateness of the study for cost-effectiveness analysis	Appropriate.

Utility by health state

In the base case, utility weights were based on a published regression of quality of life responses from a survey of patients and carers of patients with MS (Table B7.4.2). EQ-5D utility scoring system was applied, with respondent domain scores converted to a single utility weight using the UK value set [Orme et al. 2007].

Table B7.4.2 EDSS utilities [Orme et al. 2007]

EDSS state	0	1	2	3	4	5	6	7	8	9
RRMS	0.870	0.799	0.705	0.574	0.610	0.518	0.460	0.297	-0.049	-0.195
RRMS LCI	0.782	0.617	0.523	0.384	0.428	0.338	0.279	0.112	-0.289	-0.428
RRMS UCI	0.958	0.981	0.886	0.763	0.791	0.698	0.642	0.481	0.138	0.039
SPMS	0.825	0.754	0.660	0.529	0.565	0.473	0.415	0.252	-0.094	-0.240
SPMS LCI	0.706	0.541	0.447	0.308	0.352	0.262	0.203	0.036	-0.365	-0.504
SPMS UCI	0.944	0.967	0.872	0.749	0.777	0.684	0.628	0.467	0.124	0.025

Relapse disutility

The utility loss for relapse in the UK was sourced from Orme et al [Orme et al. 2007]. Currently no UK studies have been identified which report utility values by relapse type. However, a US study has reported considerably higher disutilities for relapses leading to hospitalisation and relapses that do not, -0.302 versus -0.091 respectively [Prosser et al. 2004]. The disutility associated with relapses not leading to hospitalisation in the US source (-0.091) corresponds well with the value reported for the disutility of a relapse in the UK (-0.071) [Orme et al. 2007; Prosser et al. 2004]. Therefore, to derive a disutility of relapses leading to hospitalisation in the UK, we applied the increase observed for severe relapses in the US study ((0.302-0.091)/0.091)=2.32% to the average UK disutility of relapse, equating to -0.2356.The average duration of a relapse, sourced from Gani et al. (46 days = 1.51 months) is combined with the disutility during a relapse to give the disutility per relapse.

Caregiver disutility

Disutility for carers has been included in the model using the method developed by Gani et al [Gani et al. 2008]. As actual measurements were not available, Gani et al. assumed that disutility had a maximum value of 0.14, based on the value accepted by NICE in an assessment of treatments for Alzheimer's Disease. The disutility for MS carers by patient EDSS score was calculated as the product of the percentage of time spent caring and the maximum disutility of 0.14. This was then divided by the maximum percentage of time spent caring, which occurred at EDSS 8.5–9.5. This provided an index of disutilities from 0.00 at EDSS 0 to 0.14 at EDSS 8.5–9.5. The percentage of time spent by friends and family caring for a person with MS was available from the UK MS Survey by EDSS score. The carer disutilities by EDSS are given in Table B7.4.3.

Table B7.4.3 Carer disutility used in the model [Gani, 2008]

EDSS state	0	1	2	3	4	5	6	7	8	9
Disutility	0.000	-0.001	-0.003	-0.009	-0.009	-0.020	-0.027	-0.053	-0.107	-0.140

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

EQ-5D values split by EDSS used in the base case model were derived from the literature [Orme et al. 2007]. These values were generally higher than the mean EQ-5D recorded in the CARE-MS trials (Figure B7.4.4). However, this is to be expected since the CARE-MS trials represented a cohort with lower average EDSS scores than the UK RSS cohort (see Section B7.3.2). One important difference is that the Orme study is specific analysis of UK patients' quality of life, whereas the CARE-MS trials are international studies.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

As described in section B7.3.1, the criterion for inclusion of adverse events within the model of ≥4% difference from placebo captures the common events associated with DMTs whilst the second criterion of included in Section 4.4 of the SmPC captures the more sever adverse events. Disutilities due to autoimmune conditions did not occur after year 5 due to the plateau imposed (see Section 7.3.1).

The disutility of influenza like symptoms was derived from a UK population-base study [van Hoek et al. 2011]. The final QALY loss due to the whole period of disease was 0.0075 for the influenza like symptoms group which lasted 8.7 days. The annual disutility is therefore:

$$-0.0075 / 8.7 \times 365 = -0.315$$

It is conservatively assumed that DMT associated influenza-like symptoms are only a quarter of this QALY loss, equating to an annual disutility of 0.08.

The total disutility of an event occurring is calculated using instantaneous disutility, multiplied by the duration that the event is likely to occur. Since there is so much variation in how long an event is likely to occur, and limited literature, several assumptions have been made regarding duration. Occurrences of infusion and injection-associated adverse events are assumed to last one day following each administration. Table B7.4.4 shows the disutilities and durations of adverse events in the model.

Table B 7.4.4 Utilities of adverse events, when combined with expected duration of event

	Utility of event	Source of utility of event	Utility assumptions	Duration of event	Source for duration of event	Annual disutility
Alemtuzumab						
Infusion-associated reaction	-0.011	[Boye et al. 2011]	Same as injection-site reaction for interferons	5 days	As infusion-related event in CARE-MS trials was defined as occurring within 24 hours of dose	-0.0002
Bronchitis	-0.01	[Sander et al. 2006]		2 weeks	Assumption	-0.0004
Herpes zoster	-0.026	[van Hoek, 2009]	QALY loss from herpes zoster at age 40	2.1 months	Assumed that 90% of patients will require 1	-0.0046

					months treatment and 10% will have severe herpes zoster requiring hospitalisation	
Urinary tract infection	-0.1000	[Biogen 2006]		2 weeks	[Biogen 2006]	-0.0039
Autoimmune thyroid-related adverse event	-0.11	[Razvi et al. 2005]		1 year	Assumption	-0.1081
Nephropathies	-0.29	[Brennan et al. 2007]	TBC	3 years	Assumption	-0.8700
ITP (treatment with steroids only)	-0.09	[McMillan, 2008]		0.5 months	Assumption	-0.0038
ITP (treatment with steroids, IVIG)				0.25 months		-0.0019
ITP (treatment with steroids, tranexamic acid, platelets, rituximab, IVIG)				1 month		-0.0075
ITP (treatment with steroids, platelets, rituximab)				2 months		-0.0150
ITP (treatment with steroids, platelets, IVIG)				2.7 months		-0.0203
ITP overall				0.9 months		-0.0065
Cytopenias	0		Negligable	0	Negligable	-0.0000
Vomiting	-0.103	[Lloyd et al. 2006]	Includes diarrhoea	1 week	Assumption	-0.0020
Natalizumab						
Fatigue	-0.073	[Nafees et al. 2008]	Sourced from small cell lung cancer study	1 week	Assumption	-0.0014
Arthralgia	-0.040	[Sullivan et al. 2006]	Based on ICD-9 719 Joint Disorder	1 month	Assumption	-0.0034
Headache	-0.030	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
PML	-0.200	[Biogen 2006]		2 weeks	[Biogen 2006]	-0.0078
Anaphylactic and anaphylactoid	-1.000	[Biogen 2006]		1 week	[Biogen 2006]	-0.0194

reactions						
Urinary tract infection	-0.100	[Biogen 2006]		2 weeks	[Biogen 2006]	-0.0039
Glatiramer acetate						
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (every day [Copaxone SmPC])	Assumption	-0.0110
Immediate postinjection systemic reactions	-0.041	[Sullivan et al. 2006]	Based on ICD-9 413 Angina Pectoris	0.5 days	Assumption	-0.0001
Fingolimod						
Atrioventricular block, first degree	-0.289	[Novartis 2011]	NHS Reference Cost (EB07H) Arrhythmia or conduction disorders without complications	1 days	Assumption	-0.0008
Atrioventricular block, second degree	-0.289	[Novartis 2011]	NHS Reference Cost (EB07H) Arrhythmia or conduction disorders with complications	1 days	Assumption	-0.0008
Severe infection	-0.089	[Kappo et al. 2010; Novartis 2011; van Hoek et al. 2009]	Weighted disutility of respiratory infection (67%), herpes infection (10%), influenza-like infection (15%) and UTI (9%) based on FREEDOMS trial UTI disutility from natalizumab submission, herpes disutility from Van Hoek et al. influenza disutility from Van Hoek et al. 2011, and respiratory infection assumed same as influenza-like symptoms	2 weeks	Assumption	-0.0035
Macular oedema	-0.040	[Novartis 2011]		3 months	Assumption	-0.0100

IM IFNβ-1a						
Headache	-0.030	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (once weekly [Avonex SmPC])	[van Hoek, 2011]	-0.0114
SC IFNβ-1a 44µg						
Headache	-0.030	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (thrice weekly [Rebif SmPC])	[van Hoek, 2011]	-0.0343
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (thrice weekly [Rebif SmPC])	Assumption	-0.0047
SC IFNβ-1a 22µg						
Headache	-0.0297	[Sullivan et al. 2006]	Based on ICD-9 346 Migraine	2 days	Assumption	-0.0002
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (thrice weekly [Rebif SmPC])	[van Hoek, 2011]	-0.0343
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (thrice weekly [Rebif SmPC])	Assumption	-0.0047
IFNβ-1b						
Influenza-like symptoms	-0.08	[van Hoek, 2011]		1 day every dose (every other day [Betaferon SmPC])	[van Hoek, 2011]	-0.040
Injection site reaction	-0.011	[Boye et al. 2011]	Sourced from study evaluating diabetes population	1 day every dose (every other day [Betaferon SmPC])	Assumption	-0.0055

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B7.4.5 Summary of quality of life values for cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
RRMS	EDSS 0: 0.870 EDSS 1: 0.799 EDSS 2: 0.705 EDSS 3: 0.574 EDSS 4: 0.610 EDSS 5: 0.518 EDSS 6: 0.460 EDSS 7: 0.297 EDSS 8: -0.049 EDSS 9: -0.195	(0.782, 0.958) (0.617, 0.523) (0.523, 0.886) (0.384, 0.763) (0.428, 0.791) (0.338, 0.698) (0.279, 0.642) (0.112, 0.481) (-0.289, 0.138) (-0.428, 0.039) Probabilistic variation using 10% standard error (gamma)	7.4.6	As discussed in Section B7.4.7, Orme et al. is a more comprehensive source of utility since it is specifically for UK patients, provides values across all EDSS states and has been used in previous HTA UK assessments [Orme et al. 2007; Novartis, 2011]. Probabilistic variation is not using the upper and lower confidence intervals because EDSS utility is combined with caregiver utility in calculations and upper and lower confidence intervals for caregiver disutility were not available from the source.
SPMS	0.045 less than RRMS	(-0.076, -0.014) less than RRMS Probabilistic variation using 10% standard error (gamma)	7.4.6	No specific SPMS data values area available; SPMS utilities are calculated from RRMS with a weighted coefficient to reflect the progressive disease [Orme et al. 2007]
Utility loss of relapse leading to hospitalisation	Using Orme duration: -0.0589 Using Gani duration: -0.0297	Using Orme duration: (-0.0734, -0.0444) Using Gani duration: (−0.0370, -0.0224) Probabilistic variation using 10% standard	7.4.6	Orme utility with Gani duration used in the base case. As discussed in 7.4.6, the percentage difference between relapses leading and not leading to hospitalisation from US study were applied to Orme disutility for relapse not leading to hospitalisation. This method was used as there is no reported UK literature for relapses leading to hospitalisation. Duration is applied to this disutility to calculate the

		error (gamma)		disutility per relapse event.
Utility loss of relapse not leading to hospitalisation	Using Orme duration: -0.0178 Using Gani duration: -0.0089	Using Orme duration: (-0.0240, -0.0155) Using Gani duration: (−0.0121, -0.0058) Probabilistic variation using 10% standard error (gamma)	7.4.6	Orme utility with Gani duration used in the base case. Assumption that the recent relapse disutility coefficient reported by Orme was for a relapse not leading to hospitalisation. Duration is applied to this disutility to calculate the disutility per relapse event.
Caregiver disutility	EDSS 0: 0.000 EDSS 1: -0.001 EDSS 2: -0.003 EDSS 3: -0.009 EDSS 4: -0.009 EDSS 5: -0.020 EDSS 6: -0.027 EDSS 7: -0.053 EDSS 8: -0.107 EDSS 9: -0.140	Probabilistic variation using 10% standard error (gamma)	7.4.6	From the NHS & PSS perspective, as defined by the reference case [NICE, 2008], disutility from caregivers should be included within the cost-effectiveness analysis. Gani et al. was the only source identified that detailed caregiver disutility. It is a relevant source for the economic evaluation since it includes UK perspective.
Infusion-associated reaction	-0.0002	Probabilistic variation using 10% standard error (gamma)	7.4.8	Annual disutility derived from utility loss per event, multiplied by the duration in months.
Bronchitis	-0.0004			
Herpes zoster	-0.0046			
Urinary tract infection	-0.0039			
Autoimmune thyroid-related adverse event	-0.1081			
Nephropathies	-0.8700			
ITP (weighted by severity)	-0.0065			
Cytopenias	0.0000			
Vomiting	-0.0020			
Fatigue	-0.0014			
Arthralgia	-0.0034			
PML	-0.0078			
Anaphylactic and anaphylactoid	-0.0194			

reactions				
Headache	-0.0002			
Injection site reaction	-0.0047 to -0.0110 depending on dose			
Influenza-like symptoms	-0.0114 to -0.0400 depending on dose			
Immediate postinjection systemic reactions	-0.0001			
Severe infection	-0.0035			
Macular oedema	-0.0100			
Atrioventricular block, first degree	-0.0008			
Atrioventricular block, second degree	-0.0008			

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical values in the model were estimated based on expert opinion.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Firstly, patients transition through health states based on EDSS level and classification type (RRMS vs. SPMS). As discussed in Section B7.4.1, a patient will also experience increasing physical disability as their disease status progresses, in EDSS or conversion to SPMS. This increased physical disability will consequently increase psychosocial impact of the disease [Aronson, 1997]. The HRQL of a multiple sclerosis patient will continue to decrease as their condition worsens in terms of EDSS and towards the final stages of the disease, a patient's utility will decrease below zero, i.e. worse than death [Orme, 2007]. Consequently, in the cost-effectiveness model, the patient experiences reduced utility as they progress through health states from EDSS 0 to EDSS 9.

Whilst in an EDSS state, a patient will experience relapses which will negatively impact HRQL. The disutility associated with a relapse is dependent on severity, which is associated with hospitalisation requirements (see Section B7.4.6). Finally disutility due to adverse events from treatment also affects the final utility for each patient by EDSS state.

Once a patient enters an EDSS health state, and relapses/treatment related adverse events are accounted for, the utility associated with the health state is constant for that annual cycle.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

All important health effects were included in the analysis.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

HRQL in terms of utility (Table B7.4.5) was based on EDSS level, for which the distribution is presented in Figure B7.3.1.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The HRQL associated with each health state does not change over time although progression to different health states does change over time. Please see Section B7.4.11.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

None of the utility values derived in sections 7.4.3 to 7.4.8 have been amended.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The costs of managing the condition using DMTs are captured by reference costs and the PbR tariff, in terms of administration, monitoring and adverse events. Management of multiple sclerosis patients treated with best supportive care has not been costed directly from reference costs and the payment by results (PbR) tariff.

The guide to method of technology appraisal recommends the use of reduced resource prices that are transparent and can be consistently available across the NHS. Since the UK RSS applies to England and Wales, acquisition costs of beta-interferons and glatiramer acetate have been sourced from UK RSS [DoH Health Service Circular, 2002]. The annual cost of natalizumab has been derived from the British National Formulary (BNF) [BNF Tysabri, 2013]. There is a patient access scheme for fingolimod in existence but at time of submission, the annual cost had not been provided in confidence from the manufacturer so the list price was used (Table B7.5.1). The price of alemtuzumab is indicative and will be confirmed with Department of Health.

Table B7.5.1 Acquisition costs of DMTs

Treatment	Dosage	Treatment regimen	Total annual cost	Source	Price year
Alemtuzumab*	12 mg	Initial treatment course: 12 mg/day for 5 consecutive days. Subsequent treatment course: 12 mg/day for 3 consecutive days (36 mg total dose) administered 12 months after the initial treatment course.	£35,225 first course £21,135 subsequent courses (indicative to be confirmed with DH)	Genzyme	2013
SC IFNβ-1a 44µg	44 µg	44µg 3 times per week, self-injected subcutaneously	£8,942	DoH Health Service Circular, 2002	2002
SC IFNβ-1a 22µg	22 µg	22µg 3 times per week, self-injected subcutaneously	£7,513	DoH Health Service Circular, 2002	2002

IM IFNβ-1a	30 µg	30 µg once a week, self-injected subcutaneously	£8,502	DoH Health Service Circular, 2002	2002
IFNβ-1b	250 µg	250 µg every other day, self-injected subcutaneously	£7,259	DoH Health Service Circular, 2002	2002
Glatiramer acetate	1 mL vial 20mg/mL	20 mg per day, self-injected subcutaneously	£5,823	DoH Health Service Circular, 2002	2002
Fingolimod**	7-tab pack 0.5mg capsule	0.5 mg once daily in oral form	£367.50/7 x 365 = £19,110	British National Formulary	2013
Natalizumab	15 mL vial 20 mg/mL	300 mg intravenous injection by a health professional every 4 weeks	£1130/4/7 x 365 = £14,730	British National Formulary	2013

*Please note, list price is to be confirmed with the Department of Health, after which we intend to remove this as commercial in confidence

**A commercial in confidence PAS is available to the UK NHS for fingolimod. Therefore, sensitivity analyses considered a number of potential PAS prices for fingolimod ranging from £11,000 to £15,000 per annum.

In contrast to comparator DMTs where annual acquisition costs are the same for all patients on treatment, the acquisition costs for alemtuzumab depend on the proportion of patients who have subsequent courses. It is expected that the majority of patients will only require two courses of treatment and the effect on the alemtuzumab will persist over the long-term. However, some patients may require a third or more doses of alemtuzumab to ensure continuous efficacy. In the model, the continued benefit of alemtuzumab is modelled such that patients can receive the full efficacy of alemtuzumab in cycles where they do not receive a course of treatment. Hence, no explicit link is made between treatment effectiveness and dosing following the first two courses of treatment. Nevertheless, to avoid underestimation of alemtuzumab acquisition costs conservative assumptions are made with regards to subsequent treatment courses. The justification for these assumptions can be found in Section 7.3.7.

- Firstly, CAMMS 223 informed the proportion of patients that received initial and subsequent treatment courses for the first 5 years. The data suggested that in total [redacted] of the original cohort received a third treatment course between years 3-5.

- After year 5 it was assumed that [redacted] would receive another treatment course each year. This equates to the same [redacted] of patients receiving subsequent courses (e.g. fourth, fifth, etc.) every three years, as shown in Table B7.5.2.

Table B7.5.2 Acquisition costs for alemtuzumab

Year	% patients receiving treatment	Number of vials	Aquisition cost
1	100.00%	5	£35,225
2	100.00%	3	£21,135
3	[redacted]	3	[redacted]
4	[redacted]	3	[redacted]
5	[redacted]	3	[redacted]
6 - 9	[redacted]	3	[redacted]
10 +	[redacted]	3	[redacted]

This base case assumption about retreatment rates needs to be considered in light of the full data set on alemtuzumab retreatment beyond year 2:

- CAMMS 223 (n=112 on alemtuzumab 12mg) – between years 3 and 5 – [redacted] of patients received a subsequent treatment course [Genzyme CAMMS 223 CSR]
- CARE-MS I and II extension study (n=376 and 435 respectively on alemtuzumab 12mg) –18% and 20% received an additional treatment course in year 3 [Fox, 2013]
- Cambridge observational study (n=87) [redacted] received a subsequent treatment course with median follow up of 7 years [Tuohy et al. draft manuscript]
- Observational study at 5 MS centres in England and Wales (Cambridge, Cardiff, Plymouth, Liverpool and Bristol) (n = 248), 30% received retreatment with a median follow up of 34 months [Cossburn et al. 2011].

Based on this data, the base case model assumes [redacted] of patients receive a subsequent dose in year 3 in line with the CAMMS 223 extension study data ([redacted] n years 4 and 5). Beyond year 5, a [redacted] annual rate of retreatment is assumed ([redacted]). See Section 7.5.1 for further details.

One important contextual piece of information relevant for considering retreatment is the criteria for retreatment employed in each of the studies:

- CAMMS 223 extension – a mix of scheduled courses of retreatment and clinical decision making based on relapses or imaging changes, which resulted in a significant number of patients got re-treated based on T-cell counts not disease activity (see Section 6.5.3, Alemtuzumab Long-term Data)
- CARE-MS I / II extension – One protocol defined relapse or two new or enlarging T2 lesions and / or a GAD enhancing brain or spinal lesion [Fox, 2013]

- Cambridge observational study – subsequent courses of alemtuzumab were offered if there was clinical evidence of a return of MS disease activity in the form of a relapse. Evidence for new lesion formation on a MRI scan was usually sought, but not required for retreatment [Tuohy et al. draft manuscript].

All studies in part used criteria which included relapses to determine retreatment, both annualised relapses and retreatment rates are summarised below:

- Annual relapse rate – CAMMS 223 extension years 3, 4 and 5 are [redacted], [redacted] and [redacted] respectively and the percentage of patients receiving retreatment was [redacted] in years 3-5 [Genzyme CAMMS 223 CSR]
- Annual relapse rate – CARE-MS I and II extension studies in year 3 are 0.24 and 0.25 respectively with percentage of patients retreated as 18% and 20% respectively. Hence, approximately 75% and 80% of relapses resulted in retreatment; weighted average: 78% [Fox, 2013]
- Annual relapse rate – Cambridge observational study is [redacted] with a median follow up of 7 years and the percentage of patients retreated as [redacted], which approximates to an annual retreatment of [redacted]. Hence, it appears that approximately [redacted] of relapses resulted in retreatment [Tuohy et al. draft manuscript].
- The publication of the Plymouth / Cardiff dataset did not provide details on annualized relapse rates

When considering linking ARR with retreatment, CARE-MS I and CARE-MS II extension studies were thought to be of most relevance since retreatment was based partly on relapses. On the other hand, CAMMS 223 used a broad range of retreatment criteria including scheduled visits (see Section 6.5.3, Alemtuzumab Long-term Data) and observational data from the Cambridge study may be considered biased. Hence, based on the CARE-MS extension data, ARR and retreatment are similar with retreatment approximately [redacted] of the number of relapses. This suggests that not all relapses result in retreatment. Partly, this is because those patients who experience more than one relapse in one particular year would only receive one additional treatment course because alemtuzumab retreatment is limited to a minimum period of one year between treatment courses.

If retreatment is linked to relapse rates, it is important to give consideration to the long term effect of alemtuzumab in reducing relapse rates. The following data in this regard should be noted:

- CAMMS 223 extension, 2 year, 3 year, 4 year and 5 year ARR RR versus SC IFNβ-1a 44µg is [redacted], [redacted] and [redacted] respectively [Genzyme CAMMS 223 CSR]

This suggests that there is evidence of maintenance of effect with alemtuzumab 12mg in reducing relapse rates up to 5 years. In the base case this is assumed to be maintained for the lifetime of the model. The impact of different assumptions surrounding the impact of alemtuzumab on reducing relapse rates over the long term and how this may impact on retreatment assumptions is considered as follows:

A scenario analysis was performed whereby the modelled cohort was given an additional course of treatment if a relapse occurred. The proportion of cohort that experienced a relapse and therefore required an additional dose of alemtuzumab were calculated as the sum of relapses each year (leading and not leading to hospitalisation) divided by the size of the cohort eligible to receive retreatment (i.e. RRMS, EDSS < 7). This equated to a re-treatment rate of approximately 25% each year. Consequently, 19.5% (0.25*0.78) would be retreated each year based on the CARE MS extension data. This is fairly reflective of the ARR of 0.28 for alemtuzumab which was derived from the MTC in the 80% RRMS analysis. A scenario analysis was run with 100% of the cohort receiving retreatment in years 1 and 2, and 19.5% receiving re-treatment for years 3 and onwards (see Section B7.6).

In addition to the cost of day cases for a multiple sclerosis for alemtuzumab administration, there a number of concomitant medications. It is recommended in the SmPC that patients should be pre-treated with corticosteroids immediately prior to alemtuzumab administration on each of the first 3 days of any treatment course [Alemtuzumab SmPC]. Oral prophylaxis for herpes infection should be administered to all patients starting on the first day of each treatment course and continuing for a minimum of 1 month following treatment with alemtuzumab [Alemtuzumab SmPC]. In clinical trials, patients were pre-treated with 1g methylprednisolone and aciclovir 200mg twice a day and this is also costed in the economic evaluation. Additionally, pre-treatment with antihistamines and/or antipyretics prior to alemtuzumab administration may also be considered so daily cost of chlorphenamine and paracetamol is also included.

Beta-interferons and glatiramer acetate are self-injected by patients but there is an initial one-off cost of training by a clinical nurse specialist (Table B7.5.3). Fingolimod is an oral treatment but the SmPC recommends continuous ECG and blood pressure monitoring for 6 hours after the first dose of fingolimod, which has been costed as a day case for a multiple sclerosis patient. Natalizumab is administered as an IV infusion 13 times per year, incurring costs for time at medical facility and IV methylprednisolone.

Table B7.5.3 Annual administration costs associated with DMTs

Treatment	Year 1 cost	Year 2 cost	Source	Justification
Alemtuzumab*	£2,438	£1,487	NHS Reference Costs AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit [5 days in year 1, 3 days per subsequent dose]. BNF June 2013 Methylprednisolone 1g vial £17.30 BNF June 2013	IV administration 5 days in first year, 3 days per subsequent dose. Methylprednisolone for first three vials of alemtuzumab only Chlorphenamine 10mg daily Paracetamol 2 x 500mg daily

			Chlorphenamine 10mg £1.95 BNF June 2013 Paracetamol 500mg 16pk 16p BNF June 2013 Aciclovir 200mg 56pk £7.25	Aciclovir 200mg twice daily for 28 days
IM IFNβ-1a	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
IFNβ-1b	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
SC IFNβ-1a 44µg	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
SC IFNβ-1a 22µg	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
Glatiramer acetate	£174	£0	PSSRU 2012 Clinical nurse specialist with qualifications per hour (3 hours @ £58)	3 hours required for nurse to teach self-administration; no administration following initial training
Fingolimod	£474	£0	NHS Reference Costs AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit.	Continuous ECG and blood presume monitoring for 6 hours following first dose
Natalizumab	£6,162	£6,162	NHS Reference Costs AA30C Medical Care of Patients with Multiple Sclerosis without CC Day Case @ £474 per visit. BNF 2013 Methylprednisolone 1g vial £17.30	13 infusions per year with 1g Methylprednisolone per natalizumab infusion

*Note that administration costs are based on the proportion that receive a treatment course (as specified in Table 7.5.2), years 1 and 2 are 100% therefore administration costs would decrease to £624 in year 3, £0 in years 4-5 and £208 in years 6+

The monitoring resource associated with each DMT is shown in Table B7.5.4. The references for these values are obtained from SmPCs of each product where possible, and using the NICE fingolimod costing template [NICE, 2012(b)]. The costs associated with the monitoring resource in Table B7.5.4 are given in Table B7.5.5. For alemtuzumab it is assumed that monitoring persists after dosing and / or discontinuation. This is a very conservative assumption since the SmPC states that patients would only receive 4 years of monitoring following their last treatment course. However, to model this adequately several tunnel states would be required which would unnecessarily overcomplicate the model structure.

Table B7.5.4 Monitoring resource use associated with DMTs

Treatment	Monitoring requirement	Resource use year 1	Resource use subsequent years	Reference
Alemtuzumab	Biochemistry test	12	12	[Alemtuzumab SmPC]
	Full blood count	12	12	[Alemtuzumab SmPC]
	Urinalysis	12	12	[Alemtuzumab SmPC]
	Thyroid function test	4	4	[Alemtuzumab SmPC]
	Human papilloma virus test (for women only)	1	1	[Alemtuzumab SmPC]
	Neurology visit	2	1	Assumption
	Tuberculin skin test	1	0	[Alemtuzumab SmPC]
SC IFNβ-1a	Biochemistry test	4	2	[Rebif SmPC]
	Full blood count	4	2	[Rebif SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
IM IFNβ-1a	Biochemistry test	4	2	[Avonex SmPC]
	Full blood count	4	2	[Avonex SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
IFNβ-1b	Biochemistry test	4	2	[Betaferon SmPC]
	Full blood count	4	2	[Betaferon SmPC]
	Neurology visit	2	2	[NICE, 2012(b)]
Glatiramer acetate	Neurology visit	2	2	[NICE, 2012(b)]
Fingolimod	Biochemistry test	6	2	[Gilenya SmPC]
	Full blood count	4	2	[Gilenya SmPC]
	Neurology visit	3	2	[NICE, 2012(b)]
	Ophthalmology visit	1	0	[NICE, 2012(b)]
Natalizumab	Biochemistry test	2	2	[Tysabri SmPC]
	MRI scan	1	1	[Tysabri SmPC]
	Neurology visit	2	2	Assumption

Table B7.5.5 Monitoring costs associated with DMTs

Monitoring requirement	Reference costs / payment by results tariff	Cost
Biochemistry test	NHS Reference costs 2011-12, Pathology services, Biochemistry DAP841	£1.23

Full blood count	NHS Reference costs 2011-12, Pathology services, Haematology [Excluding Anti-Coagulant Services] DAP823	£3.09
MRI scan (to detect PML)	Payment by Results other-mandatory tariff 2012-13, RA01A: Magnetic Resonance Imaging Scan, one area, no contrast, 19 years and over	£153.00
Ophthalmology visit	Payment by Results mandatory tariff 2012-13, Outpatient attendance: 130 Ophthalmology, Single professional, first attendance	£115.00
Thyroid function test	NHS Reference costs 2011-12, Pathology services, Other DAP842	£6.48
Neurology visit	NHS Reference costs 2011-12, Outpatient Attendances, Neurology 400	£169.00
HPV test	HPV test using liquid based cytology (including the costs of consumables, equipment, staff and overheads) £24.92 (range £11.25-£47.61) inflated from 2002 cost to 2012 [Moss et al. 2004].	£31.59
Urinalysis with urine cell counts	Multistix 10sg (£32.95 for 100) [MidMeds 2013]	£0.33
Tuberculin skin test	Unit cost inflated from 2006 to 2013 cost [NICE 2006]	£16.65

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS reference costs 2011-12 have been used wherever possible in the cost-effectiveness analysis. When compared to PbR Tariff values, the NHS reference costs also allow for a greater level of granularity to be assessed.

NHS reference costs and PbR tariffs have been used to differentiate the intervention costs from comparators in terms of administration, monitoring and adverse event costs.

Where NHS reference costs have not been available or are irrelevant, alternative figures from literature have been used. In particular, defining an annual cost of the disease by disease classification and severity is difficult because there are so many factors to the management of multiple sclerosis. Disease costs are likely to increase with severity, in particular: inpatient care, outpatient care, consultations with specialists, consultations with other medical professionals, investigations/tests, prescribed medication, over-the-counter medication, professional non-medical care and informal non-medical care. The total cost of a relapse is also expected to include a wide range of medical and non-medical costs and thus has not been taken from reference costs or PbR tariffs.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic review was conducted to obtain all relevant cost and resource use studies in MS.

The PICOS (population, interventions, comparators, outcomes and study type) principal was applied to define the following review questions:

- *"What are the direct and indirect costs associated with treating patients with multiple sclerosis?"*
- *"What are the direct costs per relapse that lead to hospitalisation/do not lead to hospitalisation?"*
- *"What is the acquisition costs associated with treatment for multiple sclerosis?"*
- *"What are the costs of administration and monitoring of patients treated for multiple sclerosis?"*
- *"What are the costs of adverse events associated with treating patients with multiple sclerosis?"*

Section 10.13 details the search strategies, databases searched and subsequent results from the database sites searched, resulting in 18 studies that met inclusion/exclusion criteria and as such identified as evaluating cost and resource use in MS.

Identified cost and resource use studies

Of the 18 studies included in the full review, 3 were implemented in the model and are summarised in Table B7.5.6 below.

Table B7.5.6 Summary of identified cost and resource use studies implemented in the model

	[Dee et al. 2012]
Country of study	Ireland
Date of study	24 November 2010
Applicability to UK clinical practice	Appropriate.
Cost valuations used in study	N/A
Costs for use in economic analysis	Using data from the six large neurology centres the average length of stay for a neurology bed. MS admission in 2007 was calculated as 10.71 days. Only about 20% of MS relapses are treated as in-patients, the remaining 80% attend as day cases for 5 days steroid treatment.
Technology costs	N/A
	[Karampampa et al. 2012]
Country of study	UK
Date of study	2009
Applicability to UK clinical practice	Appropriate
Cost valuations used in study	Patients self-completed a questionnaire in English using a web-based electronic data capturing system.
Costs for use in economic analysis	See Figure B7.5.1
Technology costs	N/A
	[Tyas et al. 2007]
Country of study	UK
Date of study	2005
Applicability to UK clinical practice	Appropriate
Cost valuations used in study	Questionnaires were completed by the patient.
Costs for use in economic analysis	See Figure B7.5.2
Technology costs	N/A

Figure B7.5.1 Data extracted from Karampampa et al. [Karampampa et al. 2012]

Table 2. Cost per patient per year by disease severity (in £ 2009), 95% CI.

	EDSS 0 – 3 (*n* = 77)			EDSS 4 – 6.5 (*n* = 110)			EDSS 7 – 9 (*n* = 7)		
	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Inpatient care	70	367	(25 – 229)	54	319	(17 – 146)	1838[b,c]	3205	(758 – 5191)
Outpatient care	346	973	(200 – 754)	698	1770	(435 – 1103)	435	636	(106 – 986)
Consultations	578	972	(404 – 838)	923[a]	1135	(745 – 1192)	826	910	(334 – 1609)
Investigations	82	148	(56 – 123)	74	164	(49 – 109)	29	78	(0 – 147)
MS treatments	5369	4054	(4494 – 6270)	5499	4443	(4682 – 6351)	2098[†b,c]	5552	(0 – 10,491)
Prescribed & OTC medication	269	363	(205 – 378)	851[a]	1488	(685 – 1398)	832[b]	420	(535 – 1101)
Total direct medical costs	**6714**	**4484**	**(5760 – 7717)**	**8101[a]**	**5271**	**(7153 – 9072)**	**6059**	**5716**	**(2907 – 10,735)**
Investments/modifications	48	315	(16 – 226)	1457[a]	1704	(1127 – 1761)	2989[b]	2325	(1168 – 4433)
Professional care	0	0	n.a.	950[a]	3911	(6885 – 11,462)	16,430[b,c]	18,995	(16,763 – 54,939)
Informal care	1865	7349	(789 – 5321)	7893[a]	10,522	(6115 – 10,237)	21,824[b,c]	18,263	(9957 – 34,697)
Total direct non-medical costs	**1913**	**7396**	**(811 – 5038)**	**10,299[a]**	**12,178**	**(8170 – 12,772)**	**41,242[b,c]**	**30,086**	**(17,653 – 59,378)**
Sick leave	1202	3784	(571 – 2441)	1686	4752	(963 – 2941)	654	1730	(0 – 3269)
Retirement due to MS	2011	5946	(1006 – 4023)	5808[a]	8912	(4224 – 7568)	11,063	10,348	(5531 – 19,360)
Total indirect costs	**3214**	**6691**	**(1920 – 5111)**	**7494**	**9069[a]**	**(5789 – 9200)**	**11,717[b]**	**9654**	**(6185 – 19,360)**
Total costs	**11,841**	**13,288**	**(9673 – 16,182)**	**25,894[a]**	**17,411**	**(22,861 – 29,391)**	**59,018[b,c]**	**34,435**	**(30,659 – 79,668)**

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; OTC: over-the-counter; n.a.: not applicable.
[a]Difference is statistically significant compared to the mild sub-group of patients (*p*-value<0.05).
[b]Difference is statistically significant compared to the mild sub-group of patients (*p*-value<0.05).
[c]Difference is statistically significant compared to the moderate sub-group of patients (*p*-value<0.05).

Figure B7.5.2 Data extracted from Tyas et al. [Tyas et al. 2007]

Table 1 Direct government-funded costs

Coefficient	Estimate (£)	SE (£)	95% CI (£)	P-value
a. Direct annual medical cost coefficients funded by UK government (DMG)				
EDSS 0†	250	1,975	(−3,623, 4,123)	0.90
EDSS 1	85	899	(−1,678, 1,849)	0.92
EDSS 2	213	868	(−1,489, 1,915)	0.81
EDSS 3	850	1,237	(−1,575, 3,275)	0.49
EDSS 4	806	884	(−927, 2,539)	0.36
EDSS 5	1,419	823	(−195, 3,032)	0.09
EDSS 6	2,162	851	(492, 3,832)	0.01
EDSS 6.5	3,429	909	(1,645, 5,212)	*
EDSS 7	6,583	995	(4,632, 8,534)	*
EDSS 8	10,761	1,069	(8,665, 12,857)	*
EDSS 9	15,121	2,656	(9,912, 20,330)	*
RRMS†				
SPMS	280	705	(−1,103, 1,663)	0.69
PPMS	−1,517	815	(−3,114, 81)	0.06
Relapse	1,623	545	(554, 2,692)	*
DMD + EDSS 0–2	9,174	1,161	(6,896, 11,452)	*
DMD + EDSS 3–6.5	467	1,349	(−2,179, 3,113)	0.73
DMD + EDSS 7–9	−689	3,735	(−8,015, 6,636)	0.85
b. Direct annual nonmedical cost coefficients funded by UK government (DNMG)				
EDSS 0†	2,536	2,183	(−1,745, 6,817)	0.25
EDSS 1	3,462	1,314	(886, 6,039)	0.01
EDSS 2	4,414	1,314	(1,836, 6,991)	*
EDSS 3	6,212	1,585	(3,103, 9,321)	*
EDSS 4	4,028	1,320	(1,439, 6,617)	*
EDSS 5	6,333	1,338	(3,709, 8,958)	*
EDSS 6	6,580	1,338	(3,956, 9,204)	*
EDSS 6.5	8,212	1,398	(5,471, 10,953)	*
EDSS 7	10,808	1,485	(7,895, 13,721)	*
EDSS 8	15,339	1,514	(12,369, 18,309)	*
EDSS 9	10,161	2,837	(4,598, 15,725)	*
Age	−66	25	(−116, −16)	0.01
Years since diagnosis	54	29	(−2, 110)	0.06

*$P < 0.01$. †Reference case.
CI, confidence interval.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

As discussed in Section B7.3.5, interviews were conducted with five neurologists from England and Wales. Monitoring resource use derived from SmPCs and NICE costing templates were assessed by the five experts to ensure it accurately reflects the monitoring that occurs with DMTs in clinical practice [Genzyme KOL interview report, 2013]. The experts were also asked if they believed the cost of the resource was an accurate reflection of what they would expect.

The experts' monitoring of fingolimod varied in terms of the number of liver function tests, full blood counts and neurology visits. Since the difference may be local variation or clinician preference, the conservative approach has been taken of sourcing these values from the NICE fingolimod costing template [NICE, 2012(b)]. Similarly there was local variation in the number of neurology visits for all other DMTs; the NICE fingolimod costing template states two per year but one expert believed there would be four in the first year and two in subsequent years. Again the conservative approach has been taken to use the more robust source: the NICE fingolimod costing template. However, even if the NICE fingolimod costing template does underestimate the number of neurology visits, an increase would apply to all DMTs so the ICER would not change significantly.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section B7.2.2.

A summary of the acquisition costs, administration and monitoring costs for each DMT, which were individually detailed in section B7.5.1, is summarised in Table B7.5.8. All costs in Table B7.5.7 are assumed to stay constant for all health states; they do not vary by EDSS or classification of RRMS or SPMS.

Table B7.5.7 Annual costs associated with the technologies in the economic model

Treatment	Acquisition cost		Administration cost		Monitoring cost		Total	
	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+
Alemtuzumab*	35,225.00	21,135.00	2,438	1,487	443.00	274.00	13,936.12	13,897.24
SC IFNβ-1a 44µg	8,942.00	8,942.00	174.00	0	355.28	346.64	9,471.28	9,288.64
SC IFNβ-1a 22µg	7,513.00	7,513.00	174.00	0	355.28	346.64	8,042.28	7,859.64
IM IFNβ-1a	8,502.00	8,502.00	174.00	0	355.28	346.64	9,031.28	8,848.64
IFNβ-1b	7,259.00	7,259.00	174.00	0	355.28	346.64	7,788.28	7,605.64
Glatiramer acetate	5,823.00	5,823.00	174.00	0	338.00	338.00	6,335.00	6,161.00
Fingolimod	19,162.50	19,162.50	474.00	0	641.74	346.64	20,278.24	20,001.14
Natalizumab	14,730.00	14,730.00	6162.00	6162.00	493.46	493.46	21,385.46	21,385.46

*Note, acquisition and administration are based on the proportion that receive a treatment course (as specified in Table 7.5.2-3)

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section B7.2.4.

There are significant changes in costs per health state. As seen in Figure B7.5.2 and Figure B7.5.3, the natural history costs rapidly increase by disease severity. From the literature search detailed in Section B7.5.3, two sources of natural history costs were obtained. In the base case scenario, costs are from Tyas et al as this source is well cited and consistent with two previous NICE submissions [Tyas et al. 2007; Biogen, 2006; Novartis, 2011]. Only direct medical costs and other direct costs have been applied to the analysis; indirect costs are not consistent with the NHS & PSS perspective.

An alternative source obtained through the literature search is a study by Karampampa et al which, although it is a more recent study, only provides aggregated natural history costs for EDSS 0-3, 4-6 and 7-9, rather than costs per individual EDSS state. Karampampa et al reports a greater difference between direct medical and non-medical costs, as well as a much greater % increase in costs as EDSS increases (see Figure B7.5.3). Since Karampampa et al does not provide the costs in sufficient detail i.e. not by each EDSS state, it has not been used in the base case analysis. However, it is the most recent source and thus important to consider and has therefore been tested in sensitivity analysis.

Both natural history cost sources have been inflated to Q3, 2012 and the final values used in the model shown in Table B7.5.8 [ONS CPI indices].

Figure B7.5.3 Illustration of the difference in natural history costs from available sources

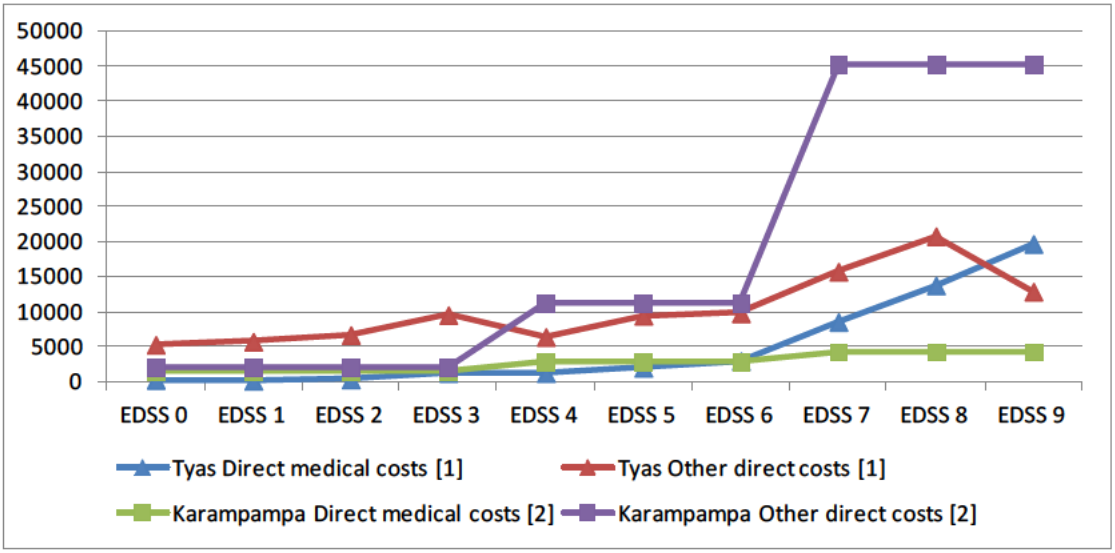


Table B7.5.8 List of health states and associated costs in the economic model

Health states (applies to RRMS and SPMS)	Items	Base case value [Tyas et al. 2007]	Sensitivity analysis value [Karampampa, 2012]
EDSS 0	Direct medical costs	336.19	1477.707
	Other direct costs	5334.58	2101.749
	Total	5670.77	3579.456
EDSS 1	Direct medical costs	200.23	1477.707
	Other direct costs	5779.54	2101.749
	Total	5979.77	3579.456
EDSS 2	Direct medical costs	399.23	1477.707
	Other direct costs	6734.96	2101.749

	Total	7134.19	3579.456
EDSS 3	Direct medical costs	1315.10	1477.707
	Other direct costs	9565.40	2101.749
	Total	10880.51	3579.456
EDSS 4	Direct medical costs	1294.09	2856.533
	Other direct costs	6461.81	11315.17
	Total	7755.90	14171.7
EDSS 5	Direct medical costs	2056.70	2856.533
	Other direct costs	9488.77	11315.17
	Total	11545.48	14171.7
EDSS 6	Direct medical costs	3025.73	2856.533
	Other direct costs	9811.37	11315.17
	Total	12837.10	14171.7
EDSS 7	Direct medical costs	8595.14	4350.72
	Other direct costs	15761.47	45311.21
	Total	24356.62	49661.93
EDSS 8	Direct medical costs	13806.12	4350.72
	Other direct costs	20810.53	45311.21
	Total	34616.65	49661.93
EDSS 9	Direct medical costs	19704.31	4350.72
	Other direct costs	12914.96	45311.21
	Total	32619.28	49661.93
EDSS 10	Direct medical costs	0	0
	Other direct costs	0	0
	Total	0	0

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section B6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section B7.2.2.

The costs associated with adverse events detailed in Section B7.3.1.are given in Table B7.5.9.

Table B7.5.9 Costs of treatment of DMT adverse events

Adverse events	Associated cost	Source	Source cost	Unit Cost
Infusion-associated reaction	Administered in hospital	N/A	N/A	£0.00
Bronchitis	2 GP consultations and one course of amoxicillin	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes BNF April 2013 amoxicillin (as trihydrate) capsules 250 mg, net price 21 [BNF amoxicillin 2013]	£43 x 2 £0.95	£86.95
Herpes zoster	10% will be hospitalised and 90% will have treated with Lyrica for one month	Hospitalised: cost per HZ case [Van Hoek et al. 2009] and NHS Reference Cost (JD05C) Minor Skin disorders category 2 without complications. Non-hospitalised: BNF July 2013 pregabalin (Lyrica) 150 mg (white) 56-cap pack [BNF Lyrica 2013]	£684.55 £82.82 £64.40	£192.66
Urinary tract infection	GP consultation + 1 week 200mg trimethoprim	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes BNF July 2013 trimethoprim 200 mg, 14-tab pack [BNF trimethoprim , 2013]	£43.00 £1.03	£44.03
Autoimmune thyroid-related adverse event	Costs per "cure" analysis with initial treatment Radioiodine. In the clinical trials less than 1% received surgical intervention (see Section B6.9)	Inflated from 2002 to 2012 costs [Patel et al. 2006]	£1,833.33	£1,833.33
Nephropathies	1 GP consultation, 1 nephrologist consultant visit, 3 doses of Cyclophosphamide (500 mg), 3 doses of IV methylprednisolone (1 g) and 1 month of oral methylprednisolone	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes NHS Reference costs 2011-12, Consultant Led: First Attendance Non-Admitted Face to Face 361 Nephrology BNF July 2013 Cyclophosphamide Injection, powder for reconstitution, cyclophosphamide, net price 500-mg vial BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17	£43.00 £203.88 £7.67 £17.30 £17.17	£338.96

ITP (treatment with steroids only)	Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month	NHS Reference costs 2011-12, SA12D Thrombocytopenia with CC BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17	£1,277.00 £17.30 £17.17	£1,328.77
ITP (treatment with steroids, IVIG)	Based on cost of thrombocytopenia, immunoglobulin 1 g/kg/d for 2 days assuming 75kg adult, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month	Vigam Intravenous infusion, human normal immunoglobulin (protein 5%) 10 g (200 mL) = NHS Reference costs 2011-12, SA12D Thrombocytopenia with CC BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17	£5,700.00 £1,277.00 £17.30 £17.17	£7,028.77
ITP (treatment with steroids, tranexamic acid, platelets, rituximab, IVIG)	Based on cost of thrombocytopenia, immunoglobulin 1 g/kg/d for 2 days assuming 75kg adult, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month Rituximab 375mg/m2 once a week for 4 weeks, assuming average male is 1.7m2 – dose = 638mg	Vigam Intravenous infusion, human normal immunoglobulin (protein 5%) 10 g (200 mL) NHS Reference costs 2011-12, SA12D Thrombocytopenia with CC BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17 BNF July 2013 MabThera (Roche) Concentrate for intravenous infusion, rituximab 10 mg/mL, net price 10-mL vial = £174.63, 50-mL vial = £873.15 BNF April 2013 Tranexamic acid (Non-proprietary) ablets, 500 mg, net price 60-tab pack NHS Blood and Transport 2013/14 platelet transfusion	£5,700.00 £1,277.00 £17.30 £17.17 £4,889.64 £5.21 £208.09	£12,131.71
ITP (treatment with steroids, platelets, rituximab)	Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone	NHS Reference costs 2011-12, SA12D Thrombocytopenia with CC BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial	£1,277.00 £17.30	£6,426.50

	16mg for one month Rituximab 375mg/m2 once a week for 4 weeks, assuming average male is 1.7m2 – dose = 638mg	BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17 BNF July 2013 MabThera (Roche) Concentrate for intravenous infusion, rituximab 10 mg/mL, net price 10-mL vial = £174.63, 50-mL vial = £873.15 NHS Blood and Transport 2013/14 platelet transfusion	£17.17 £4,889.64 £208.09	
ITP (treatment with steroids, platelets, IVIG)	Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month	Vigam Intravenous infusion, human normal immunoglobulin (protein 5%) 10 g (200 mL) NHS Reference costs 2011-12, SA12D Thrombocytopenia with CC BNF July 2013 Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 1-g vial BNF July 2013 Tablets, scored, methylprednisolone 16 mg, 30-tab pack = £17.17 NHS Blood and Transport 2013/14 platelet transfusion	£5,700.00 £1,277.00 £17.30 £17.17 £208.09	£7,236.86
Cytopenias	GP consultation	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes	£43	£43.00
Vomiting	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Headache	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Severe infection	Weighted cost based on FREEDOMS trial [Kappos et al. 2010] of respiratory infection (67%) [GP consultation and respiratory infection], herpes infection (10%) [GP consultation and minor skin disorder], influenza-like infection (15%) [2 GP consultations and viral infection] and UTI (9%) [GP	PSSRU 2012 GP with qualifications cost per patient contact lasting 11.7 minutes BNF July 2013 trimethoprim 200 mg, 14-tab pack [BNF trimethoprim , 2013] NHS Reference costs 2011-12 (JD05C) Minor Skin disorders category 2 without CC. NHS Reference costs 2011-12 (PA11Z) acute respiratory tract infection NHS Reference costs 2011-12 (PA19A) viral infections with LOS < 1 day	£43 £1.03 £684.55 £574.63 £521.51	£581.66

	consultation and trimethoprim].			
Macular oedema	2 ophthalmology consultations	National Reference costs 2011-12 Consultant Led: First Attendance Non-Admitted Face to Face outpatients (service code 130) National Reference costs 2011-12 Consultant Led: Follow up Attendance Non-Admitted Face to Face outpatients (service code 130)	£106.18 £79.74	£185.92
Injection-site reaction	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Influenza-like symptoms	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Immediate post injection systemic reaction	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Fatigue	MS nurse phone call	PSSRU 2012 Clinical nurse specialist with qualifications and average length of telephone call	£58 per hour 6 minutes	£5.80
Arthralgia	GP consultation and 3 days treatment with methylprednisolone	BNF April 2013 methylprednisolone 1 mg injection [BNF methylprednisolone, 2013] National Reference costs 2011-12 Consultant lead Pain management (service code 191)	£17.30 £114.63	£166.53
PML	Cost of non-elective inpatient (long-stay), MRI scan, JC virus PCR and Lumbar Puncture from natalizumab manufacturer submission	NHS Reference Cost Non-elective inpatient (long-stay) (AA227) MRI scan JC virus PCR Lumbar Puncture (inflated from 2006 to 2012)	£2,959.05	
Anaphylactic and anaphylactoid reactions	Hospitalisation	NHS Reference Cost Non-elective inpatient short stay (WA16Y) Shock and Anaphylaxis without CC	£362.37	£362.37
Atrioventricular block, first degree	Hospitalisation	NHS Reference Cost (EB07H) Arrhythmia or conduction disorders without complications	£818.42	£818.42
Atrioventricular block, second degree	Hospitalisation	NHS Reference Cost (EB07H) Arrhythmia or conduction disorders with complications	£1,357.49	£1,357.49

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

In addition to costs associated with DMTs and natural history costs, there are also costs associated with hospitalisations. As detailed in section B7.2.5, relapses in the model are captured by those that lead to hospitalisation and those that do not. Two sources were identified in the literature review for relapses costs (see Section B7.5.3). As discussed in section B7.5.6, Tyas et al is a robust study of costs associated with MS. However, Tyas does not differentiate between costs of relapses leading to hospitalisation and those that do not. Therefore, although natural history costs are sourced from Tyas in the base case, costs of relapse are sourced from Dee et al. which used data collected from Irish neurology centres to obtain a length of hospital stay of 10.7 days from relapse. Relapses not leading to hospitalisation require 5 days steroid treatment as day cases. UK NHS reference costs have been substituted for the HIPE Irish costs used in the publication to gain a UK equivalent cost. Table B7.5.10 provides details of the calculation of relapse costs. The relapse costs used in the base case are detailed in Table B7.5.11.

Table B7.5.10 Cost calculations for costs associated with relapses [Dee et al. 2012]

Parameter	Resource use	Number of days	Source of cost	Cost per day
Cost calculation for relapses leading to hospitalisation	Length of stay of relapse leading to hospitalisation	10.71	National Reference Costs 2011-12 Regular Day / Night Admissions. Service code AA30B: Medical Care of Patients with Multiple Sclerosis without CC	£575.58
Cost calculation for relapses not leading to hospitalisation	Days of steroid treatment	5	National Reference Costs 2011-12- Outpatient Attendances Data. Service code 400: Neurology	£168.93

Table B7.5.11 Costs associated with relapses included in the economic model

Category	Base case cost [Dee, 2012]
Relapse not leading to hospitalisation	£ 844.65
Relapse leading to hospitalisation	£ 6,164.46

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

To test structural uncertainty within the cost-effectiveness model, a number of scenario analyses were performed (Table B7.6.1).

As discussed in Section 7.2.7, the economic evaluation focussed on the comparison of alemtuzumab and SC IFNβ-1a 44µg, and therefore structural uncertainty was investigated in active RRMS primarily for this comparison. The rationale for using SC IFNβ-1a 44µg was that it was the most efficacious treatment of the beta-interferons and glatiramer acetate according to the MTC (see Section B6.7.7), in terms of reduction in SAD and relapse. In addition, this concurs with the EMA regulators perspective that SC IFNβ-1a 44µg was an appropriate comparator in the CARE MS trials. It is thought that those patients being managed on alemtuzumab in place of interferons or glatiramer acetate would be those in whom a more efficacious treatment would be perceived as being needed and in the absence of alemtuzumab it is thought that Rebif 44 would be used. In addition, since the CARE-MS trials provide a direct comparison of alemtuzumab vs. IFNβ-1a 44µg, of all the DMTs available on the UK RSS, results from the economic evaluation have focussed on this comparison since it allows direct comparison as well as MTC comparison data to be used.

Sensitive scenarios were also tested in the HA RRMS despite treatment with a beta interferon and RES RRMS populations versus fingolimod and natalizumab, respectively (see Section B7.9).

Table B7.6.1 Structural uncertainty analyses per**formed for alemtuzumab versus SC IFNβ-1a 44µg in the** active RRMS population, fingolimod in the HA RRMS despite treatment with a beta interferon population and natalizumab in the RES RRMS population

Area of uncertainty	Base case	Alternative scenarios	Justification	Comparison / Population
RRMS natural history transition probabilities	London Ontario (active RRMS) combined with TOWER and TEMSO transitions probabilities from EDSS 0	London Ontario (all RRMS) combined with TOWER and TEMSO transitions probabilities from EDSS 0	See Section B7.2.5	Active RRMS

Evaluation of efficacy	Natural history method with MTC data	Direct comparison method	See Section B7.3.2	Active RRMS
Extrapolation of clinical parameters over duration of model	No waning of treatment effect	Treatment effect reduction by 50% after 5 years for all comparators	See Section B7.3.2	Active RRMS, HA RRMS despite treatment with a beta interferon, RES RRMS
Natural history costs	Tyas 2007	Karampampa, 2012	See Section B7.5.3	Active RRMS
Retreatment with alemtuzumab	Year 3 = [redacted]%, Year 4-5 = [redacted]%; Year 6+ = [redacted]%	Year 3+ = 19.5% - source CARE MS I / II extension study and linking retreatment rates to relapse rates	See Section B7.5.1. (p301)	Active RRMS, HA RRMS despite treatment with a beta interferon, RES RRMS
Discount rates for costs and outcomes	3.5%	0% and 6%	Recommended by NICE [NICE, 2008]	Active RRMS

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section B7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Full one-way deterministic sensitivity analyses (DSA) were performed for alemtuzumab versus SC IFNβ-1a 44µg in the active RRMS population to test variation of a wide range of parameters through 95% confidence intervals where possible and 10% variation in the absence of confidence intervals (Table B7.6.2 and B7.6.3). Drug costs were omitted as these are assumed to have no variation. Furthermore, one-way sensitivity analyses were performed for additional comparisons and populations on the top five most sensitive parameters in the one-way analysis of alemtuzumab versus SC IFNβ-1a 44µg in the active RRMS population. These additional abridged one-way analyses were performed for alemtuzumab versus fingolimod in both the active RRMS and HA RRMS despite treatment with a beta interferon population, as well as alemtuzumab versus natalizumab in both the active RRMS and RES RRMS population. Additionally, three-way parameter sensitivity analysis was performed for the clinical parameters sourced from the MTC (3-month SAD, ARR, withdrawal) on alemtuzumab versus all comparators in the active RRMS population.

All scenario and one-way sensitivity analyses were conducted deterministically as opposed to probabilistically, since the deterministic and probabilistic results were comparable, suggesting that any sensitivity in the model could be identified through a deterministic approach.

Table B7.6.2 Deterministic one-way parameter uncertainty analyses performed in the economic model presented through tornado diagrams for alemtuzumab **versus SC IFNβ-1a 44µg in the active RRMS** population, with abridged analysis also performed for fingolimod and natalizumab

Area of uncertainty	Parameter	Variation	Reference to submission
Clinical data	Hazard ratio of sustained accumulation of disability	95% confidence intervals	Section B7.3.2
	ARR	95% confidence intervals	Section B7.3.1
	Withdrawal	95% confidence intervals	Section B7.3.1
	Proportion hospitalised RR	10%	Section B7.3.1
Quality of life	EQ-5D utilities by EDSS score and MS classification	95% confidence intervals	Section B7.4.6
	Adverse event disutility	10%	Section B7.4.8
	Carer disutility	10%	Section B7.4.6
	Disutility of relapse leading to hospitalisation	10%	Section B7.4.6
	Disutility of relapse not leading to hospitalisation	10%	Section B7.4.6
Cost and resource use parameters	Administration costs	10%	Section B7.4.1
	Monitoring costs	10%	Section B7.4.1
	Total adverse events	10%	Section B7.4.7
	Cost of relapse leading to hospitalisation	10%	Section B7.4.8
	Cost of relapse not leading to hospitalisation	10%	Section B7.4.8
	Disease costs (direct medical, indirect medical, other direct)	10%	Section B7.5.6

Table B7.6.3 Deterministic parameter uncertainty analyses performed in the economic model to test sources of data used

Area of uncertainty	Base case	Alternative scenarios	Reference to submission
Clinical data	Post-2000, ≥80% RRMS	Post-2000, 100% RRMS	See Additional Appendix 2 and Section B7.3.1
		All-years, ≥80% RRMS	See Additional Appendix 2 and Section B7.3.1
		All-years, 100% RRMS	See Additional Appendix 2 and

			Section B7.3.1

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section B7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Table B7.6.4 details which parameters were included in the PSA along with the distribution used to generate stochastic values. Natural history transition probabilities from London Ontario and placebo arms of TEMSO/TOWER were omitted from the PSA because there are small sample sizes in high RRMS EDSS states and low SPMS EDSS states resulting in unrealistic stochastic transition probabilities that would not be feasible in clinical practice. The probabilities of conversion from RRMS to SPMS estimated from London Ontario were also excluded for the same reason. Transition probability variation was captured by varying the hazard ratio of sustained accumulation of disability probabilistically which is applied to the natural history transitions to create the treatment transitions matrices (see Section B7.3.2). Furthermore, parameter sensitivity analysis was performed using all RRMS patients rather than the base case of active RRMS patients.

The PSA was performed for alemtuzumab versus all comparators in active RRMS with a multi-CEAC and CEAF presented. However, ICER planes are only presented for SC IFNβ-1a 44µg, fingolimod and natalizumab in line with the discussion of comparators. The PSA was performed for alemtuzumab versus fingolimod and SC IFNβ-1a 44µg in the HA RRMS despite treatment with a beta interferon population but only the ICER plane and CEAC were presented versus fingolimod as it is the more appropriate comparator in the subgroup. Similarly, PSA was performed for alemtuzumab versus natalizumab and SC IFNβ-1a 44µg in the RES RRMS population, with ICER plane and CEAC for the comparison against natalizumab only.

Table B7.6.4 Parameters included in probabilistic sensitivity analysis (PSA)

Parameter	Included in PSA	Distribution	Derivation of priors or assumptions
Discount rates on costs and outcomes	No	-	-
Time horizon	No	-	-
Initial EDSS distribution		-	-
Baseline characteristics of cohort (male to female ratio and age)	No	-	-
Natural history transition matrices	No	-	-
Natural history RRMS to	No	-	-

SPMS conversion probabilities			
Natural history relapse rate	Yes	Normal	Assumption of 10% standard error
Natural history proportion of relapses leading to hospitalisation	Yes	Beta	-
3-month SAD HRs	Yes	Gamma	Standard error derived from 95% confidence intervals sourced from MTC
ARRs	Yes	Gamma	Standard error derived from 95% confidence intervals sourced from MTC
Proportion hospitalised	Yes	Gamma	Assumption of 10% standard error
Withdrawal rates	Yes	Beta	Standard error derived from 95% confidence intervals sourced from MTC
Disease costs (direct medical, indirect medical, other direct)	Yes	Gamma	Assumption of 10% standard error
Cost of relapse	Yes	Gamma	Assumption of 10% standard error
Drug acquisition costs	No	-	-
Administration costs	Yes	Gamma	Assumption of 10% standard error
Monitoring costs	Yes	Gamma	Assumption of 10% standard error
Adverse event costs	Yes	Gamma	Assumption of 10% standard error
Utility values per EDSS and MS classification	Yes	Gamma	Assumption of 10% standard error. 95% confidence intervals were available for utility per EDSS but utility is calculated in the model as a combination of utility per EDSS and caregiver disutility, for which confidence intervals were not available
Disutility per relapse	Yes	Gamma	Assumption of 10% standard error
Disutility of adverse events	Yes	Gamma	Assumption of 10% standard error
Caregiver disutility	Yes	Gamma	Assumption of 10% standard error: see Utility values per EDSS and MS classification above

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any

differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

A comparison between clinical and model output is made in Table B7.7.1 for alemtuzumab versus SC IFNβ-1a 44µg in the base case model. All clinical trial outputs have been taken from published literature where possible, however, EQ-5D data were not available from published literature so have been extracted from the CSRs [Cohen et al. 2012; Coles et al. 2012; Genzyme CARE-MS I CSR; Genzyme CARE-MS II CSR]. All model results have been taken from the end of year 2, with the exception of EQ-5D which was taken from the mid-cycle corrections between year 1 and year 2 (which equates to month 18) due to complexity in calculation.

There appear to be differences between the model outputs and the clinical trial results. Nevertheless, the percentage difference in outcomes observed between alemtuzumab and SC IFNβ-1a 44µg in the CARE MS trials do appear to translate to the percentage difference observed in the model:

- Firstly, patients in the model start at a higher EDSS, which is due to the fact that baseline characteristics of the model population is based on the UK RSS as opposed to a multicentre study. In addition, the increase in EDSS is more pronounced in the model, which is likely due to the fact that patients are unable to regress in EDSS. This is a consequence of the model design.

- Secondly there are generally more relapses in the model than the trials; this is likely a consequence of relapses being calculated based on EDSS state and not using the clinical trial data directly.

- Thirdly quality of life is lower in the model than the clinical trial. This is due to the fact that patients are in a worse EDSS state when starting the model, and are not able to regress which therefore may accelerate their decline to an extent, leading to poorer quality of life outcomes.

- Mortality is similar between the model and clinical trials.

Table B7.7.1 Summary of alemtuzumab and SC IFNβ-1a 44µg model results compared with clinical data from CARE-MS I and CARE-MS II

Outcome tested	Specific parameter	Time point	Alemtuzumab clinical trial result	Alemtuzumab model result	**SC IFNβ**-1a **44µg clinical** trial result	**SC IFNβ**-1a **44µg model** result
Disability / Symptoms of multiple sclerosis / Freedom of disease activity	EDSS change from baseline	Base line	CARE-MS I [redacted] CARE-MS II [redacted]	3.3	CARE-MS I [redacted] CARE-MS II [redacted]	3.3
		Year 2	CARE-MS I - [redacted] CARE-MS II [redacted]	0.9	CARE-MS I - [redacted] CARE-MS II [redacted]	1.1
Relapse rate / Severity of relapse / Resource utilisation: hospitalisation	Average number of relapses per patient	Year 2	CARE-MSI [redacted] CARE-MSII [redacted]	0.7	CARE-MS I [redacted] CARE-MS II [redacted]	1.3
Health related quality of life	Mean EQ-5D	Year 2	CARE-MS [redacted] CARE-MS II [redacted]	0.54	CARE-MS I mean [redacted] CARE-MS II [redacted]	0.48
	Change in EQ-5D from baseline	Year 2	CARE-MS I [redacted] CARE-MS II [redacted]	-0.06	CARE-MS I [redacted] CARE-MS II [redacted]	-0.12
Mortality	2-year mortality	Year 2	CARE-MS I [redacted] CARE-MS II [redacted]	0.2%	CARE-MS I [redacted] CARE-MS II [redacted]	0.2%

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The mid-year estimate Markov traces for alemtuzumab and SC IFNβ-1a 44µg are presented in Additional Appendix 16. Presented below in Tables B7.7.2-3, the Markov traces show that after one year of treatment, [redacted] of patients are still receiving benefit of alemtuzumab. [redacted] are receiving the benefit of BSC; this is a consequence of disease progression to SPMS and stopping rule at EDSS 7. In comparison, only [redacted] of the cohort remains on treatment with SC IFNβ-1a 44µg after one year.

Table B7.7.2 Alemtuzumab (mid-year estimates)

Year	RRMS											SPMS											Total
	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10	
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

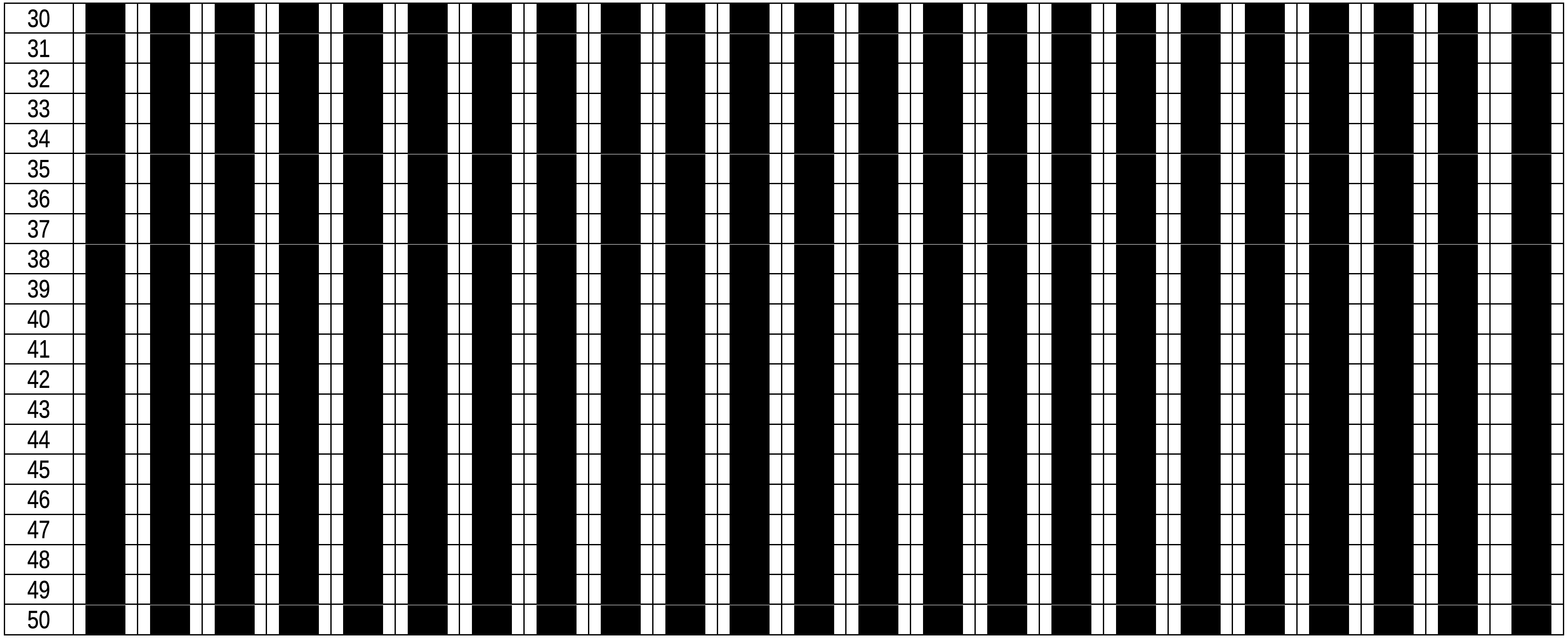
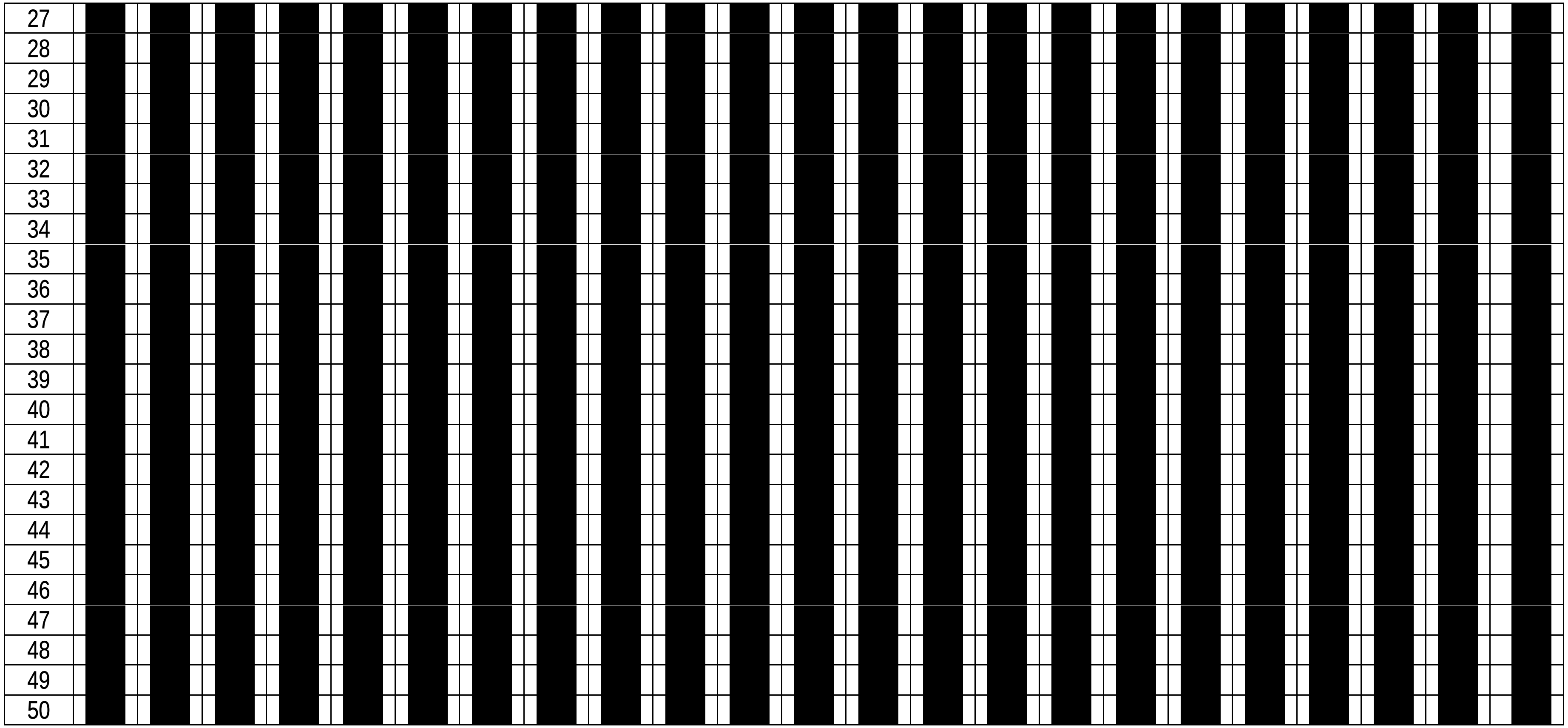

30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

Table B7.7.3 SC IFNβ-1a 44µg (mid-year estimates)

Year	RRMS											SPMS											Total
	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10	
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]


27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The total QALYs from a cohort are composed of: health state utility, adverse event disutility, caregiver disutility and relapse disutility. Utility scores for each health state are added to caregiver disutility per health state and applied to the Markov trace for each treatment to give the EDSS utility for the cohort. Relapse rates and adverse event disutilities are also applied to Markov traces separately. The three sets of the utility per health state over time are combined and accrued QALYs calculated. Discounted cumulative QALYs over time for alemtuzumab and the SC IFNβ-1a 44µg are presented in Table B7.7.4.

Table B7.7.4 Alemtuzumab and SC IFNβ-1a 44µg accrued deterministic QALYs over time

	Alemtuzumab					**SC IFNβ-1a 44µg**				
Year	EDSS utility	Non-hospital relapse disutility	Hospital relapse disutility	Adverse event disutility	Cumulative QALYs	EDSS utility	Non-hospital relapse disutility	Hospital relapse disutility	Adverse event disutility	Cumulative QALYs
1	0.57	0.00	0.00	0.00	0.56	0.56	0.00	0.00	-0.02	0.54
2	1.08	-0.01	0.00	-0.01	1.06	1.06	-0.01	-0.01	-0.03	1.01
3	1.54	-0.01	0.00	-0.02	1.52	1.49	-0.02	-0.01	-0.04	1.43
4	1.96	-0.01	-0.01	-0.02	1.92	1.87	-0.02	-0.01	-0.05	1.79
5	2.33	-0.01	-0.01	-0.03	2.28	2.20	-0.02	-0.02	-0.05	2.11
6	2.65	-0.02	-0.01	-0.03	2.60	2.48	-0.03	-0.02	-0.06	2.37
7	2.94	-0.02	-0.01	-0.03	2.88	2.71	-0.03	-0.02	-0.06	2.59
8	3.19	-0.02	-0.01	-0.03	3.12	2.90	-0.04	-0.03	-0.06	2.77
9	3.40	-0.03	-0.02	-0.03	3.33	3.05	-0.04	-0.03	-0.06	2.92
10	3.58	-0.03	-0.02	-0.03	3.51	3.18	-0.05	-0.03	-0.06	3.03
11	3.74	-0.03	-0.02	-0.03	3.66	3.28	-0.05	-0.04	-0.07	3.13
12	3.87	-0.04	-0.02	-0.03	3.79	3.35	-0.06	-0.04	-0.07	3.19
13	3.99	-0.04	-0.03	-0.03	3.89	3.41	-0.06	-0.04	-0.07	3.24
14	4.08	-0.04	-0.03	-0.03	3.98	3.45	-0.06	-0.05	-0.07	3.27
15	4.15	-0.05	-0.03	-0.03	4.05	3.48	-0.07	-0.05	-0.07	3.29
16	4.21	-0.05	-0.03	-0.03	4.10	3.49	-0.07	-0.05	-0.07	3.30
17	4.26	-0.05	-0.03	-0.03	4.14	3.49	-0.07	-0.05	-0.07	3.30
18	4.29	-0.06	-0.04	-0.03	4.18	3.49	-0.07	-0.06	-0.07	3.29
19	4.32	-0.06	-0.04	-0.03	4.20	3.48	-0.08	-0.06	-0.07	3.28
20	4.34	-0.06	-0.04	-0.03	4.21	3.47	-0.08	-0.06	-0.07	3.26

21	4.35	-0.06	-0.04	-0.03	4.22	3.45	-0.08	-0.06	-0.07	3.24
22	4.36	-0.06	-0.04	-0.03	4.22	3.43	-0.08	-0.06	-0.07	3.21
23	4.36	-0.07	-0.05	-0.03	4.22	3.41	-0.09	-0.07	-0.07	3.18
24	4.36	-0.07	-0.05	-0.03	4.21	3.38	-0.09	-0.07	-0.07	3.16
25	4.35	-0.07	-0.05	-0.03	4.20	3.36	-0.09	-0.07	-0.07	3.13
26	4.34	-0.07	-0.05	-0.03	4.19	3.33	-0.09	-0.07	-0.07	3.10
27	4.33	-0.07	-0.05	-0.03	4.18	3.31	-0.09	-0.07	-0.07	3.08
28	4.32	-0.08	-0.05	-0.03	4.17	3.29	-0.10	-0.07	-0.07	3.05
29	4.31	-0.08	-0.05	-0.03	4.16	3.27	-0.10	-0.07	-0.07	3.03
30	4.30	-0.08	-0.06	-0.03	4.14	3.24	-0.10	-0.08	-0.07	3.00
31	4.29	-0.08	-0.06	-0.03	4.13	3.23	-0.10	-0.08	-0.07	2.98
32	4.28	-0.08	-0.06	-0.03	4.12	3.21	-0.10	-0.08	-0.07	2.96
33	4.27	-0.08	-0.06	-0.03	4.10	3.19	-0.10	-0.08	-0.07	2.94
34	4.26	-0.08	-0.06	-0.03	4.09	3.18	-0.10	-0.08	-0.07	2.93
35	4.25	-0.08	-0.06	-0.03	4.08	3.16	-0.10	-0.08	-0.07	2.91
36	4.24	-0.08	-0.06	-0.03	4.07	3.15	-0.10	-0.08	-0.07	2.90
37	4.24	-0.08	-0.06	-0.03	4.06	3.14	-0.10	-0.08	-0.07	2.89
38	4.23	-0.08	-0.06	-0.03	4.06	3.13	-0.10	-0.08	-0.07	2.88
39	4.22	-0.08	-0.06	-0.03	4.05	3.13	-0.10	-0.08	-0.07	2.87
40	4.22	-0.08	-0.06	-0.03	4.05	3.12	-0.10	-0.08	-0.07	2.87
41	4.22	-0.09	-0.06	-0.03	4.04	3.12	-0.10	-0.08	-0.07	2.86
42	4.21	-0.09	-0.06	-0.03	4.04	3.11	-0.11	-0.08	-0.07	2.86
43	4.21	-0.09	-0.06	-0.03	4.04	3.11	-0.11	-0.08	-0.07	2.86
44	4.21	-0.09	-0.06	-0.03	4.04	3.11	-0.11	-0.08	-0.07	2.85
45	4.21	-0.09	-0.06	-0.03	4.04	3.11	-0.11	-0.08	-0.07	2.85
46	4.21	-0.09	-0.06	-0.03	4.03	3.11	-0.11	-0.08	-0.07	2.85
47	4.21	-0.09	-0.06	-0.03	4.03	3.11	-0.11	-0.08	-0.07	2.85
48	4.21	-0.09	-0.06	-0.03	4.03	3.11	-0.11	-0.08	-0.07	2.85
49	4.21	-0.09	-0.06	-0.03	4.03	3.11	-0.11	-0.08	-0.07	2.85
50	4.21	-0.09	-0.06	-0.03	4.03	3.11	-0.11	-0.08	-0.07	2.85

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Life years per health state are presented in Table B7.7.5. QALYs accrued for the clinical outcomes of sustained accumulation of disability and relapse are presented in Table B7.7.4.

Table B7.7.5 Summary of deterministic LY gain by health state over 50 year time horizon of model

Health state	LY Alemtuzumab	LY **SC IFNβ**-1a **44µg**	Increment	Absolute increment	% absolute increment
RRMS EDSS 0	0.05	0.03	0.02	0.02	1%
RRMS EDSS 1	0.47	0.32	0.15	0.15	5%
RRMS EDSS 2	1.28	0.92	0.36	0.36	13%
RRMS EDSS 3	1.63	1.26	0.37	0.37	13%
RRMS EDSS 4	0.87	0.63	0.23	0.23	8%
RRMS EDSS 5	0.50	0.39	0.11	0.11	4%
RRMS EDSS 6	1.64	1.47	0.17	0.17	6%
RRMS EDSS 7	0.22	0.28	-0.06	0.06	2%
RRMS EDSS 8	0.26	0.37	-0.11	0.11	4%
RRMS EDSS 9	0.00	0.00	0.00	0.00	0%
SPMS EDSS 0	0.00	0.00	0.00	0.00	0%
SPMS EDSS 1	0.00	0.00	0.00	0.00	0%
SPMS EDSS 2	0.03	0.03	0.00	0.00	0%
SPMS EDSS 3	0.19	0.17	0.02	0.02	1%
SPMS EDSS 4	0.32	0.31	0.02	0.02	1%
SPMS EDSS 5	0.28	0.27	0.02	0.02	1%
SPMS EDSS 6	1.82	1.74	0.09	0.09	3%
SPMS EDSS 7	1.05	1.10	-0.05	0.05	2%
SPMS EDSS 8	6.41	7.01	-0.60	0.60	21%
SPMS EDSS 9	1.58	2.08	-0.50	0.50	17%
Total	18.62	18.38	0.23	2.89	100%

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B7.7.6 Summary of deterministic QALY gain by health state over 50 year time horizon of model

Health state	QALY Alemtuzumab	QALY **SC IFNβ-1a 44µg**	Increment	Absolute increment	% absolute increment
RRMS EDSS 0	0.04	0.03	0.02	0.02	2%
RRMS EDSS 1	0.37	0.25	0.12	0.12	10%
RRMS EDSS 2	0.90	0.64	0.25	0.25	20%
RRMS EDSS 3	0.92	0.71	0.21	0.21	17%
RRMS EDSS 4	0.52	0.38	0.14	0.14	11%
RRMS EDSS 5	0.25	0.20	0.06	0.06	4%
RRMS EDSS 6	0.71	0.64	0.07	0.07	6%
RRMS EDSS 7	0.05	0.07	-0.02	0.02	1%
RRMS EDSS 8	-0.04	-0.06	0.02	0.02	1%
RRMS EDSS 9	0.00	0.00	0.00	0.00	0%
SPMS EDSS 0	0.00	0.00	0.00	0.00	0%
SPMS EDSS 1	0.00	0.00	0.00	0.00	0%
SPMS EDSS 2	0.02	0.02	0.00	0.00	0%
SPMS EDSS 3	0.10	0.09	0.01	0.01	1%
SPMS EDSS 4	0.18	0.17	0.01	0.01	1%
SPMS EDSS 5	0.13	0.13	0.01	0.01	1%
SPMS EDSS 6	0.76	0.72	0.04	0.04	3%
SPMS EDSS 7	0.26	0.28	-0.01	0.01	1%
SPMS EDSS 8	-0.60	-0.66	0.06	0.06	5%
SPMS EDSS 9	-0.38	-0.50	0.12	0.12	10%
Adverse event utilities	-0.03	-0.07	0.04	0.04	3%
Relapse leading to hospitalisation utility	-0.06	-0.08	0.02	0.02	2%
Relapse not leading to hospitalisation utility	-0.09	-0.11	0.02	0.02	2%
Total	4.03	2.85	1.18	1.24	100%

Table B7.7.7 Summary of deterministic costs by health state

Cost parameter	Health state	Cost Alemtuzumab	Cost SC **IFNβ**-1a **44µg**	Inc	Absolute inc	% absolute inc
Disease costs (direct medical, direct non-medical)	RRMS EDSS 0	291	169	122	122	0%
	RRMS EDSS 1	2,788	1,890	897	897	1%
	RRMS EDSS 2	9,099	6,529	2,570	2,570	2%
	RRMS EDSS 3	17,725	13,698	4,026	4,026	4%
	RRMS EDSS 4	6,712	4,897	1,816	1,816	2%
	RRMS EDSS 5	5,783	4,508	1,275	1,275	1%
	RRMS EDSS 6	20,993	18,869	2,125	2,125	2%
	RRMS EDSS 7	5,295	6,843	-1,548	1,548	1%
	RRMS EDSS 8	9,055	12,697	-3,642	3,642	3%
	RRMS EDSS 9	76	105	-29	29	0%
	SPMS EDSS 0	0	0	0	0	0%
	SPMS EDSS 1	0	0	0	0	0%
	SPMS EDSS 2	212	183	29	29	0%
	SPMS EDSS 3	2,039	1,839	199	199	0%
	SPMS EDSS 4	2,511	2,383	128	128	0%
	SPMS EDSS 5	3,269	3,054	215	215	0%
	SPMS EDSS 6	23,337	22,233	1,104	1,104	1%
	SPMS EDSS 7	25,418	26,689	-1,271	1,271	1%
	SPMS EDSS 8	221,204	241,923	-20,718	20,718	19%
	SPMS EDSS 9	51,408	67,756	-16,348	16,348	15%
Treatment costs (Acquisition, administration, monitoring, adverse events)	RRMS EDSS 0	1,270	226	1,044	1,044	1%
	RRMS EDSS 1	5,318	1,819	3,499	3,499	3%
	RRMS EDSS 2	14,451	5,049	9,402	9,402	9%
	RRMS EDSS 3	15,804	6,289	9,515	9,515	9%
	RRMS EDSS 4	12,325	3,674	8,651	8,651	8%
	RRMS EDSS 5	6,594	2,199	4,395	4,395	4%
	RRMS EDSS 6	14,585	6,875	7,710	7,710	7%
	RRMS EDSS 7	63	0	63	63	0%
	RRMS EDSS 8	57	0	57	57	0%
	RRMS EDSS 9	1	0	1	1	0%
	SPMS EDSS 0	0	0	0	0	0%
	SPMS EDSS 1	0	0	0	0	0%

	SPMS EDSS 2	19	0	19	19	0%
	SPMS EDSS 3	86	0	86	86	0%
	SPMS EDSS 4	137	0	137	137	0%
	SPMS EDSS 5	100	0	100	100	0%
	SPMS EDSS 6	72	0	72	72	0%
	SPMS EDSS 7	277	0	277	277	0%
	SPMS EDSS 8	0	0	0	0	0%
	SPMS EDSS 9	0	0	0	0	0%
Cost of relapse leading to hospitalisation	All health states – not captured separately	12,870	16,991	-4,121	4,121	4%
Cost of relapse not leading to hospitalisation	All health states – not captured separately	8,102	9,968	-1,866	1,866	2%
Total Cost		499,347	489,354	9,993	109,079	100%
Inc, increment						

Table B7.7.8 Summary of predicted resource use by category of cost (£)

Item	Cost Alemtuzumab	**Cost SC IFNβ-1a 44µg**	Increment	Absolute increment	% absolute increment
Technology cost	63,468	24,985	38,483	38,483	48%
Administration cost	4,429	127	4,302	4,302	5%
Monitoring cost	2,750	993	1,757	1,757	2%
Adverse event cost	514	26	488	488	1%
Relapse cost	20,972	26,959	-5,987	5,987	7%
Disease cost	407,214	436,264	-29,050	29,050	36%
Total	499,347	489,354	9,993	80,067	100%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The base case results presented are probabilistic since the model is a complex non-linear model. The use of probabilistic base case results were recommended by the ERG reviewing the fingolimod STA submission [Novartis, 2011]. The probabilistic and deterministic results are presented in Tables B7.7.9 and B7.7.12. The corresponding incremental analysis in Tables B7.7.10-11 and Tables B7.7.13-14 subsequently removes technologies which are strongly or extendedly dominated.

The probabilistic and deterministic base case shows that the relevant comparison (after removing technologies strongly and extendedly dominated) is alemtuzumab vs. glatiramer acetate. ICERs of £7,017 (probabilistic) and £8,924 (deterministic) were estimated.

As discussed previously, the EPAR stated that SC IFNβ-1a 44µg is the most appropriate active comparator from a regulatory perspective. In addition, of the interferons and glatiramer acetate provided by the UK RSS, SC IFNβ-1a 44µg has been shown to be the most effective based on the MTC. Hence, it appears that the most appropriate comparator within active RRMS is SC IFNβ-1a 44µg and not glatiramer acetate. When considering the incremental analysis, alemtuzumab extendedly dominates SC IFNβ-1a 44µg, and when directly comparing alemtuzumab with SC IFNβ-1a 44µg an ICER of £8,445 per QALY was calculated, which strengthens the conclusion that alemtuzumab is the most cost-effective treatment in active RRMS.

Table B7.7.9 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS ranked by cost

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Glatiramer acetate	484,590	2.887				
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	77,453
SC IFNβ-1a 22µg	487,642	3.034	3,052	0.147	20,713	2,459
IM IFNβ-1a	492,860	2.872	8,270	-0.014	Dominated	Dominated
Alemtuzumab	494,319	4.273	9,729	1.386	7,017	1,042

IFNβ-1b	497,009	2.632	12,420	-0.255	Dominated	Dominated
Fingolimod (assumed PAS price £13,000)	506,377	3.089	21,788	0.202	107,778	20,503
Natalizumab	510,726	3.434	26,136	0.547	47,757	12,599
Fingolimod	528,570	3.106	43,980	0.220	200,200	Dominated
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.10 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are strongly dominated

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Glatiramer acetate	484,590	2.887				
SC IFNβ-1a 44µg	487,368	2.923	2,778	0.036	77,453	77,453
SC IFNβ-1a 22µg	487,642	3.034	3,052	0.147	20,713	2,459
Alemtuzumab	494,319	4.273	9,729	1.386	7,017	5,388
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.11 Incremental probabilistic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are extendedly dominated

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Glatiramer acetate	484,590	2.887				
Alemtuzumab	494,319	4.273	9,729	1.386	7,017	7,017
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.12 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Glatiramer acetate	487,842	2.745				

SC IFNβ-1a 44µg	489,354	2.850	1,512	0.106	14,277	14,277
SC IFNβ-1a 22µg	490,388	2.854	2,545	0.110	23,227	280,045
IM IFNβ-1a	494,626	2.764	6,784	0.019	354,272	Dominated
Alemtuzumab	499,347	4.034	11,505	1.289	8,924	3,717
IFNβ-1b	502,969	2.329	15,127	-0.416	Dominated	Dominated
Fingolimod (assumed PAS price £13,000)	507,049	3.068	19,207	0.323	59,443	5,520
Fingolimod	529,094	3.068	41,252	0.323	127,672	Dominated
Natalizumab	530,800	3.373	42,958	0.628	68,383	5,591
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.13 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are strongly dominated

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Glatiramer acetate	487,842	2.745				
SC IFNβ-1a 44µg	489,354	2.850	1,512	0.106	14,277	14,277
SC IFNβ-1a 22µg	490,388	2.854	2,545	0.110	23,227	280,045
Alemtuzumab	499,347	4.034	11,505	1.289	8,924	7,595
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.14 Incremental deterministic base-case results of alemtuzumab versus all comparators in active RRMS after removing treatments which are extendedly dominated

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Glatiramer acetate	487,842	2.745				
Alemtuzumab	499,347	4.034	11,505	1.289	8,924	8,924

ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

As described in Section B7.6.2, deterministic one-way sensitivity analyses were run for the base case of alemtuzumab versus SC IFNβ-1a 44µg, fingolimod and natalizumab. The results of the one-way analysis are presented in a tornado diagram in Figures B7.7.1-3 and Table B7.7.15-17. For active RRMS all of the parameters were varied in the one-way sensitivity analysis, and many parameters for which results were insensitive to were noted. Therefore, to reduce the number of sensitivity analyses presented for HA disease despite treatment with a beta interferon and RES, only the top 5 most sensitive parameters were analysed. Tornados considered net monetary benefit as opposed to ICERs since some sensitivity analyses resulted in dominance.

As illustrated in Figure B7.7.1, SAD HRs are the key drivers within the cost-effectiveness model. The range of uncertainty in the probabilistic results (Figure B7.7.1) is a consequence of the relatively wide confidence intervals in hazard ratios of 3 month sustained accumulation of disability obtained from the MTC.

Figure B7.7.1 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS

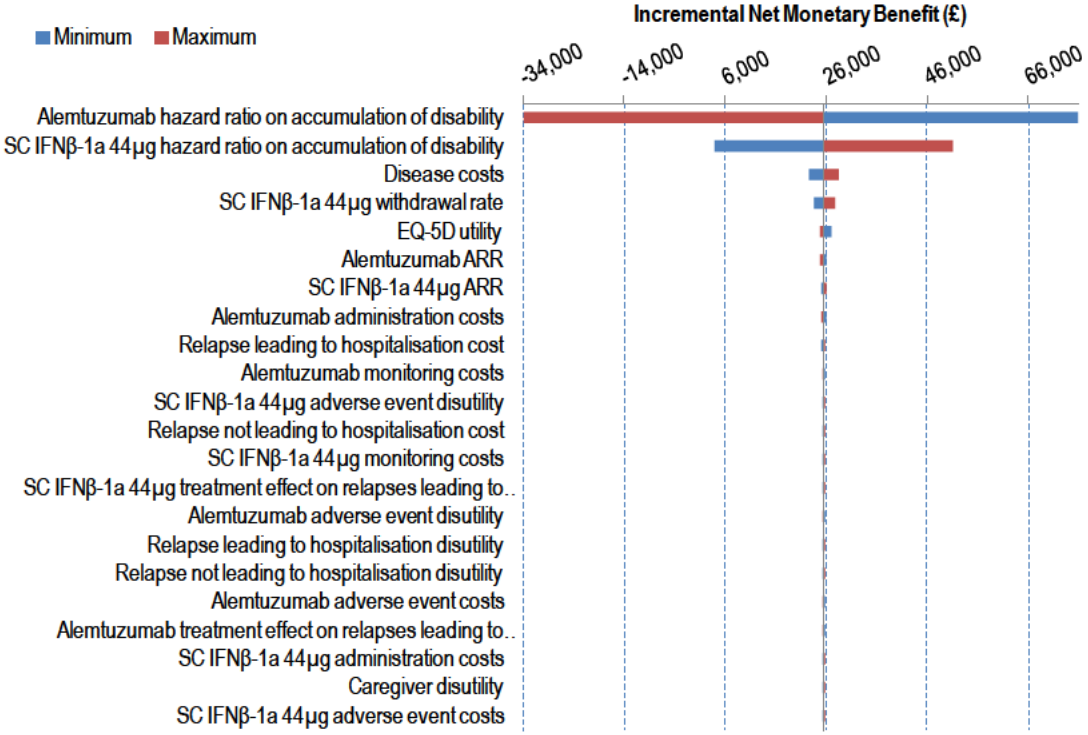


Figure B7.7.2 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS

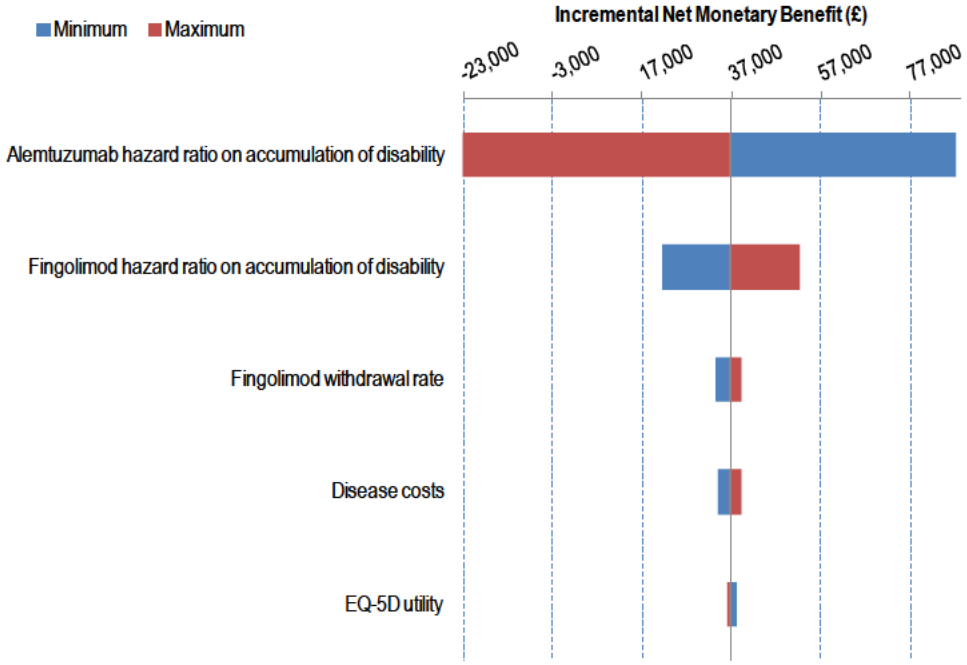


Figure B7.7.3 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus natalizumab in active RRMS

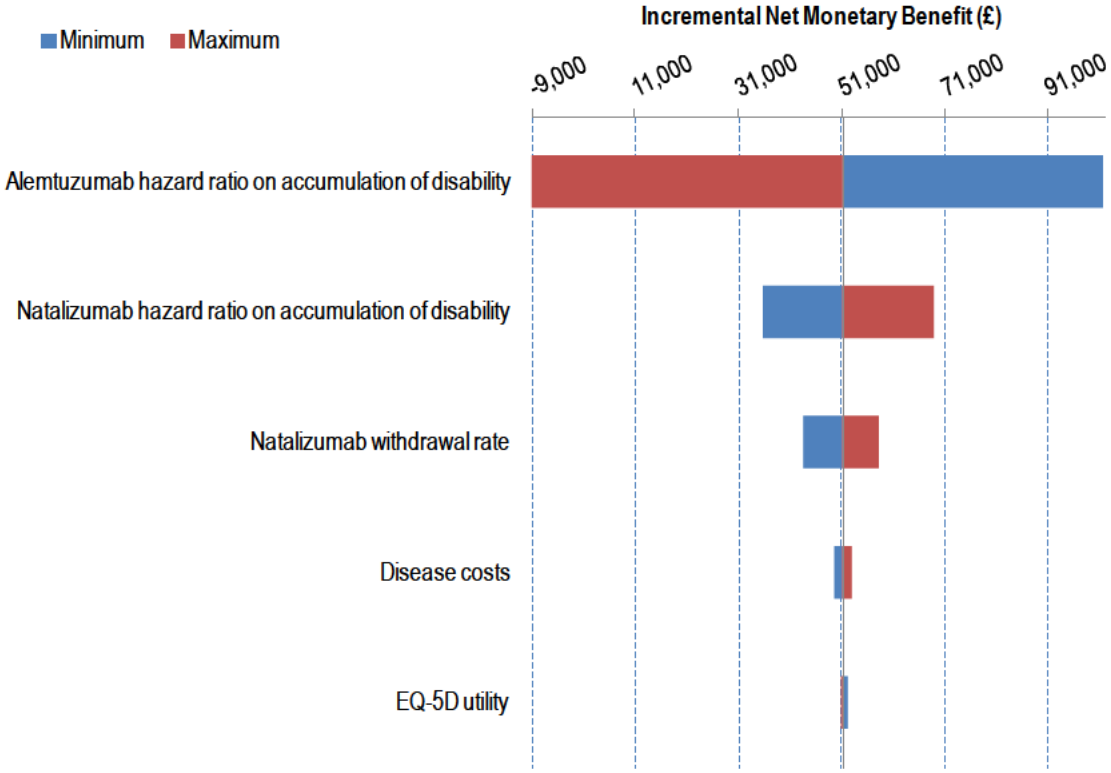


Table B7.7.15 One way sensitivity analysis results of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS

		Minimum						Maximum					
	Variation	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB
Base case		499,347	4.034	9,993	1.183	8,445	25,505						
Alemtuzumab hazard ratio on sustained accumulation of disability	95% CI	477,963	5.003	-11,391	2.152	Dominates	75,958	525,050	2.880	35,696	0.030	1,200,973	-34,804
SC IFNβ-1a 44µg hazard ratio on sustained accumulation of disability	95% CI	499,347	4.034	18,642	0.756	24,668	4,029	499,347	4.034	-325	1.695	Dominates	51,184
Disease costs	+/- 10%	458,626	4.034	12,898	1.183	10,900	22,600	540,069	4.034	7,088	1.183	5,990	28,410
SC IFNβ-1a 44µg withdrawal rate	95% CI	499,347	4.034	12,946	1.220	10,613	23,649	499,347	4.034	6,356	1.139	5,580	27,812
EQ-5D utility	95% CI	499,347	-0.195	9,993	1.238	8,071	27,152	499,347	7.905	9,993	1.164	8,582	24,938
Alemtuzumab ARR	95% CI	498,913	4.038	9,559	1.187	8,052	26,057	499,843	4.029	10,488	1.179	8,898	24,874
SC IFNβ-1a 44µg ARR	95% CI	499,347	4.034	10,366	1.180	8,783	25,041	499,347	4.034	9,517	1.187	8,018	26,094
Alemtuzumab administration costs	+/- 10%	498,904	4.034	9,550	1.183	8,071	25,948	499,790	4.034	10,436	1.183	8,819	25,062
Relapse leading to hospitalisation cost	+/- 10%	498,060	4.034	10,405	1.183	8,793	25,093	500,634	4.034	9,581	1.183	8,097	25,917
Alemtuzumab monitoring costs	+/- 10%	499,072	4.034	9,718	1.183	8,213	25,780	499,622	4.034	10,268	1.183	8,678	25,230
SC IFNβ-1a 44µg adverse event disutility	+/- 10%	499,347	4.034	9,993	1.176	8,494	25,300	499,347	4.034	9,993	1.190	8,397	25,710
Relapse not leading to hospitalisation cost	+/- 10%	498,537	4.034	10,179	1.183	8,603	25,318	500,157	4.034	9,806	1.183	8,288	25,691
SC IFNβ-1a 44µg monitoring costs	+/- 10%	499,347	4.034	10,092	1.183	8,529	25,405	499,347	4.034	9,894	1.183	8,361	25,604
SC IFNβ-1a 44µg treatment effect on relapses leading to hospitalisation	+/- 10%	499,347	4.034	10,074	1.183	8,516	25,414	499,347	4.034	9,912	1.184	8,375	25,595
Alemtuzumab adverse event disutility	+/- 10%	499,347	4.036	9,993	1.186	8,426	25,585	499,347	4.031	9,993	1.181	8,464	25,425
Relapse leading to hospitalisation disutility	+/- 10%	499,347	4.040	9,993	1.181	8,459	25,445	499,347	4.028	9,993	1.185	8,431	25,564
Relapse not leading to hospitalisation	+/- 10%	499,347	4.042	9,993	1.181	8,459	25,445	499,347	4.025	9,993	1.185	8,431	25,564

disutility													
Alemtuzumab adverse event costs	+/- 10%	499,296	4.034	9,941	1.183	8,402	25,556	499,399	4.034	10,044	1.183	8,489	25,453
Alemtuzumab treatment effect on relapses leading to hospitalisation	+/- 10%	499,309	4.034	9,955	1.183	8,412	25,547	499,385	4.034	10,031	1.183	8,479	25,462
SC IFNβ-1a 44µg administration costs	+/- 10%	499,347	4.034	10,006	1.183	8,456	25,492	499,347	4.034	9,980	1.183	8,434	25,517
Caregiver disutility	+/- 10%	499,347	4.046	9,993	1.183	8,446	25,501	499,347	4.022	9,993	1.183	8,444	25,508
SC IFNβ-1a 44µg adverse event costs	+/- 10%	499,347	4.034	9,995	1.183	8,447	25,502	499,347	4.034	9,990	1.183	8,443	25,507

Table B7.7.16 One way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS

		Minimum						Maximum					
	Variation	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB
Base case		499,347	4.034	-7,702	0.966	Dominates	36,683						
Alemtuzumab hazard ratio on sustained accumulation of disability	95% CI	477,963	5.003	-29,086	1.935	Dominates	87,137	525,050	2.880	18,001	-0.187	Dominated	-23,626
Fingolimod hazard ratio on sustained accumulation of disability	95% CI	499,347	4.034	-2,725	0.627	Dominates	21,533	499,347	4.034	-12,792	1.314	Dominates	52,221
Fingolimod withdrawal rate	95% CI	499,347	4.034	-2,676	1.027	Dominates	33,497	499,347	4.034	-11,717	0.918	Dominates	39,242
Disease costs	+/- 10%	458,626	4.034	-5,172	0.966	Dominates	34,153	540,069	4.034	-10,232	0.966	Dominates	39,214
EQ-5D utility	95% CI	499,347	-0.195	-7,702	1.013	Dominates	38,104	499,347	7.905	-7,702	0.950	Dominates	36,208

Table B7.7.17 One way sensitivity analysis results of alemtuzumab versus natalizumab in active RRMS

		Minimum						Maximum					
	Variation	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB
Base case		499,347	4.034	-31,453	0.661	Dominates	51,282						
Alemtuzumab hazard ratio on sustained accumulation of disability	95% CI	477,963	5.003	-52,837	1.630	Dominates	101,735	525,050	2.880	-5,750	-0.493	11,673	-9,027

Natalizumab hazard ratio on sustained accumulation of disability	95% CI	499,347	4.034	-28,260	0.253	Dominates	35,845	499,347	4.034	-34,993	1.133	Dominates	68,979
Natalizumab withdrawal rate	95% CI	499,347	4.034	-19,512	0.806	Dominates	43,692	499,347	4.034	-42,219	0.532	Dominates	58,190
Disease costs	+/- 10%	458,626	4.034	-29,736	0.661	Dominates	49,565	540,069	4.034	-33,170	0.661	Dominates	52,999
EQ-5D utility	95% CI	499,347	-0.195	-31,453	0.692	Dominates	52,202	499,347	7.905	-31,453	0.652	Dominates	51,010

The sensitivity of the incremental results to the clinical parameters sourced from the MTC was tested for the SA MTCs of studies from all-years and 100% RRMS rather than the base case of post-2000 80% RRMS with corresponding results presented in Tables B7.7.18-20.

Table B7.7.18 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (all-years, 80% RRMS) for 3-month SAD, ARR and withdrawal

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Glatiramer acetate	481,311	3.009				
SC IFNβ-1a 44µg	486,669	2.950	5,357	-0.059	Dominated	Dominated by GA
SC IFNβ-1a 22µg	487,192	2.990	5,881	-0.019	Dominated	Dominated by GA
IFNβ-1b	492,497	2.769	11,185	-0.240	Dominated	Dominated by GA
IM IFNβ-1a	492,611	2.831	11,300	-0.178	Dominated	Dominated by GA
Alemtuzumab	493,981	4.278	12,670	1.269	9,982	9,982
Fingolimod (assumed PAS price £13,000)	506,427	3.081	25,116	0.072	Dominated	Dominated by alemtuzumab
Natalizumab	530,669	3.370	49,358	0.361	Dominated	Dominated by alemtuzumab
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.19 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (all-years, 100% RRMS) for 3-month SAD, ARR and withdrawal

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Glatiramer acetate	479,197	3.087				
IFNβ-1b	486,844	2.964	7,647	-0.122	Dominated	Dominated by GA
SC IFNβ-1a 22µg	489,570	2.777	10,372	-0.309	Dominated	Dominated by GA
SC IFNβ-1a 44µg	489,997	2.776	10,800	-0.310	Dominated	Dominated by GA

IM IFNβ-1a	494,745	2.718	15,547	-0.369	Dominated	Dominated by GA
Alemtuzumab	502,012	3.918	22,815	0.832	27,434	27,434
Fingolimod (assumed PAS price £13,000)	506,462	3.082	27,264	-0.005	Dominated	Dominated by alemtuzumab
Natalizumab	531,380	3.379	52,183	0.292	Dominated	Dominated by alemtuzumab
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

Table B7.7.20 Incremental deterministic results of alemtuzumab versus all comparators using sensitivity analysis MTC (post-2000, 100% RRMS) for 3-month SAD, ARR and withdrawal

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Glatiramer acetate	487,944	2.745				
SC IFNβ-1a 22µg	489,143	2.830	1,200	0.085	14,098	Extendedly Dominated by alemtuzumab
SC IFNβ-1a 44µg	489,929	2.823	1,985	0.078	25,401	Dominated by IFNβ-1a 22µg
IM IFNβ-1a	495,198	2.735	7,255	-0.010	Dominated	Dominated by IFNβ-1a 22µg
Alemtuzumab	501,055	3.957	13,111	1.212	10,822	10,822
IFNβ-1b	503,531	2.312	15,588	-0.433	Dominated	Dominated by alemtuzumab
Fingolimod (assumed PAS price £13,000)	507,358	3.071	19,414	0.326	59,524	Dominated by alemtuzumab
Natalizumab	530,740	3.372	42,797	0.627	68,281	Dominated by alemtuzumab
ICER, incremental-cost effectiveness ratio, QALY, quality-adjusted life year						

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Mean results of the PSA with 10,000 simulations are given in Table B7.7.9 as the base case. The corresponding scatter plots are given in Figure B7.7.4 for alemtuzumab versus SC IFNβ-1a 44µg, Figure B7.7.5 versus fingolimod with assumed PAS price of £13,000 per annum and Figure B7.7.6 versus natalizumab.

Figure B7.7.4 PSA scatter plot of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS

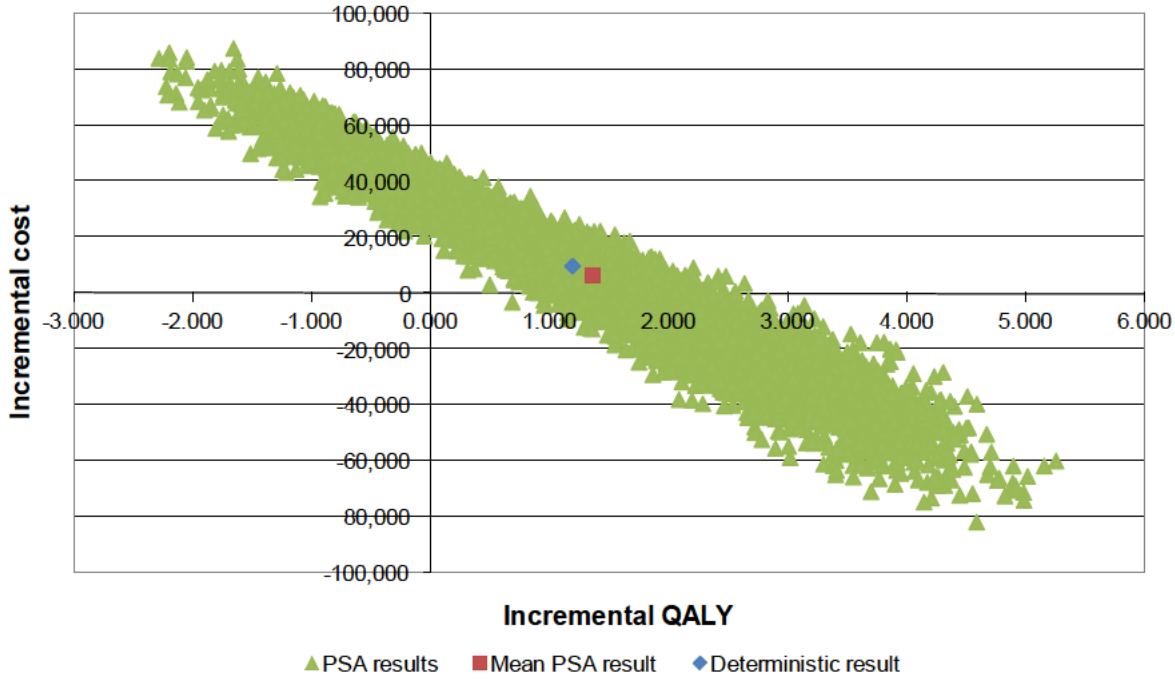


Figure B7.7.5 PSA scatter plot of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in active RRMS

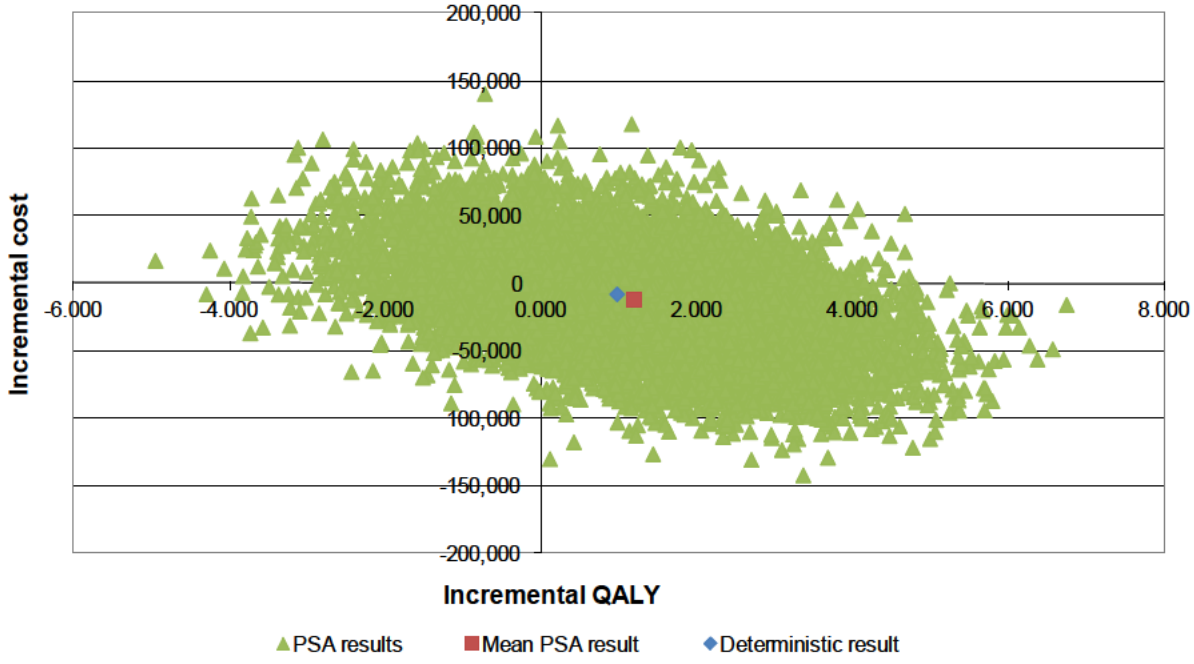
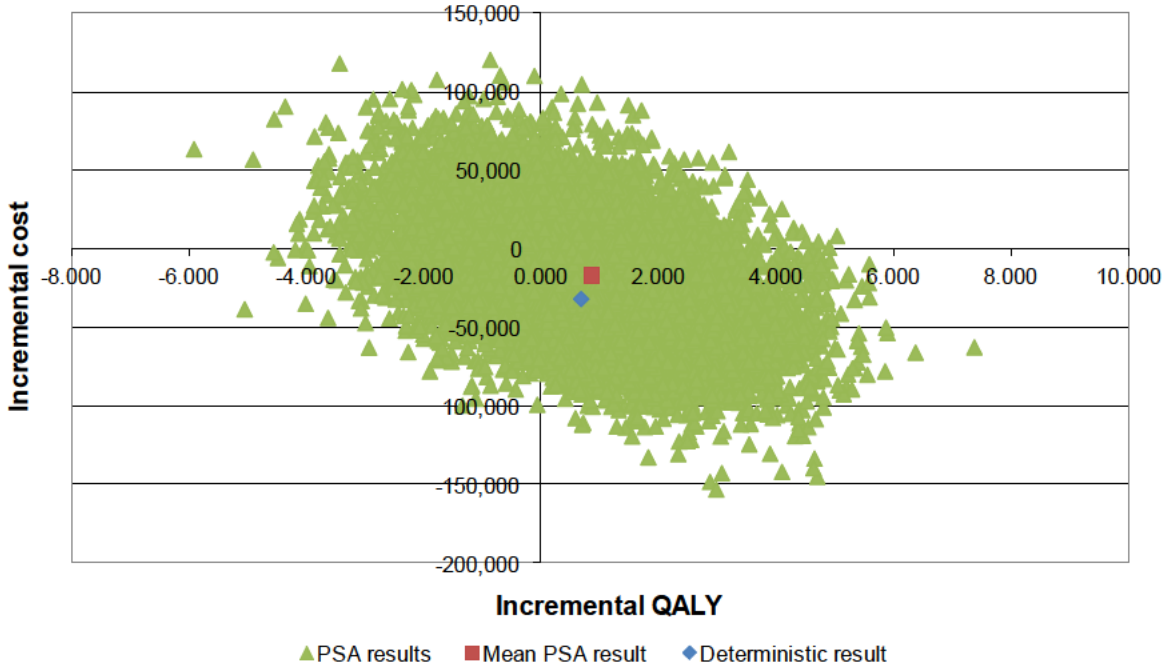


Figure B7.7.6 PSA scatter plot of alemtuzumab versus natalizumab in active RRMS



In addition, PSA was conducted against all beta-interferons, glatiramer acetate, fingolimod and natalizumab. Figure B7.7.7 shows the resulting multi-CEAC; the corresponding CEAF presented in Figure B7.7.8 shows that alemtuzumab is the most cost-effective treatment above a willingness to pay (WTP) threshold of £7,100.

Figure B7.7.7 Multi-CEAC of alemtuzumab versus all beta-interferons, glatiramer acetate, fingolimod and natalizumab in active RRMS

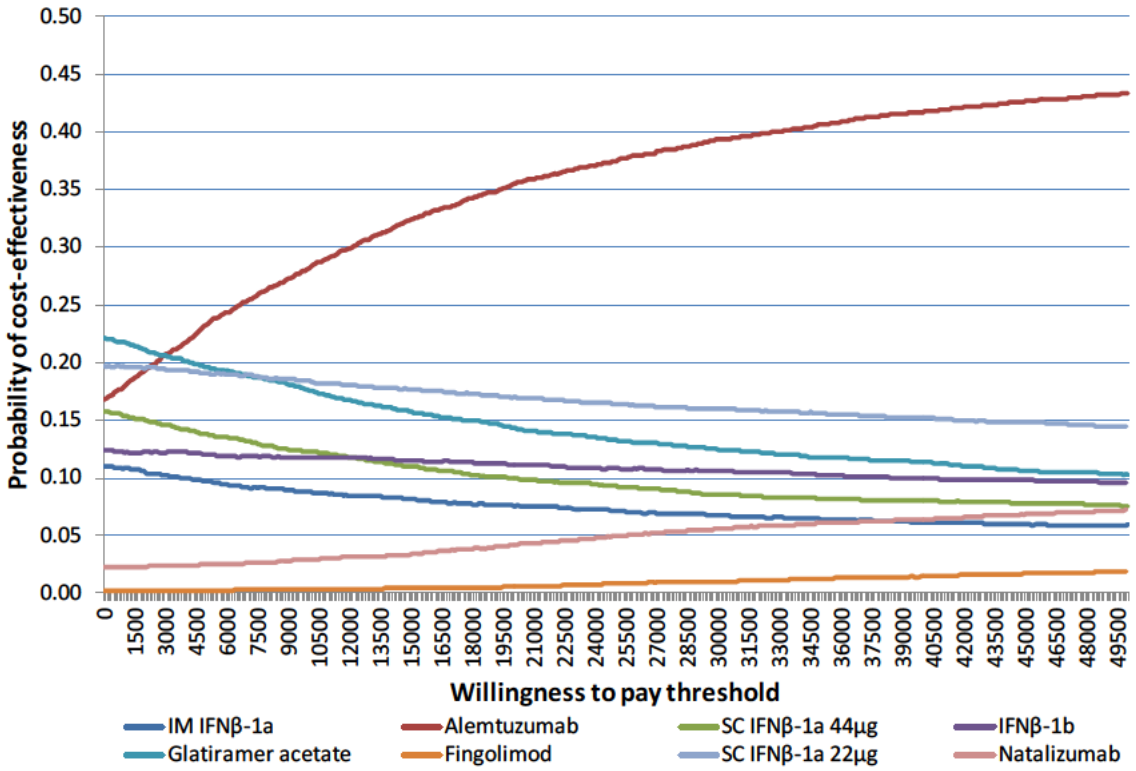
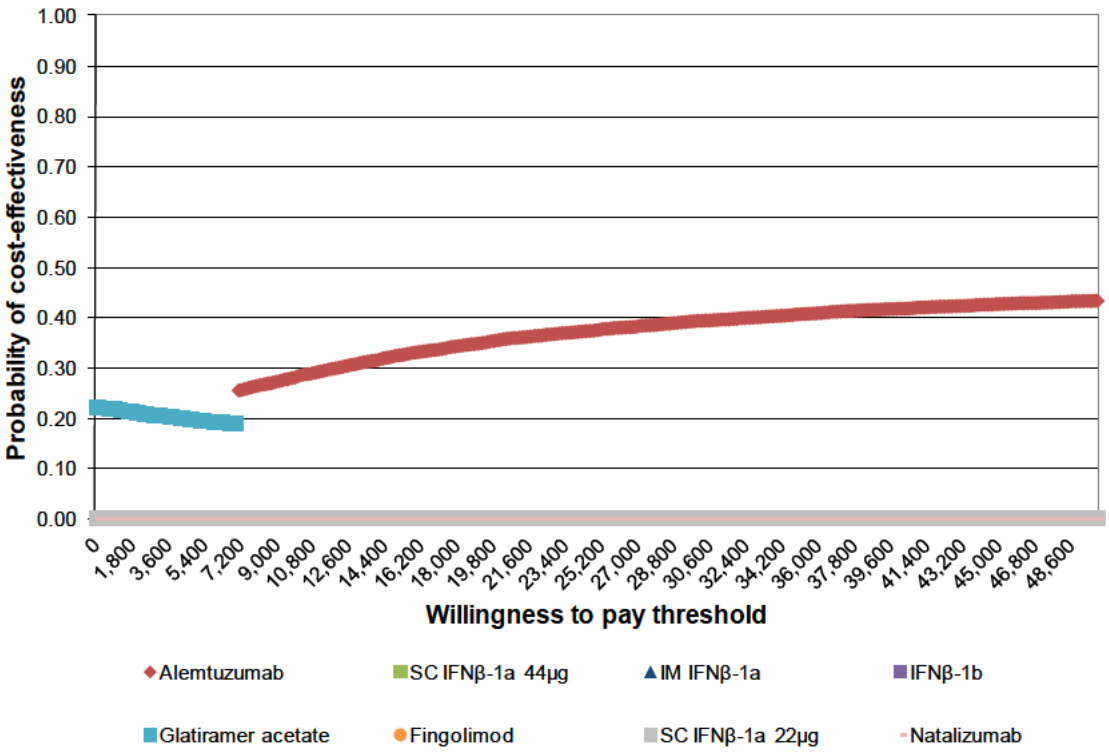


Figure B7.7.8 CEAF of alemtuzumab versus all beta-interferons, glatiramer acetate, fingolimod and natalizumab in active RRMS



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Scenario analyses were explored for alemtuzumab versus SC IFNβ-1a 44µg to understand structural sensitivities of the model (Table B7.7.21). As discussed in Section B7.6, given the uncertainty around long-term dosage of alemtuzumab, analysis of a different dosing scenario has also been performed (Table B7.7.22).

Table B7.7.21 Deterministic parameter sensitivity analysis of alemtuzumab versus SC IFNβ-1a 44µg in active RRMS

Scenario	Alemtuz total costs (£)	Alemtuz total QALYs	SC IFNβ-1a 44µg total costs (£)	SC IFNβ-1a 44µg total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) Inc (QALYs)
Base case	499,347	4.034	489,354	2.850	9,993	1.183	8,445
Baseline characteristics from CARE-MS studies	480,425	6.417	479,013	4.793	1,412	1.624	869
Natural history costs from Karampampa, 2012	653,402	4.034	667,736	2.850	-14,334	1.183	Dominates

Natural history transition probabilities for All RRMS	496,816	4.143	486,669	2.963	10,147	1.180	8,597
Long-term treatment effect 25% waning after year 5 for all treatments	503,798	3.845	489,702	2.835	14,095	1.010	13,956
Long-term treatment effect 50% waning after year 5 for all treatments	507,638	3.683	490,036	2.819	17,602	0.863	20,388
No waning of discontinuation	499,347	4.034	486,421	2.816	12,926	1.218	10,617
No treatment effect on relapses or proportion leading to hospitalisation	508,523	3.975	491,977	2.835	16,546	1.140	14,517
No discounting of costs or outcomes	861,221	4.532	860,798	2.621	423	1.910	221
6% discounting of costs and outcomes	370,275	3.669	354,880	2.781	15,395	0.889	17,322
Using direct comparison method: transition probabilities derived directly from pooled CARE-MS I and CARE-MS II	377,329	10.236	449,695	4.826	-72,366	5.410	Dominates
Treatment of SPMS with SC IFNβ-1a 44µg assuming 50% efficacy	499,347	4.034	495,661	2.866	3,686	1.168	3,156
Duration of autoimmune disease 10 years	499,587	4.021	489,354	2.850	10,233	1.171	8,739
INC, Incremental, ICER, Incremental cost-effectiveness ratio, Alemtuz, Alemtuzumab							

As discussed in Section B7.5.1. page 301, if we were to consider relapses linked to retreatment based on extension data from the CARE MS trials then retreatment from year 3 and onwards would be calculated as 19.5%. The results for this scenario are shown below.

Table B7.7.22 Results of deterministic scenario **analysis of dosage of alemtuzumab versus SC IFNβ**-1a 44µg in active RRMS

Scenario	Dosage per year	Alemtuz total costs (£)	Alemtuz total QALYs	Inc costs (£)	Inc QALYs	ICER (£) inc (QALYs)

	2	3	4	5	6-9	10+					
Base case	100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	499,347	4.034	9,993	1.183	8,445
Retreatment based on relapses	100%	19.5 %	19.5 %	19.5 %	19.5 %	19.5 %	504,404	4.034	15,050	1.183	12,719
Inc, incremental, QALY, quality adjusted life-year, Alemtuz, Alemtuzumab											

7.7.10 What were the main findings of each of the sensitivity analyses?

The deterministic sensitivity analysis indicated that the model was most sensitive to the 3-month SAD HR, when using the 95% upper and lower confidence intervals from the MTC. The model was also fairly sensitive to the inclusion criteria applied in the derivation of MTC results in terms of sustained accumulation of disability, ARR and withdrawal. The impact of the wider inclusion criteria, (not limiting to post-2000 studies) needs to be interpreted in light of the increased study heterogeneity as outlined in Section B6.7.8 and Additional Appendix 2. The probabilistic results indicate that alemtuzumab is cost-effective in the active RRMS population against all comparators above a WTP of approximately £7,100. Finally, scenario analyses showed that results were sensitive to long term waning of efficacy, natural history costs and assumptions regarding dosage of retreatment with alemtuzumab.

7.7.11 What are the key drivers of the cost-effectiveness results?

As discussed in Section B7.7.10, the model was most sensitive to the SAD HRs sourced from the MTC, natural history costs, dosage of retreatment of alemtuzumab and assumptions regarding the long-term treatment effect of alemtuzumab. The incremental net monetary benefit ranged from approximately -£34,000 to £76,000 when using the upper and lower 95% confidence intervals of sustained accumulation of disability for alemtuzumab in the active RRMS population.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Quality assurance of the model included two independent health economists involved in the design and build, as well as clinical expertise ratifying plausibility of results. The model outputs have been compared to published literature to validate outputs (see Section B7.7.1); although differences were observed there were reasonable justifications particularly in terms of the variation in severity of observed versus modelled cohort.

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section B6.3.7.

Subgroup analyses were undertaken to align with the requirements of the NICE scope. A comparison of alemtuzumab versus fingolimod (assumed PAS price £13,000) were conducted in HA RRMS despite treatment with a beta interferon. A comparison of alemtuzumab versus natalizumab in RES RRMS was also performed.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Please see Section B6.7.7.2.

7.9.3 Please describe how the statistical analysis was undertaken.

A MTC was conducted for the subgroup of patients with HA RRMS despite treatment with a beta interferon and RES RRMS. Please see Section B6.7.6 and Section B6.7.7.2 for further details. The outcomes used in the cost-effectiveness model are summarised in Tables B7.9.1and B7.6.2. Odds ratios versus teriflunomide have been derived by indirect comparison applied to the method outlined in Section B7.3.1 to derive the all-cause withdrawal rates versus placebo used in the model.

Table B7.9.1 RES MTC outcomes for the model, Post 2000 100% RRMS

Treatment effect in comparison to placebo	3-month sustained accumulation of disability HR	Relative annualised relapse rate	Annual all-cause withdrawal rate
Natalizumab	[redacted]	[redacted]	[redacted]
SC IFNβ-1a 44µg	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]

Table B7.9.2 HA disease despite treatment with a beta interferon MTC outcomes for the model, Post 2000 100% RRMS

Treatment effect in comparison to placebo	3-month sustained accumulation of disability HR	Relative annualised relapse rate	Annual all-cause withdrawal rate
SC IFNβ-1a 44µg	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section B7.7.6 (Base-case analysis).

As discussed in Section 7.7.6, the most appropriate results to present as the base case are probabilistic rather than deterministic but both are presented here for completeness. The probabilistic and deterministic results of the HA RRMS despite treatment with a beta interferon cost-effectiveness analyses are presented in Tables B7.9.3 and B7.9.4 respectively.

Table B7.9.3 Probabilistic subgroup results for HA RRMS despite treatment with a beta interferon

Treatment	Total cost (£)	Total QALYs	Inc cost (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Alemtuzumab	467,667	5.487				
Fingolimod (assumed PAS price £13,000)	493,760	3.669	26,093	-1.818	Dominated	Dominated

Table B7.9.4 Deterministic subgroup results for HA RRMS despite treatment with a beta interferon

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Alemtuzumab	492,374	4.327				
Fingolimod (assumed PAS price £13,000)	501,581	3.151	9,207	-1.176	Dominated	Dominated

As described in Section B7.6.2, deterministic one-way sensitivity analyses were run for HA RRMS despite treatment with a beta interferon and the results are presented in a tornado diagram in Figure B7.9.1 and Table B7.9.5.

As illustrated in Figure B7.9.1, SAD HRs are the key drivers within the cost-effectiveness model. The range of uncertainty in the probabilistic results (Figure B7.9.1) is a consequence of the relatively wide confidence intervals in HRs of 3 month SAD obtained from the MTC.

Figure B7.9.1 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon

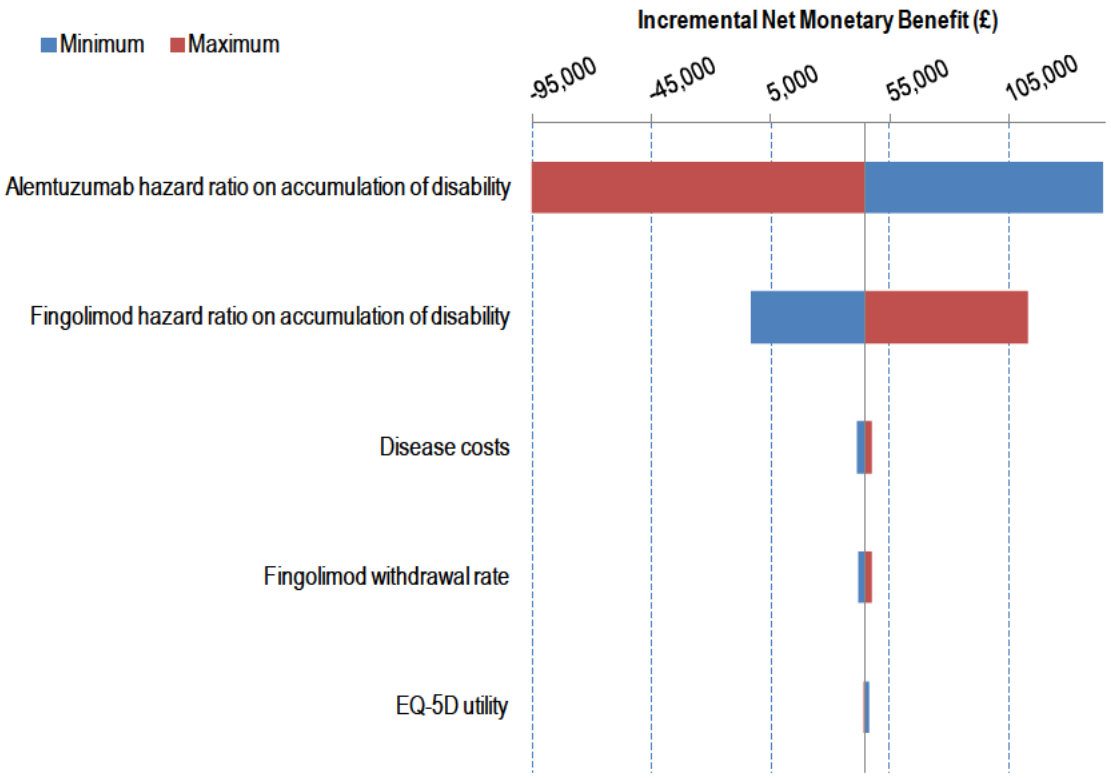


Table B7.9.5 One way sensitivity analysis results of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon

		Minimum						Maximum					
	Variation	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB
Base case		492,374	4.327	-9,207	1.176	Dominates	44,492						
Alemtuzumab hazard ratio on sustained accumulation of disability	95% CI	450,253	6.252	-51,329	3.101	Dominates	144,372	552,090	1.637	50,508	-1.514	Dominated	-95,940
Fingolimod hazard ratio on sustained accumulation of disability	95% CI	492,374	4.327	7,191	0.139	51,751	-3,022	492,374	4.327	-32,491	2.687	Dominates	113,102
Disease costs	+/- 10%	452,399	4.327	-6,154	1.176	Dominates	41,439	532,349	4.327	-12,260	1.176	Dominates	47,545
Fingolimod withdrawal rate	95% CI	492,374	4.327	-3,605	1.273	Dominates	41,799	492,374	4.327	-14,880	1.079	Dominates	47,265
EQ-5D utility	95% CI	492,374	0.112	-9,207	1.232	Dominates	46,168	492,374	8.194	-9,207	1.159	Dominates	43,965

Mean results of the PSA with 10,000 simulations are given in Table B7.9.3; the corresponding scatter plot and CEAC are given in Figures B7.9.2 and B7.9.3 for alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum in HA RRMS. In addition, PSA was conducted with incremental results and Figure B7.9.3 shows the resulting CEAC. Alemtuzumab was the most cost-effective treatment at all WTP thresholds.

Figure B7.9.2 PSA scatter plot of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon

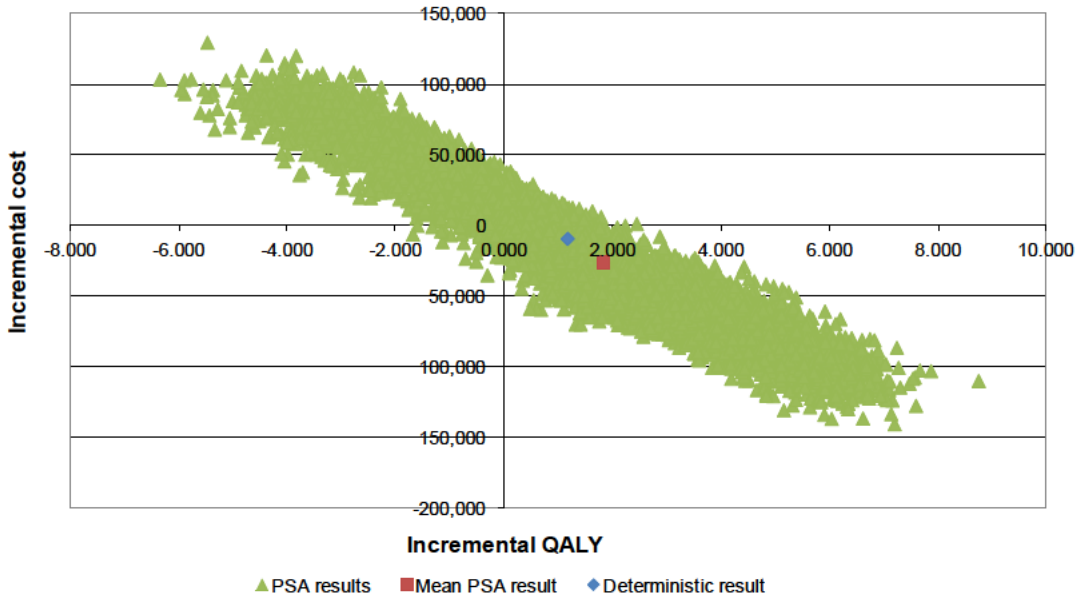
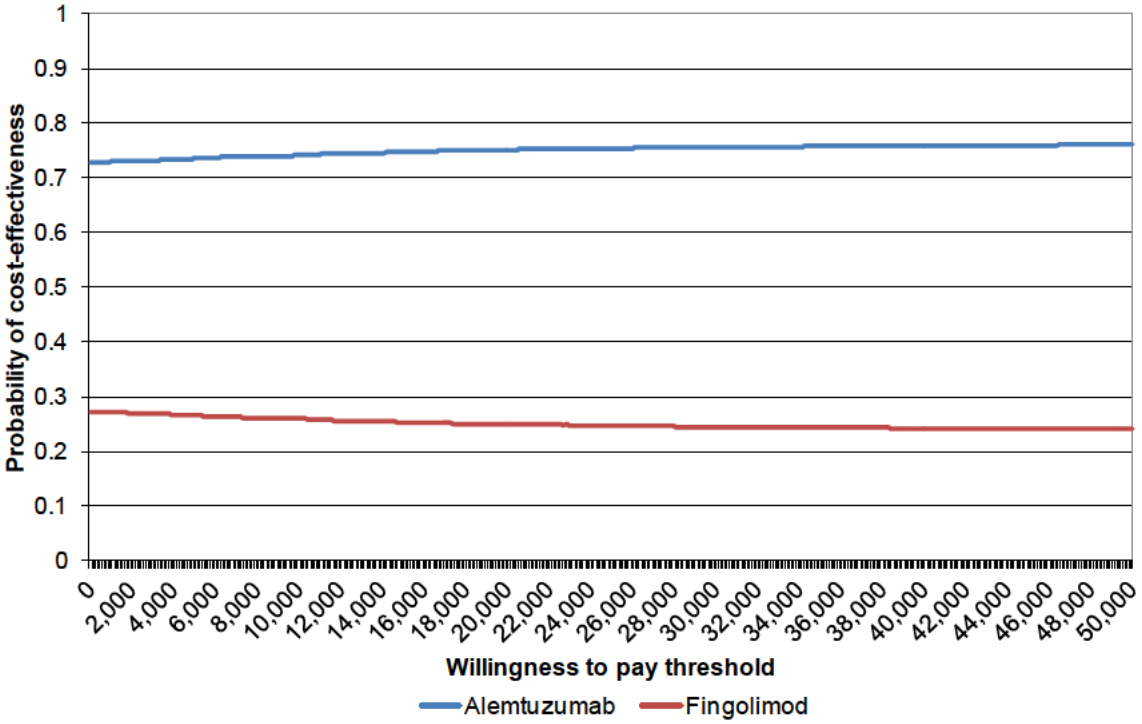


Figure B7.9.3 CEAC of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon



Scenario analyses were run for alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon (Table B7.9.6). As discussed in Section 7.3.7, given the uncertainty around long-term dosage of alemtuzumab, analysis of an alternative dosing scenario has also been performed linking relapses to retreatment using the CARE MS extension data.

Table B7.9.6 Deterministic parameter sensitivity analysis of alemtuzumab versus fingolimod with assumed PAS price of £13,000 per annum for HA RRMS despite treatment with a beta interferon

Scenario	Alemtuz. total costs (£)	Alemtuz . total QALYs	Fingol. total costs (£)	Fingol. total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) Inc (QALYs)
Base case	492,374	4.327	501,581	3.151	-9,207	1.176	Dominates
Long-term treatment effect 25% waning after year 5 for all treatments	498,149	4.080	502,250	3.113	-4,101	0.967	Dominates
Long-term treatment effect 50% waning after year 5 for all treatments	503,008	3.874	502,872	3.078	136	0.796	170
Re-treatment based on relapses (19.5% receive dose in year 3 onwards)	497,895	4.327	501,581	3.151	-3,686	1.176	Dominates
INC, Incremental, ICER, Incremental cost-effectiveness ratio, Alemtuz, Alemtuzumab, Fingol, Fingolimod							

The probabilistic and deterministic results of the RES cost-effectiveness analyses are presented in Tables B7.9.7 and B7.9.8 respectively.

Table B7.9.7 Probabilistic subgroup results for RES RRMS

Treatment	Total cost (£)	Total QALYs	Inc cost (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) Inc (QALYs)
Alemtuzumab	459,512	5.856				
Natalizumab	509,757	4.325	50,245	-1.531	Dominated	Dominated

Table B7.9.8 Deterministic subgroup results for RES RRMS

Technologies	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£) versus baseline (QALYs)	ICER (£) inc (QALYs)
Alemtuzumab	490,016	4.419				

Natalizumab	536,379	3.750	46,363	-0.669	Dominated	Dominated

As described in Section B7.6.2, deterministic one-way sensitivity analyses were run for RES and the results are presented in a tornado diagram in Figure B7.9.4 and Table B7.9.9.

As illustrated in Figure B7.9.4, SAD HRs are the key drivers within the cost-effectiveness model. The range of uncertainty in the probabilistic results (Figure B7.9.4) is a consequence of the relatively wide confidence intervals of 3 month SAD HRs obtained from the MTC.

Figure B7.9.4 Tornado diagram illustrating one-way sensitivity analysis results of alemtuzumab versus natalizumab for RES RRMS

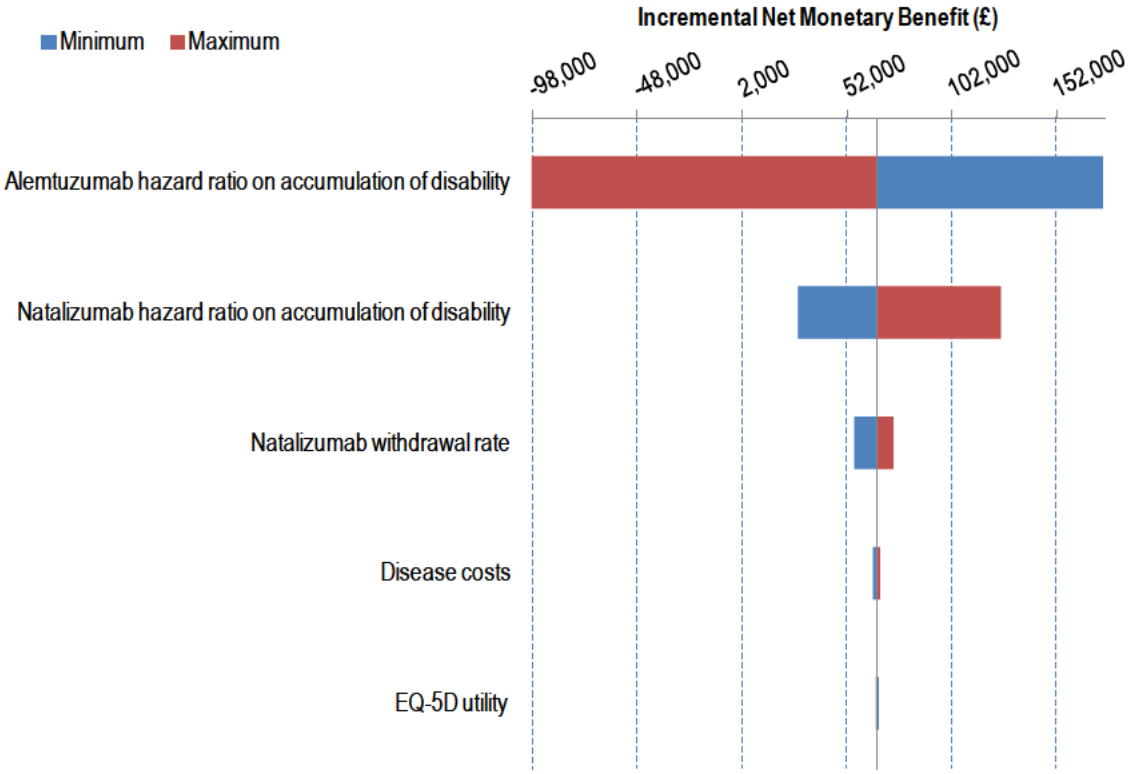


Table B7.9.9 One way sensitivity analysis results of alemtuzumab versus natalizumab for RES RRMS

		Minimum						Maximum					
Base case	Variation	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB	Alemtuzumab cost	Alemtuzumab QALY	Inc Cost	Inc QALY	ICER	INMB
Alemtuzumab hazard ratio on sustained accumulation of disability	95% CI	490,016	4.419	-46,363	0.669	Dominates	66,431						
Natalizumab hazard ratio on sustained accumulation of disability	95% CI	444,467	6.504	-91,912	2.754	Dominates	174,519	559,778	1.261	23,400	-2.489	Dominated	-98,069
Natalizumab withdrawal rate	95% CI	490,016	4.419	-39,629	-0.351	112,896	29,098	490,016	4.419	-55,946	2.316	Dominates	125,424
Disease costs	+/- 10%	490,016	4.419	-25,458	1.017	Dominates	55,969	490,016	4.419	-61,714	0.422	Dominates	74,374
EQ-5D utility	95% CI	450,268	4.419	-44,646	0.669	Dominates	64,714	529,764	4.419	-48,079	0.669	Dominates	68,147
Base case	95% CI	490,016	0.208	-46,363	0.698	Dominates	67,303	490,016	8.285	-46,363	0.662	Dominates	66,215

Mean results of the PSA with 10,000 simulations are given in Table B7.9.7; the corresponding scatter plot and CEAC are given in Figures B7.9.5 and B7.9.6 for alemtuzumab versus natalizumab.

Figure B7.9.5 PSA scatter plot of alemtuzumab versus natalizumab for RES RRMS

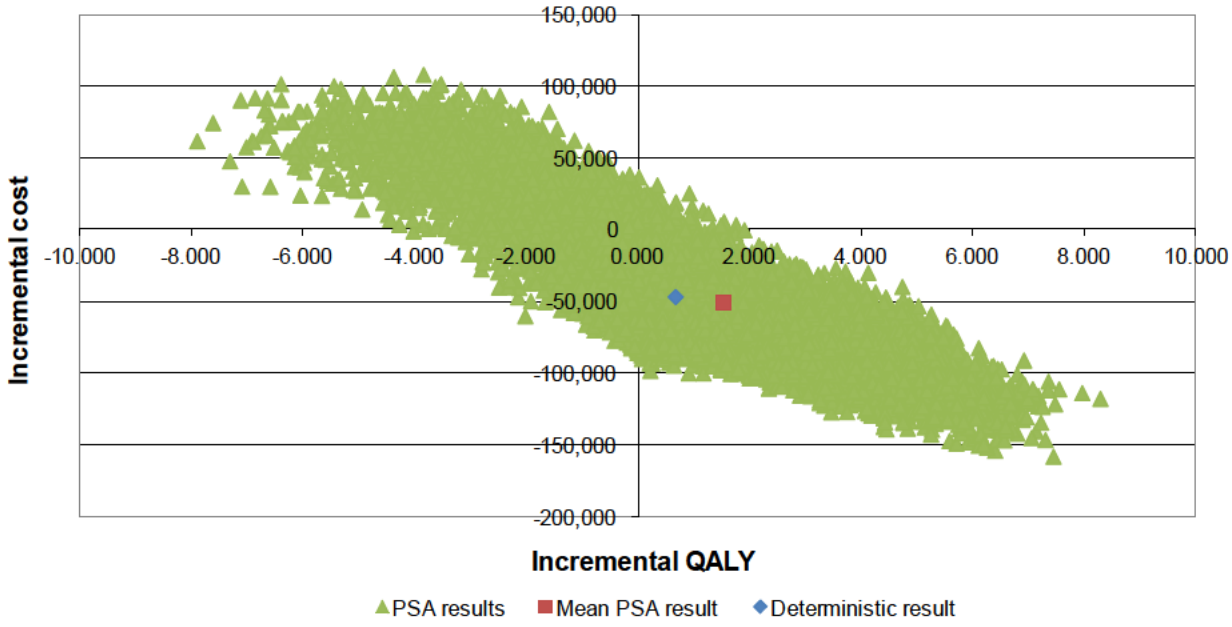
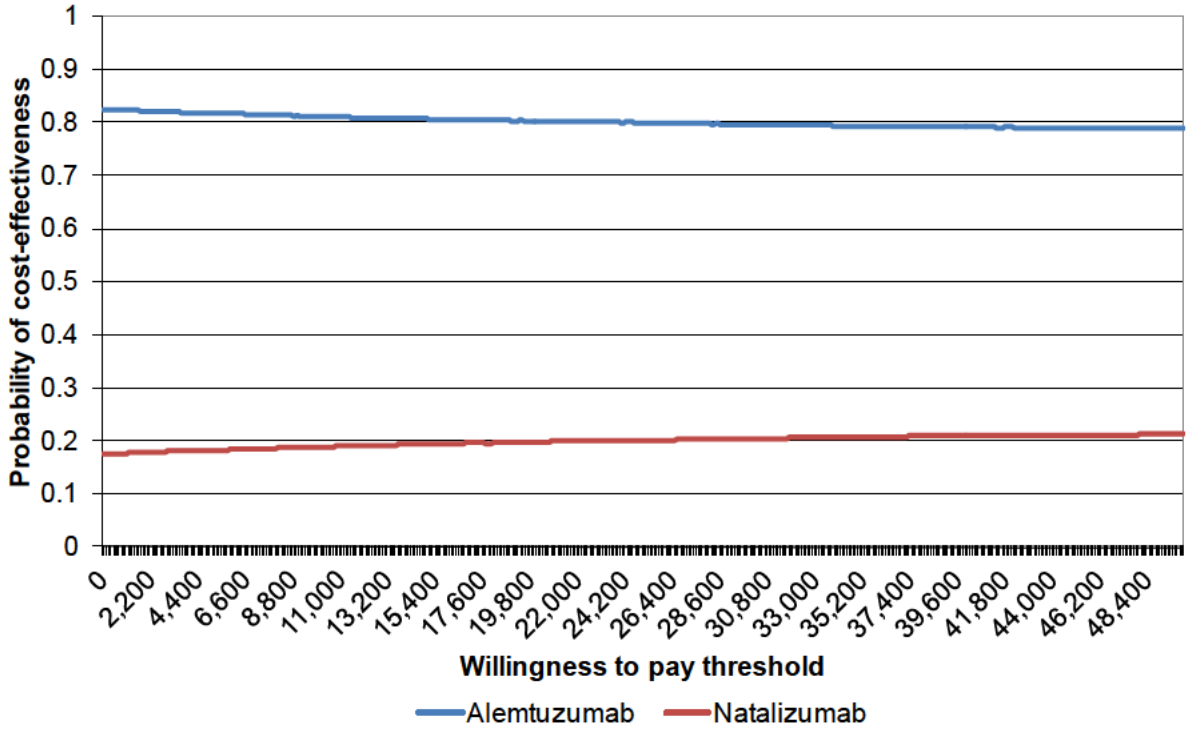


Figure B7.9.6 CEAC of alemtuzumab versus natalizumab for RES RRMS



Scenario analyses were run for alemtuzumab versus natalizumab RES (Table B7.9.10) to understand structural sensitivities of the model. As discussed in Section 7.3.7, given the uncertainty around long-term dosage of alemtuzumab, analysis of an alternative dosing scenario has also been performed linking relapses to retreatment using the CARE MS extension data.

Table B7.9.10 Deterministic parameter sensitivity analysis of alemtuzumab versus natalizumab for RES RRMS

Scenario	Alemtuz total costs (£)	Alemtuz total QALYs	Nataliz total costs (£)	Nataliz total QALYs (£)	Inc costs (£)	Inc QALYs	ICER (£) Inc (QALYs)
Base case	490,016	4.419	536,379	3.750	-46,363	0.669	Dominates
Long-term treatment effect 25% waning after year 5 for all treatments	496,257	4.153	537,171	3.632	-40,914	0.520	Dominates
Long-term treatment effect 50% waning after year 5 for all treatments	501,468	3.933	537,851	3.530	-36,382	0.403	Dominates
Re-treatment based on relapses (19.5% receive dose in year 3 onwards)	495,679	4.419	536,379	3.750	-40,700	0.669	Dominates
INC, Incremental, ICER, Incremental cost-effectiveness ratio, Alemtuz, Alemtuzumab, Nataliz, Natalizumab							

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

The Final Scope also identified possible subgroup analyses of treatment-naive and treatment-experienced RRMS populations. The clinical effectiveness in the treatment naïve studies (CARE MS I and CAMMS 223) and the treatment experienced study (CARE MS II) are described separately. No subgroup treatment experienced or naïve CE analysis is provided because it is thought that the CE analysis of active RRMS using the pooled results from both the treatment naïve and experienced studies captures more appropriately use across the broad range of the licence.

Patients with highly active relapsing-remitting multiple sclerosis despite a full couse of interferon (vs fingolimod in line with its licence) and patients with rapidly evolving severe relapsing-remitting multiple sclerosis (vs natlaizumab in line with its licence) are covered in a subgroup analysis.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this

evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

N/A. A systematic review concluded there is no published literature for the cost-effectiveness of alemtuzumab.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The population specified by NICE was in the treatment of RRMS patients. However, this economic evaluation is in the treatment of active RRMS population, in line with the positive recommendation issued by the CHMP. As detailed in Section 7.2.1, this active RRMS population is a subset of the all RRMS population.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Table B7.10.1 Strengths and limitations of the evaluation

Strength	Limitation
• The model is based on the model developed by ScHARR to assess the cost effectiveness of beta-interferons • The ScHARR model was also used in STA submissions for fingolimod and natalizumab and accepted by NICE [Novartis, 2011; Biogen, 2006]	
• Clinical parameters have been derived from comprehensive MTC	• MTC did not include clinical parameters for SC IFNβ-1a 22µg
	• London Ontario data set has been used in the base case which has a number of limitations; however, it was the best source available at time of analysis

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

None.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Alemtuzumab is licensed for the treatment of active RRMS in adult patients [EMA 2013]. This relatively broad definition includes the following subpopulations: previously untreated RRMS (treatment-naïve) patients both with and without rapidly evolving severe (RES) RRMS and patients with RRMS who have experienced a lack of tolerability on another disease-modifying therapy DMT (treatment-experienced) with and without highly active (HA) disease.

As detailed in Section A2.2, there are approximately 88,766 MS patients in England and Wales [MS-UK, 2013]. It is estimated that 35.5% of the prevalent MS population will be diagnosed with RRMS [Kobelt et al. 2006]. Therefore, the estimated prevalence of patients with RRMS in England and Wales in 2013 will be a 31,512. Of the prevalent active RRMS patients, 31% (9,769) will be prevalent treated or treated within the last 12 months (treatment-experienced), and could potentially receive alemtuzumab [Zajicek et al, 2010]. It is assumed from Zajicek et al, 2010 that all patients within the population are RRMS active.

Also in England and Wales there are 1,588 [Boggild et al. 2009] patients initiated on treatment each year. Of these treatment-naive active RRMS patients, 349 (22%) will have RES [NICE, 2012] leaving 1,239 as treatment-naive non-RES patients.

Therefore, there are potentially 9,769 treatment experienced prevalent patients of whom 5,177 (53%) based on the NICE costing template for fingolimod are assumed to have HA disease despite treatment with a beta interferon and 4,591 (47%) are assumed to have non HA disease, 349 treatment-naïve RES incident patients and 1,239 treatment-naïve non-RES incident patients per annum in England and Wales that could be treated with alemtuzumab.

The proportion of patients who are eligible to receive treatment with alemtuzumab for treatment experienced with / without HA disease despite treatment with a beta interferon and treatment naïve with / without RES disease is assumed to be [redacted] and [redacted] respectively. The total maximum annual uptake of alemtuzumab based on these four subgroups is [redacted] (see Table C8.1).

Table C8.1 Derivation of patient populations eligible for treatment with alemtuzumab

Country	England and Wales
Population	56,100,000

	%	n	Ref
Prevalence of multiple sclerosis (MS)		88,766	1
Number with relapsing remitting MS (RRMS)	35.5%	31,512	2
Prevalent treated / treated in previous 12 months	31%	9,769	3
Previously treated patients with HA disease (i.e. 1 or more relapses in the last 12 months and the relapse frequency unchanged or increased)	53%	5,177	4
Eligible to receive alemtuzumab: previously treated HA patients	[redacted]	[redacted]	5
Previously treated patients with non HA disease (i.e. 1 or more relapses in the last 12 months and the relapse frequency unchanged or increased)	47%	4,591	
Eligible to receive alemtuzumab: previously treated non HA patients	[redacted]	[redacted]	5

	%	n	Ref
Treatment naïve (incident patients for beta interferon and glatiramer acetate)		1,588	6
Treatment naive patients with RES	22%	349	7
Those with RES (treatment naive) who will receive alemtuzumab annually	[redacted]	[redacted]	8

	%	n	Ref
Treatment naïve (incident patients for incident patients for beta interferon and glatiramer acetate)		1,588	6
Treatment naive patients without RES	78%	1,239	7
Those without RES (treatment naive) who will receive alemtuzumab annually	[redacted]	[redacted]	8

Total annual uptake of alemtuzumab (previously treated HA + previously treated non-HA + treatment naive RES + treatment naive non-RES)	[redacted]

The total maximum uptake assumptions are combined with assumed percentage of maximum annual uptake with alemtuzumab (Table C8.2). Given that NICE will be assessing the evidence for alemtuzumab from July 2013, it is assumed in 2013 there would be negligible market uptake.

The assumed percentage of maximum annual uptake with alemtuzumab was [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5. All patients are assumed to receive a second dosing regime in year two and [redacted] (Coles 2013, CAMMS 223) receive a third dose in year three. The sum of patients receiving first, second and third dose gives the total number of patients receiving alemtuzumab from years 1 to 5. With [redacted] of

patients receiving a third dose in year 3, it is assumed that [redacted] patients would receive treatment with alemtuzumab in 2014 (Year 1), and [redacted] patients would receive treatment with alemtuzumab by 2018 (Year 5).

Table C8.2 Derivation of total patients receiving alemtuzumab and total patients whose DMT treatment is alemtuzumab

	Year 1	Year 2	Year 3	Year 4	Year 5
	2014	2015	2016	2017	2018
Uptake of incident patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving first dose (100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving second dose (100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients receiving third dose (42%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients receiving alemtuzumab in year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients whose DMT treatment is alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

- Beta interferon and glatiramer acetate in active RRMS (non HA and non RES)

Beta interferons and glatiramer acetate are used when patients meet the requirement of two clinically significant relapses in the previous two years in line with ABN guidelines (a consensus of British Neurologists regarding the appropriate use of DMTs) and the Department of Health Risk Sharing Scheme and we anticipate this is where alemtuzumab will be used [DoH 2002; ABN 2009].

- Fingolimod for patients with highly active RRMS (HA RRMS) who have an unchanged or increased relapse rate or ongoing relapses compared with the previous year despite treatment with DMTs

Fingolimod is currently used for HA RRMS patients despite treatment with a beta interferon (i.e. patients who have failed to respond to a full and adequate course of beta interferon. Patients should have had at least one relapse in the previous year while on therapy and have at least nine T2-hyperintensive lesions in cranial MRI or at least one gadolinium-enhancing lesion.) Patients with high disease activity were included in clinical trials for alemtuzumab and this subgroup is another area where alemtuzumab is expected to be used.

- Natalizumab for patients with RES

Natalizumab is currently used for RRMS patients with RES disease (i.e. two or more disabling relapses in one year with 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.) Patients with RES were included in clinical trials for alemtuzumab and this subgroup is another area where alemtuzumab is expected to be used.

- Natalizumab and fingolimod in non-RES and non-HA

It is anticipated that fingolimod and natalizumab are also used outside of NICE recommendations and thus are relevant comparators for alemtuzumab outside of the HA disease despite treatment with a beta interferon and RES subgroups for patients that fall into the following categories:

  - Patients receiving natalizumab who switch to alemtuzumab. Whilst they will have been initiated on natalizumab to treat RES RRMS, many will no longer be experiencing RES symptoms. It is thought possible that natalizumab patients may switch to alemtuzumab, particularly those who are JCV positive after 2 years in line with monitoring requirements (see Section A2.5)
  - Treatment experienced patients who would receive natalizumab outside of NICE guidance and who instead of being initiated on natalizumab will be initiated on alemtuzumab
  - Patients receiving fingolimod who switch to alemtuzumab
  - Treatment experienced patients who would receive fingolimod outside of NICE guidance and who instead of being initiated on fingolimod will be initiated on alemtuzumab

The anticipated uptake of alemtuzumab in relation to these technologies is given in Table C8.3.

Table C8.3 Current MS treatment options and uptake of alemtuzumab

	HA (prev tx)	Non HA (prev tx)	RES tx naïve	Non RES tx naïve	All
% of total patients	54%	24%	18%	3%	100%

	% DMT treatment split				
Treatment	HA (prev tx)	Non HA (prev tx)	RES tx naïve	Non RES tx naïve	% DMT treatment split relative to sub-group population
Beta interferons and glatiramer acetate	0%	15%	0%	100%	7%
Natalizumab	70%	80%	100%	0%	76%
Fingolimod	30%	5%	0%	0%	18%
Total	100%	100%	100%	100%	100%

8.3 What assumption(s) were made about market share (when relevant)?

The proportions of eligible prevalent patients who are treatment experienced with / without HA disease and incident patients who are treatment naïve with / without RES disease are assumed to be [redacted], [redacted], [redacted] and [redacted] respectively. The assumed percentage of maximum annual uptake with alemtuzumab was [redacted] in year 1, [redacted] in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the differences in technology acquisition costs between alemtuzumab and comparators, there are savings in administration costs and monitoring costs as well as there being adverse event costs. These costs are in line with those used in the cost-effectiveness analysis (see Section B7.5.1).

The average cost of the UK Risk-sharing scheme (RSS) displaced treatments when split between the market shares is £7,712 (see Table C8.4).

Table C8.4 Acquisition costs associated with beta-interferons and glatiramer acetate

Treatment	Annual Cost	% split (between interferons and GA)	Reference
IM IFNβ-1a	£8,502	29%	DoH HSC 2002/004
IFNβ-1b (including 2% Extavia)	£7,259	11%	DoH HSC 2002/004
Glatiramer acetate	£5,823	23%	DoH HSC 2002/004
SC IFNβ-1a 44µg	£8,942	23%	DoH HSC 2002/004
SC IFNβ-1a 22µg	£7,513	14%	DoH HSC 2002/004
Mean acquisition cost for beta interferon and glatiramer acetate	£7,712	100%	N/A

The annual acquisition cost of alemtuzumab in year 1 is [redacted] and from year 2+ is [redacted]. This is based on:

- Cost per vial of alemtuzumab being [redacted]
- Year 1: 5 doses of alemtuzumab [redacted])
- Year 2+: 3 doses of alemtuzumab [redacted]

The annual acquisition costs of natalizumab and fingolimod are £14,690 and £19,110, respectively. In the budget impact analysis , fingolimod is assumed to have a price equivalent list price although using the estimated PAS price of £13,000 per year would have provided lower cost offsets and a higher net drug budget impact.

Alemtuzumab has associated administration costs as a result of it being administered intravenously. For each dose, a patient is required to remain in hospital for a day and is given the following medication:

- Methylprednisolone 1g vial at £17.30 (first 3 days of course only)
- Chlorphenamine 10mg daily at £1.95

- Paracetamol 2 x 500mg daily at 16 pence for a 16 pack
- Aciclovir 200mg twice daily for 28 days at £7.25 for a 56 pack

The total cost of administration per year is dependent upon the year of treatment and percentage of patients receiving treatment with alemtuzumab. The administration cost of alemtuzumab for the first 3 vials is £496 and the cost for subsequent vials is £476, in line with the cost-effectiveness analysis. The administration cost in years 1, 2 and 3+ will be £2,438, £1,487 and £624, respectively.

The administration costs associated with SC IFNβ-1a 44µg, SC IFNβ-1a 22µg-, IM IFNβ-1a, IFNβ-1b, glatiramer acetate, natalizumab and fingolimod for year 1 and subsequent years are in line with the cost-effectiveness analysis. Natalizumab was seen to have the greatest administration costs due to the 13 infusions of the medicine required each year. The mean administration cost of displaced treatments split by market share to be £4,755, £4,661 and £4,661 for years 1 to 3, respectively. Taking into consideration the annual cost of alemtuzumab to be £2,438, £1,487 and £624 for years 1 to 3, respectively, provides a cost saving of £2,317, £3,174 and £4,036 for years 1 to 3, respectively, per patient when using alemtuzumab (Table C8.5).

Table C8.5 Additional cost of administration cost associated with alemtuzumab

	Year 1	Year 2	Year 3+
Mean administration cost of displaced drugs	£4,755	£4,661	£4,661
Annual administration cost of alemtuzumab	£2,438	£1,487	£624
Additional cost of alemtuzumab	-£2,317	-£3,174	-£4,036

For those alemtuzumab patients not administered drug within year the administrative cost saving will be £4661 (the mean administrative cost of the displaced drugs)

Treatment with alemtuzumab requires greater monitoring resource in terms of additional biochemistry tests, full blood counts, urinalysis with urine cell count and thyroid function tests as required as per the SPC [Alemtuzumab SPC, 2013]. Further details can be seen in Section B7.5.1. Monitoring costs of displaced treatments when split between the market shares were £510 per patient in year 1 and £458 per patient in each subsequent year. The monitoring costs for alemtuzumab were £460 per patient in year 1 and £274 per patient in each subsequent year resulting in cost savings of £50 in year 1 and £183 in each subsequent year when using alemtuzumab rather than current practice, as detailed in Table C8.6.

Table C8.6 Additional monitoring cost associated with alemtuzumab

	Year 1	Subsequent years
Mean monitoring cost of displaced treatments	£510	£458
Annual monitoring cost of alemtuzumab	£460	£274
Additional cost of alemtuzumab	-£50	-£183

The costs incurred through the treatment of adverse events associated with alemtuzumab are greater than the costs of all other comparators for both year 1 and subsequent years. Further details can be seen in Section

B7.5.7. The costs of treating adverse events are estimated per patient and were adjusted for probability of occurrence. The costs of treating adverse events of displaced treatments when split between the market shares were £20 in year 1 and £22 in subsequent years. The average costs of treating the adverse events associated with alemtuzumab were £72 in year 1 and £160 in subsequent years. Therefore, treatment with alemtuzumab results in a cost increase per patient of £51 in year 1 and £137 in subsequent years, as detailed in Table C8.7.

Table C8.7 Additional adverse event cost associated with alemtuzumab

	Year 1	Subsequent years
Mean adverse cost of displaced treatment	£20	£22
Annual adverse event cost of alemtuzumab	£72	£160
Additional cost of alemtuzumab	£51	£137

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs of treatment were sourced from the UK Risk-sharing scheme and the British National Formulary [DoH HSC 2002/004; BNF Extavia, 2013]. See section B7.5.1 for details. Administration, monitoring and adverse event costs were sourced from National reference costs and the PbR tariff. See Section B7.5.2 for details where possible.

8.6 Were there any estimates of resource savings? If so, what were they?

As described in Section C8.4, the cost of administering alemtuzumab is relatively high in year 1 and year 2. Since alemtuzumab replaces 67% of natalizumab treatment, which has an even higher administration cost associated with it, means overall there will be an incremental administrative cost saving for being treated with alemtuzumab. In fact cost savings of £2,317, £3,174 and £4,036 will be generated from years 1 to 3 for those treated on alemtuzumab within year and for those alemtuzumab patients not administered drug within year this annual administrative cost saving will be £4661. Furthermore, there are resource savings included within the cost savings associated with monitoring costs.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

As illustrated in Table C8.8 the estimated net drug budget impact in England and Wales is [redacted] in 2014 (year 1); [redacted] in 2015 (year 2), and [redacted] in 2016 (year 3) and [redacted] in 2017 (year 4) and [redacted] in 2018 (year 5) .

Table C8.8 Net budget impact of introducing alemtuzumab into England and Wales assuming the list price with fingolimod

	2014	2015	2016	2017	2018
1st year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4th year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5th year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6th year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not need DMT administered in year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Alemtuzumab acquisition costs

	2014	2015	2016	2017	2018
1st year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3rd year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Drug acquisition cost offset - administered alemtuzumab within year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost offset - alemtuzumab not administered within year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net drug acquisition impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost offset					
Administration cost offset - administered alemtuzumab - year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost offset - administered alemtuzumab - year 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost offset - administered alemtuzumab - year 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration cost offset – drug not administered within year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring cost offset					
Monitoring cost offset - administered alemtuzumab - year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring - administered alemtuzumab – subsequent years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adverse event cost offset					
Adverse event cost offset - administered alemtuzumab - year 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost offset – subsequent years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total budget impact including administration, monitoring and adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No opportunities for additional savings have been identified.

9 References

Amato MP, Ponziani G, Bartolozzi ML, et al. (1999). A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. J Neurol Sci 1999 Oct 15;168(2):96-106.

Antel J, Montalban X, O'Connor P, et al. (2012). Long-term (7-year) data from a phase 2 extension study of fingolimod in relapsing multiple sclerosis. Neurology 78(Meeting Abstracts1); P01-129

Aronson KJ, (1997). Quality of life among persons with multiple sclerosis and their caregivers. Neurology 1997 Jan;48(1):74-80.

Arroyo R, Arnold DL, Cohen J, et al. (2013). Alemtuzumab Improves Quality Of Life Compared To SC IFNB-1a In CARE-MS II. Poster presented at the 23rd ENS, Spain, 2013.

Association of British Neurologists. Revised (2009). Association of British Neurologist's Guidelines for Prescribing in Multiple Sclerosis. 2009. Available at: http://www.theabn.org/abn/userfiles/file/ABN_MS_Guidelines_2009_Final(1).pdf [Accessed 1 July 2013]

Bar-Or A, Gold R, Kappos L, et al. (2012). Effect of BG-12 in Subgroups of Patients with Relapsing–Remitting Multiple Sclerosis: Findings from the DEFINE Study. P01.130. Presented at the 64th AAN, New Orleans, 2012.

Belachew S, Butzkueven H, Kappos L et al. (2010) Natalizumab (Tysabri) Observational Program: associations with baseline disease activity and treatment history with post-baseline relapses in multiple sclerosis patients treated with natalizumab. Presented at 26th ECTRIMS and 15th RIMS, Gothenburg, Sweden, 2010.

Bloomgren G, Richman S, Hotermans C, et al. (2012) - Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy. N Engl J Med 2012;366:1870-80.

Biogen Idec (2006). Natalizumab (Tysabri®) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis. Manufacturer submission (NICE Single Technology Appraisal submission).

Boggild M, Palace J, Barton P, et al. (2009). Multiple sclerosis risk sharing scheme: two year results of clinical cohort study with historical comparator. BMJ 2009;339:b4677

Bornstein NB, Miller A, Slagle S, et al. (1987). A Pilot Trial of Cop 1 in Exacerbating-Remitting Multiple Sclerosis. N Engl J Med 1987;317(7):408-14.

Boye KS, Matza LS, Walter KN, et al. (2011). Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ 2011 Jun;12(3):219-30.

Boyko A on behalf of the CAMMS223 Study Group (2011). Alemtuzumab's durable efficacy in multiple sclerosis four years after last treatment cycle. Presented at the 5th Joint Triennial Congress ECTRIMS and ACTRIMS, Amsterdam, 2011.

Brennan A, Akehurst R, Davis S, et al. (2007). The Cost-Effectiveness of Lanthanum Carbonate in the Treatment of Hyperphosphatemia in Patients with End-Stage Renal Disease (Health Economics and Decision Science, ScHARR, University of Sheffield, Sheffield, UK). Value in Health 2007;10(1):32-41.

British National Formulary (BNF) (2013) - Aciclovir Drug Information. 200mg 56pk £7.25 Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP3846-aciclovir-non-proprietary.htm#PHP3846-aciclovir-non-proprietary [Accessed 5 June 2013]

British National Formulary (BNF) (2013). Amoxicillin Drug Information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP3328-amoxicillin-non-proprietary.htm [Accessed 10 July 2013].

British National Formulary (BNF) (2013). Anti thyroid drugs. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP4309-antithyroid-drugs.htm [Accessed 8 July 2013].

British National Formulary (BNF) (2013). Chlorphenamine 10mg information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP1935-chlorphenamine-non-proprietary.htm#PHP1935-chlorphenamine-non-proprietary [Accessed 5 June 2013]

British National Formulary (BNF) (2013). Cyclophosphamide Injection, powder for reconstitution, 500-mg vial information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP5266-cyclophosphamide-non-proprietary.htm?q=Cyclophosphamide%20&t=search&ss=text&p=1#PHP5266-cyclophosphamide-non-proprietary [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Extavia Drug Information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP5685-extavia.htm?q=extavia&t=search&ss=text&p=1#PHP5685-extavia [Accessed 22 May 2013]. 2013.

British National Formulary (BNF) (2013). Fingolimod/Gilenya information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP5702-gilenya.htm#PHP5702-gilenya [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Methylprednisolone powder for reconstitution, 1g vial information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP4373-solu-medrone.htm?q=methylprednisolone%20vial&t=search&ss=text&p=1#PHP4373-solu-medrone [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Methylprednisolone 16 mg 30-tab pack information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP4372-medrone.htm?q=methylprednisolone%20tablets&t=search&ss=text&p=1#PHP4372-medrone [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Natalizumab/Tysabri information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP5725-tysabri.htm#PHP5725-tysabri [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Paracetamol 500mg 16pk information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP2633-paracetamol-non-proprietary.htm?q=Paracetamol&t=search&ss=text&p=1#PHP2633-paracetamol-non-proprietary [Accessed 5 June 2013]

British National Formulary (BNF) (2013). Pregabalin (Lyrica) 150 mg (white) 56-cap pack information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP2934-lyrica.htm#PHP2934-lyrica [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Concentrate for intravenous infusion, rituximab 10 mg/mL (MabThera) information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP5664-mabthera.htm#PHP5664-mabthera [Accessed 10 July 2013]

British National Formulary (BNF) (2013). trimethoprim 200 mg, 14-tab pack information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP3587-trimethoprim-non-

proprietary.htm?q=trimethoprim%20&t=search&ss=text&p=1#PHP3587-trimethoprim-non-proprietary [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Vigam Intravenous infusion, human normal immunoglobulin (protein 5%) 10 g (200 ml) information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP8457-vigam.htm?q=Vigam%20Intravenous%20infusion&t=search&ss=text&p=1#PHP8457-vigam [Accessed 10 July 2013]

British National Formulary (BNF) (2013). Tranexamic acid (Non-proprietary) tablets, 500 mg, 60-tab pack information. Available at: http://www.medicinescomplete.com/mc/bnf/current/PHP1601-tranexamic-acid-non-proprietary.htm#PHP1601-tranexamic-acid-non-proprietary [Accessed 5 June 2013]

Bronnum-Hansen H, Koch-Henriksen N, Stenager, E, et al. (2004). Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 2004. 127(Pt 4): 844-850.

Buljevac D, Flach HZ, Hop WCJ, et al. (2002). Prospective study on the relationship between infections and multiple sclerosis exacerbations. Brain 2002.125:952-960.

Cadavid D, Wolansky LJ, Skurnick J, et al. (2009). Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology 2009 Jun 9;72(23):1976-83.

Calabresi P, Radue EW, Goodin D, et al. (2012). Efficacy and Safety of Fingolimod in Patients with Relapsing Remitting Multiple Sclerosis (RRMS): Results from an Additional 24-month Double-blind, Placebo-controlled Study (FREEDOMS II Study). Poster presented at 64th AAN, New Orleans, 2012.

Cascione MC (2011). Alemtuzumab positively affects disability outcomes using a one-year-sustained criterion for relapsing-remitting multiple sclerosis patients in CAMMS223. Neurol 76 (Suppl 4): A73-A74, 2011. Paper presented at: AAN, 2011; Honolulu, Hawaii.

Chilcott J, McCabe C, Tappenden P, et al. (2003). Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosis. Commentary: evaluating disease modifying treatments in multiple sclerosis. BMJ 2003 Mar 8;326(7388):522.

Clinicaltrials.gov (2009), A Phase II Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Rebif® in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis [NCT00050778; CAMMS223]. 2009. Available at: http://clinicaltrials.gov/ct2/show/NCT00050778?term=NCT00050778&rank=1 [Accessed 24 June 2013]

Clinicaltrials.gov (2013), Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study One (CARE-MS I) [NCT00530348; CAMMS323]. Available at: http://clinicaltrials.gov/ct2/show/NCT00530348?term=CAMMS323%2C+CARE-MS+I&rank=1 [Accessed 24 June 2013]

Clinicaltrials.gov (2013), Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Study Two (CARE-MS II) [NCT00548405; CAMMS324]. Available at: http://clinicaltrials.gov/ct2/show/NCT00548405?term=CAMMS324%2C+CARE-MS+II&rank=1 [Accessed 24 June 2013]

Clinicaltrials.gov (2013), An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab [NCT00930553, CAMMS03409 Phase 3 extension]. Available at: http://clinicaltrials.gov/show/NCT00930553 [Accessed 5 June 2013]

Clinicaltrials.gov (2013), Long Term Safety and Efficacy Study of Teriflunomide 7 mg or 14 mg in Patients With Relapsing-Remitting Multiple Sclerosis [NCT00803049, TEMSO Phase 3 extension]. Available at: http://clinicaltrials.gov/show/NCT00803049 Accessed 25 April 2013]

Cohen JA, Rovaris M, Goodman AD et al. (2007). Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS. Neurology 2007 Mar 20;68(12):939-44.

Cohen JA, Barkhof F, Comi G, et al. (2010). Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med 2010 Feb 4;362(5):402-15.

Cohen JA, Coles AJ, Arnold, SL, et al. (2012). Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012 Nov 24;380(9856):1819-28.

Coles AJ, Wing MG, Molyneux P, et al. (1999). Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol. 46(3): 296-304.

Coles AJ, Sox A., Le Page E, et al (2006). "The window of therapeutic opportunity in multiple sclerosis. Evidence from monoclonal antibody therapy. J Neurol 2006 253: 98–108.

Coles AJ, Compston DAS, Selmaj KW, et al. (2008). Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008 Oct 23;359(17):1786-801.

Coles A, (2009a). Multiple sclerosis. Pract Neurol 2009 Apr;9(2):118-26.

Coles A on behalf of the CAMMS223 Study Group (2009b). Alemtuzumab treatment benefit is durable: primary efficacy outcomes of CAMMS223 at 4 years. Mult Scler. 2009;15:S277.

Coles A, (2010). Alemtuzumab long-term safety and efficacy: Five years of the CAMMS223 trial. Mult Scler. 2010;16(10):S134-S135 (P410).

Coles AJ, Brinar V, Arnold DL, et al. (2011a). Efficacy and Safety Results from CARE-MS I: A Phase 3 Study Comparing Alemtuzumab and Interferon Beta-1a. (Paper presented at: 5th Joint Triennial Congress of ECTRIMS/ACTRIMS, 2011; Amsterdam).

Coles AJ, Fox E, Vladic A, et al. (2011b). Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes - *Supplementary webappendix*. Lancet Neurol. 2011;10(4):338-348.

Coles AJ, Twyman CL., Arnold, DL, et al. (2012a). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012 Nov 24;380(9856):1829-39.

Coles A, Brinar V, Arnold D, et al. (2012b). Efficacy and safety results from comparison of alemtuzumab and Rebif ® efficacy in multiple sclerosis I (CARE-MS I): A phase 3 study in relapsing-remitting treatment-naive patients. Neurology. 2012;78(1).

Coles AJ, Fox E, Vladic A, et al. (2012c). Alemtuzumab more effective than interferon beta-1a at 5 year follow up of CAMMS223 Clinical Trial. Neurology 2012 Apr 3: 78: 1069-78.

Coles AJ, Fox E, Vladic A, et al. (2012c). Alemtuzumab more effective than interferon beta-1a at 5 year follow up of CAMMS223 Clinical Trial. *Supplementary web appendix*. Neurology 2012 Apr 3: 78: 1069-78.

CombiRx (2012). The CombiRx Trial: A Multi-Center, Double-Blind, Randomized Study Comparing the Combined Use of Interferon Beta-1a and Glatiramer Acetate to Either Agent Alone in Participants with Relapsing Remitting Multiple Sclerosis - Clinical and MRI Outcomes. Presented at 64th AAN, New Orleans, 2012.

Comi G, Filippi M, Wolinsky JS and the European/Canadian Glatiramer Acetate Study Group Comi (2001). European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging–Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis. Ann Neurol 2001;49:290–297.

Comi G, Pulizzi A, Rovaris M, et al. (2008). Effect of laquinimod on MRI-monitored disease activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008 Jun 21;371(9630):2085-92.

Comi G, Martinelli V, Rodegher M, et al. (2010). Benefit of early treatment with glatiramer acetate (COPAXONE): Results from the 5-year prospectively planned follow up in patients with clinically isolated syndrome from the PreCISe study. Presented at the 26th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and 15th Annual Conference of Rehabilitation in MS (RIMS), Gothenburg, Sweden, 2010. Mult Scler Oct 2010 16:S37(135).

Comi G, Cohen JA, Arnold DL, et al. (2011). Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. Ann Neurol 2011 Jan;69(1):75-82.

Comi G, Jeffery D, Kappos L, et al. (2012) Placebo-controlled trial of oral laquinimod for multiple sclerosis. N Engl J Med 2012 Mar 15;366(11):1000-9.

Compston A, Coles A (2002). Multiple sclerosis. Lancet 2002 Apr 6;359(9313):1221-31.

Compston A, Coles A (2008). Multiple sclerosis. Lancet 2008 Oct 25;372(9648):1502-17.

Confavreux C, Vukusic S, Adeleine P, (2003). Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126:770-782.

Confavreux C, Vukusic S (2006). Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. Clin Neurol Neurosurg 2006 Mar;108(3):327-32.

Confavreux C, Twyman CL, Arnold DL, et al. (2012). Efficacy of Alemtuzumab in Relapsing-Remitting Multiple Sclerosis (RRMS) Patients with Highly-Active Disease Despite Therapy. (Presented at 16th EFNS, Sweden, 2012). European Journal of Neurology 19 (Suppl. 1), 22–89

Correale J, Fiol M, Gilmore W, (2006). The risk of relapses in multiple sclerosis during systemic infections. Neurology. 2006 Aug 22;67(4):652-9. Epub 2006 Jul 26.

Cossburn M, Pace AA, Jones J, et al. (2011). Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort. Neurology. 2011 Aug 9;77(6):573-9.

Costello K, Kennedy P, Scanzillo J, (2008). Recognizing non adherence in patients with multiple sclerosis and maintaining treatment adherence in the long term. Medscape J Med. 2008;10(9): 225. Published online September 30 2008.

Crayton HJ, Rossman HS, (2006). Managing the symptoms of multiple sclerosis: a multimodal approach. Clin Ther 2006 Apr;28(4):445-60.

Cuker A, Coles AJ, Sullivan H, et al. (2011). A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Blood. 118(24): 6299-6305.

Cutter GR, Baier ML, Rudick RA, et al. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999 May;122 (Pt 5):871-82.

Cutter G, Fahrbach K, Huelin R, et al. (2013). Relative efficacy of teriflunomide 14mg among the approved disease-modifying therapies in relapsing form of multiple sclerosis: a mixed treatment comparison [Abstract in draft to be presented at ACTRIMS, May 2013, Orlando]. 2013 Mar.

Dee A, Hutchinson M, De La Harpe D (2012). A budget impact analysis of natalizumab use in Ireland. Ir J Med Sci 181:199–204

De Judicibus MA, McCabe MP (2007). The impact of the financial costs of multiple sclerosis on quality of life. Int J Behav Med 2007;14(1):3-11.

Department of Health (2002). Health Service Circular HSC 2002/004, Cost Effective Provision Of Disease Modifying Therapies For People With Multiple Sclerosis - Risk Sharing Scheme for Disease Modifying Therapies in MS.

Department of Health (2007). The Risk Sharing Scheme for Disease Modifying Therapies in MS. 2007 Nov.

Department of Health (2012). NHS National Schedule of Reference Costs 2011-12. Available at https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 [Accessed 7 May 2013].

Devonshire V, Havrdova E, Radue EW, et al. (2012). Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 11(5): 420-428.

Devonshire V, Havrdova E, Radue EW, et al. (2012). Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Supplementary web appendix.* Lancet Neurol. 11(5): 420-428.

Downs S and Black N (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52:377-384.

Duquette P, Girard M, Despault L, et al. (IFNB Multiple Sclerosis Study Group) (1993). Interferon beta-lb is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology Apr 1993;43:655-661.

Dutta R. and Trapp B.D (2011). Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis. Prog Neurobiol 2011 Jan;93(1):1-12.

Ebers GC, Rice G, Lesaix J, et al. (1998). Randomised double-blind placebo-controlled study of interferon ß-1a in relapsing/remitting multiple sclerosis. Lancet. Nov 7;352: 1498-1504.

Ebers GC, Traboulsee A, Li D, et al. (2010) Analysis of clinical outcomes according to original treatment groups 16 years after the pivotal IFNB-1b trial. J Neurol Neurosurg Psychiatry 2010 81: 907-912.

Etemadifar M, Janghorbani M, Shaygannejad V, (2006). Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand 2006 May;113(5):283-7.

European Medicines Agency (EMEA)/ Committee for Medicinal Products for Human Use (CHMP) (2006). Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (CPMP/EWP/561/98 *Rev. 1*). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003485.pdf [Accessed 17 July 2013].

EMEA/ CHMP (2012). Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis (EMA/CHMP/771815/2011, *Rev 2*). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133438.pdf [Accessed 17 July 2013].

EMEA/ European Public Assessment Report (EPAR) (2011). *Gilenya/ fingolimod, Novartis* [EMEA/H/C/2202]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002202/WC500104529.pdf [Accessed 22 May 2013]. 2011 Feb 17.

EMEA/ CHMP (2013). *Alemtuzumab/ Lemtrada*, Summary of opinion (initial authorisation), [EMA/377379/2013]. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/003718/WC500144904.pdf [Accessed 1 May 2013].

Fattore G, Lang M, Pugliatti M, (2012). The Treatment experience, burden, and unmet needs (TRIBUNE) study - measuring the socioeconomic consequences of Multiple Sclerosis. Mult Scler. 18(2 Suppl): 5-6.

Filippi M, Rocca, MA, Camesasca, F et al. (2011). “Interferon ß-1b and glatiramer acetate effects on permanent black hole evolution”. Neurology 2011;76:1222-1228.

Fisk JD, Pontefract A, Ritvo PG, et al. (1994), The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci, 1994;21:9–14.

Ford HL, Gerry E, Johnson MH, et al. (2001). Health status and quality of life of people with multiple sclerosis. Disability and rehabilitation 2001; 23(12):516-521.

Ford C, Goodman AD, Johnson K, et al. (2010). Continuous long-term immunomodulatory therapy in relapsing multiple sclerosis: results from the 15-year analysis of the US prospective open-label study of glatiramer acetate. Mult. Scler. 16(3):342–350.

Fox EJ, Arnold DL, Brinar V, et al. (2012). Relapse Outcomes with Alemtuzumab vs. Rebif in Treatment-naive Relapsing-Remitting Multiple Sclerosis (CARE-MS I): Secondary and Tertiary Endpoints. Neurology 2012; 78 (Meeting Abstracts 1). PD5.004. Poster presented at 64th AAN, New Orleans, 2012.

Fox E, Arnold DL, Cohen, J, et al. (2013). Durable efficacy of Alemtuzumab in Relapse-Remitting Multiple Sclerosis Patients who participated in the CARE-MS Studies: Three Year Follow-Up. AAN 2013 S41.001. Poster presented at 65th AAN, San Diego, 2013.

Freedman MS, Francis GS, Sanders EACM et al. (2005). Randomized study of once-weekly interferon ß-1a therapy in relapsing multiple sclerosis: three-year data from the OWIMS study. Mult Scler 2005; 11; 41.

Freedman MS, Arnold DL, Cohen J, et al. (2012). Efficacy of alemtuzumab in relapsing-remitting multiple sclerosis patients who relapsed on prior therapy (CARE-MS-II): subgroup analyses by previous DMT use. ECTRIMS, Lyon 2012: Abstract No. P483.

Freedman M, Arnold D, Cohen J, et al (2013). Efficacy of Alemtuzumab vs IFNB-1a in Relapsing-Remitting Multiple Sclerosis Patients Who Experienced Disease Activity While On Prior Therapy (CARE-MS II): Subgroup analysis by Previous Disease Modifying Therapy (DMT) use. P07.111

Frischer JM, Bramow S, Dal-Bianco A, et al (2009). The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain 2009 May;132(Pt 5):1175-89.

Galetta SL (2001). The controlled high risk Avonex multiple sclerosis trial (CHAMPS Study). J Neuroophthalmol. 2001 Dec;21(4):292-5.

Gani R, Giovannoni G, Bates D, et al. (2008). Cost-Effectiveness Analyses of Natalizumab (Tysabri®) Compared with Other Disease-Modifying Therapies for People with Highly Active Relapsing-Remitting Multiple Sclerosis in the UK. Pharmacoeconomics 2008; 26 (7): 617-627

Genzyme (2010), Phase 2 CSR (CAMMS223); A Phase 2, Randomized, Open-Label, Three-Arm Study Comparing Low- and High-Dose Alemtuzumab and High-Dose Subcutaneous Interferon Beta-1a (Rebif®) in Patients With Early, Active Relapsing-Remitting Multiple Sclerosis.

Genzyme (2012), Phase 3 CSR (CARE-MS I, CAMMS323), A Phase 3 Randomized, Rater-Blinded Study Comparing Two Annual Cycles of Intravenous Alemtuzumab to Three-Times Weekly Subcutaneous Interferon Beta-1a (Rebif®) in Treatment-Naïve Patients with Relapsing-Remitting Multiple Sclerosis.

Genzyme (2012), Phase 3 CSR (CARE-MS II, CAMMS324), A Phase 3 Randomized, Rater- and Dose-Blinded Study Comparing Two Annual Cycles of Intravenous Low- and High-Dose Alemtuzurnab to Three-Times Weekly Subcutaneous Interferon Beta-la (RebitEd) in Patients with Relapsing-Remitting Multiple Sclerosis who Have Relapsed on Therapy.

Genzyme (2010), Phase 3 Clinical Study Protocol, An Extension Protocol For Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab (Protocol Number: CAMMS03409)

Genzyme (2012), Integrated Summary of Efficacy for LEMTRADA (alemtuzumab) – Appendix 8.8

Genzyme (2012), Integrated Summary of Safety for LEMTRADA (alemtuzumab)

Genzyme (2012), Summary of clinical safety for LEMTRADA (alemtuzumab), Module 2.7.4

Genzyme SUR March (2013). Lemtrada (alemtuzumab) 4-Month Safety Update Report.

Genzyme (2013). KOL Interview report: Treatment of Multiple Sclerosis. Clinical Practice in England and Wales and Positioning of Teriflunomide (Aubagio®) in the Treatment Pathway. April 2013.

Genzyme data on file (2013). Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy in an open-label cohort (draft manuscript).

Giovannoni G, Gold R, Selmaj K, et al. (2011). A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of daclizumab HYP monotherapy in relapsing-remitting multiple sclerosis: primary results of the SELECT trial (Presented at 5th Joint Congress ECTRIMS/ACTRIMS, Amsterdam, 2011). Mult Scler 2011;17(149):S508-S509.

Giovannoni G, Arnold D, Cohen J (2012). Disease activity-free status in comparison of alemtuzumab and Refib efficacy in multiple sclerosis I (CARE-MS I) phase 3 study. Slides presented at 22nd ENS, Prague, 2012.

Giovannoni G, Arnold DL, Cohen J, et al. (2013). Disability improvement with alemtuzumab vs. interferon-beta-1a in relapsing remitting multiple sclerosis patients who relapsed on prior therapy (CARE-MS II). P07.120. Presented at 65th AAN, San Diego, 2013: Poster P07.120.

Gold R, Wolinsky JS, Amato MP, et al. (2010). Evolving expectations around early management of multiple sclerosis. Available at: http://tan.sagepub.com/content/3/6/351 [Accessed 13 July 2012]. Therapeutic Advances in Neurological Disorders 2010 3: 351.

Gold R, Kappos L, Arnold DL, et al. (2012). Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012 Sep 20;367(12):1098-107.

Gray OM, McDonnell GV and Hawkins SA, (2009). Tried and tested: the psychometric properties of the multiple sclerosis impact scale (MSIS-29) in a population-based study. Mult Scler 2009;15:75. Originally published online 1 October 2008.

Gupta A, Arnold DL, Cohen J, et al. for the CARE-MS I investigators (2012). Alemtuzumab Improves Quality Of Life Compared To SC IFNB-1A In CARE-MS I. DX40. Poster presented at CMSC, San Diego, 2012.

Hartung H, Arnold DL, Cohen AJ, (2012). Disability outcomes for alemtuzumab in RRMS patients who relapsed on prior therapy: CARE-MS II. Presented at 22nd ENS, Prague, 2012.

Haas T, Hartung HP, von Rosenstiel P, et al (2011). Fingolimod reduces the number of severe relapses in patients with relapsing multiple sclerosis: results from phase III TRANSFORMS and FREEDOMS studies. Presented at 21st ENS, Lisbon Portugal, 2011. P902.

Hauser SL, Waubant E, Arnold DL, et al. (2008). B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008 Feb 14;358(7):676-88.

Healy B, Chitnis T, Engler D, (2011). Improving power to detect disease progression in multiple sclerosis through alternative analysis strategies. J Neurol 2011 Oct;258(10):1812-9.

Held U, Heigenhauser L, Shang C, et al. (2005). Predictors of relapse rate in MS clinical trials. Neurology December 2005; 65(1 of 2):1769-1773.

Hirst C, Ingram G, Pearson O, et al. (2008). Contribution of relapses to disability in multiple sclerosis. J Neurol 2008; 255: 280-7.

Honarmand K, Akbar N, Kou N, et al. (2010). Predicting employment status in multiple sclerosis patients: the utility of the MS functional composite, J Neurol, 2010;258:244–9.

Hurwitz BJ (2011). Analysis of current multiple sclerosis registries. Neurology 2011 Jan 4;76(1 Suppl 1):S7-13.

Hutchinson M, Fox RJ, Miller DH, (2013). Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing-remitting multiple sclerosis: subgroup analyses of the CONFIRM study. J Neurol 2013, Jun 8; Epublication ahead of printed version.

The IFNB Multiple Sclerosis Study Group (1995). Interferon beta-lb in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. Neurology 1995;45:1277-1285.

Jacobs LD, Cookfair DL, Rudick RA, et al. (1996). Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996 Mar;39(3):285-94.

Johnson KP, Brooks BR, Cohen JA, et al. (1995). Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995 Jul;45(7):1268-76.

Jones JL, Anderson JM, Phuah CL, et al. (2010). Improvement in disability after alemtuzumab treatment of multiple sclerosis is associated with neuroprotective autoimmunity. Brain 2010: 133; 2232-2247.

Kappos L, Traboulsee A, Constantinescu C, et al. (2006). Long-term subcutaneous interferon beta-1a therapy in patients with relapsing-remitting MS. Neurology 2006 Sep 26;67(6):944-53.

Kappos L, Gold R, Miller DH, et al. (2008). Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet 2008 Oct 25;372(9648):1463-72.

Kappos L, Radue EW, O'Connor P, et al. (2010). A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010 Feb 4;362(5):387-401.

Kappos L, Belachew S, Butzkueven H, et al. (2011) Assessment of baseline characteristics, treatment efficacy, and serious adverse events among natalizumab-treated MS patients with prior immunosuppressant use. Posters II Mult Scler 2011 17: S277 p976.

Kappos L, Radue EW, O'Connor P, et al. (2012). Phase III FREEDOMS study extension: fingolimod (FTY720) efficacy in patients with relapsing–remitting multiple sclerosis receiving continuous or placebo-fingolimod switched therapy for up to 4 years. Presented at the 28th ECTRIMS, Lyon, 2012.

Karampampa K, Gustavsson A, Miltenburger C, et al. (2012). Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. Mult Scler 2012 18:41.

Khatri B, Barkhov F, Comi G et al. (2012). Long-term efficacy data from the extension of the Phase III TRANSFORMS study of fingolimod versus interferon beta-1a in relapsing-remitting multiple sclerosis: 4.5 year follow-up. Presented at 22nd ENS, Prague, 2012.

Kingwell E, van der Kop M, Zhao Y, et al. (2012). Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry 2012 Jan;83(1):61-6.

Kobelt G, Berg J, Lindgren P, et al. (2006a). Costs and quality of life of multiple sclerosis in the United Kingdom. Eur J Health Econ 2006 Sep;7 Suppl 2:S96-104.

Kobelt G, Berg J, Lindgren P, et al. (2006b) Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry. 77(8): 918-926.

Krieger S, Arnold DL, Cohen J, et al. on behalf of CARE-MS II Investigators (2013); Alemtuzumab Is Efficacious In Highly Active RRMS Patients In CARE-MS II; slides ref: at CMSC 2013, DX01

Kurtzke J.F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983 Nov;33(11):1444-52.

Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005 Nov;128(Pt 11):2705-12.

Langer-Gould A, Popat RA, Huang SM, et al. (2006). Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol. 63(12): 1686-1691.

Leone MA, Bonissoni S, Collimedaglia L, et al (2007). Factors predicting incomplete recovery from relapses in multiple sclerosis: a prospective study. Mult Scler 2007; 14: 485-93.

Leray E, Yaouanq J, Le Page E, et al. (2010). Evidence for a two-stage disability progression in multiple sclerosis. Brain 2010 Jul;133(Pt 7):1900-13.

Lloyd A, Nafees B, Narewska J, et al. (2006) Health state utilities for metastatic breast cancer. British Journal of Cancer 2006;95:683-690.

Lublin FD, (2011). Relapses do not matter in relation to long-term disability: No (they do). Mult Scler 2011 17: 1415.

Lublin F, Cofield S, Cutter G, et al. (2012). The CombiRx trial: a multi-center, double-blind, randomized study comparing the combined use of interferon beta-1a and glatiramer acetate to either agent alone in participants with relapsing remitting multiple sclerosis - clinical outcomes. Presented at 64th AAN, New Orleans, 2012.

Mallam E, Scolding N (2009). The Diagnosis of MS. Int MS J 2009 Apr;16(1):19-25.

McCabe MP, De Judicibus M, (2005). The Effects of Economic Disadvantage on Psychological Wellbeing and Quality of Life among People with Multiple Sclerosis. Journal of Health Psychology. Vol 10(1) 163–173

McMillan R, Bussel JB, George JN, et al. (2008) Self-reported health-related quality of life in adults with chronic immune thrombocytopenic purpura. Am. J. Hematol. 83:150-154.

Meyer D, Coles A, Oyuela P, et al. (2012). Case report of anti-glomerular basement membrane disease following alemtuzumab treatment of relapsing-remitting multiple sclerosis. Multiple Sclerosis and Related Disorders.(2): 60-63.

Mikol DD, Barkhof F, Chang P, et al. (2008). Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol 2008 Oct;7(10):903-14.

Minagar A, Alexander JS, Sahraian MA, et al. (2010). Alemtuzumab and multiple sclerosis: therapeutic application. Expert Opin Biol Ther. 2010 Mar;10(3):421-9

Minden SL, Frankel D, Hadden L, et al. (2006). The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. Mult Scler 2006 Feb;12(1):24-38.

Miltenburger C, Kobelt G. (2002). Quality of life and cost of multiple sclerosis. Clin Neurol Neurosurg. 2002 104(3): 272-275.

Montalban X, O'Connor P, Izquierdo G, et al. (2011). Long-term fingolimod (FTY720) in relapsing MS: 5-year results from an extension of a phase II, multicentre study show a sustained low level of disease activity. Mult.Scler.17(10 SUPPL 1), S422-S433. P978. Presented at 5th ECTRIMS and ACTRIMS, Amsterdam, 2011.

Moreau T, Miller D, Mosely I, et al. (1994). Preliminary evidence from magnetic resonance imaging for reduction in disease activity after lymphocyte depletion in multiple sclerosis. Lancet July 30 1994; 344:298-301.

Moreau T, Coles A, Wing M, et al. (1996). Transient increase in symptoms associated with cytokine release in patients with multiple sclerosis. Brain (1996); 119:225-237.

Moss SM, Gray A, Marteau T, et al (2004). Evaluation of HPV/LBC Cervical Screening Pilot Studies Report to the Department of Health (Revised October 2004). Available at: http://www.cancerscreening.nhs.uk/cervical/evaluation-hpv-2006feb.pdf [Accessed 10 July 2013]

Mowry EM, Pesic M, Grimes B, et al. (2009). Demyelinating events in early multiple sclerosis have inherent severity and recovery. Neurology 2009; 72: 602-8.

Multiple Sclerosis International Federation (2012). Treatments That Affect the Long-Term Course of the Disease ("Disease Modifying Therapy"). Available at: http://rm2-msif-live.torchboxapps.com/print.rm?id=969 [Accessed 17 July 2012].

Multiple Sclerosis Trust: Prevalence and incidence of MS. Available at: http://www.mstrust.org.uk/atoz/prevalence_incidence.jsp [Accessed 4 April 2013]

Mid Meds (2013). Siemens/Bayer Multistix 10 S.G. Available at: http://www.midmeds.co.uk/siemens-bayer-multistix-p-234.html [Accessed 20 April 2013]

Murray T, (2006). Diagnosis and Treatment of multiple sclerosis. BMJ 332: 525-7

Nafees B, Stafford M, Gavriel S, et al. (2008). Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes 2008, 6:84.

National Institute for Health and Clinical Excellence (NICE) (2002). Technology Appraisal Guidance 32: Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. January 2002. Available at: http://www.nice.org.uk/TA32 [Accessed 18 July 2013]

NICE, (2003). Clinical Guideline 8: Multiple sclerosis: management of multiple sclerosis in primary and secondary care. Available at: http://guidance.nice.org.uk/CG8/NICEGuidance/pdf/English [Accessed 10 July 2013]

NICE, (2006). Costing report: Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. Ref: NICE clinical guideline no. 33, March 2006. Available at: http://www.nice.org.uk/nicemedia/live/13422/53840/53840.pdf [Accessed 11 July 2013]

NICE, (2007). TA127 Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. Available at: http://guidance.nice.org.uk/TA127 [Accessed 10 July 2013]

NICE, (2008). Guide to the methods of technology appraisal. Available at: http://www.nice.org.uk/aboutnice/howwework/devnicetech/GuideToMethodsTechnologyAppraisal2008.jsp?domedia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459 [Accessed 10 July 2013]

NICE, (2011a). Multiple sclerosis (relapsing-remitting) – fingolimod: appraisal consultation document (ACD). Available at: http://guidance.nice.org.uk/TA/Wave20/71/ACD1/ACD1 [Accessed 3 April 2013].

NICE, (2011b). Evidence Review Group (ERG) report: fingolimod for the treatment of relapsing remitting multiple sclerosis.

NICE, (2012a). TA254 Fingolimod for the treatment if highly active relapsing-remitting multiple sclerosis. Available at: http://publications.nice.org.uk/fingolimod-for-the-treatment-of-highly-active-relapsingremitting-multiple-sclerosis-ta254 [Accessed 10 July 2013]

NICE, (2012b). Costing Template: Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. Available at: http://guidance.nice.org.uk/TA254/CostingTemplate/xls/English [Accessed 10 July 2013]

NICE, (2013). Single Technology Appraisal Final Scope. Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Available at: http://guidance.nice.org.uk/TA/WaveR/151/Scope/pdf/English [Accessed 10 July 2013]

National Multiple Sclerosis Society (2009). Multiple Sclerosis Trend Report, 2nd Edition. Available at: http://www.nationalmssociety.org/research/research-news/ms-trend-report/index.aspx [Accessed 5 July 2013]

NHS Blood and Transport Price List 2013/14. Available at: http://hospital.blood.co.uk/library/pdf/price_list_2013_14.pdf [Accessed 11 July 2013]

Nicholas R, Straube S, Schmidli H, et al. (2011). Trends in annualized relapse rates in relapsing-remitting multiple sclerosis and consequences for clinical trial design. Mult Scler 2011 Oct;17(10):1211-7.

Novartis Pharmaceuticals UK Ltd (2011). Fingolimod for the Treatment of Relapsing-Remitting Multiple Sclerosis in Adults. Manufacturer submission (NICE Single Technology Appraisal).

Noyes K, Bajorska A, Chappel A, et al. (2011). Cost-effectiveness of disease-modifying therapy for multiple sclerosis: A population-based study. Neurology 2011;77:355–363.

O'Connor PW, Li D, Freedman MS, et al. (2006). A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006 Mar 28;66(6):894-900.

O'Connor P, Filippi M, Arnason B, et al. (2009). 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol 2009 Oct;8(10):889-97.

O'Connor P, Wolinsky JS, Confavreux C, et al. (2011). Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011 Oct 6;365(14):1293-303

O'Connor P, Wolinsky JS, Confavreux C, et al. (2011). Randomized trial of oral teriflunomide for relapsing multiple sclerosis – Supplementary Appendix to N Engl J Med 2011 Oct 6;365(14):1293-303.

Office for National Statistics (ONS, 2011). England & Wales, Interim Life tables, 2008-2010. Available at http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-223324 [Accessed 28 November 2012].

Office for National Statistics (ONS, 2012). 2011 Census: Population Estimates for the United Kingdom, 27 March 2011 (Statistical Bulletin). Available at: http://www.ons.gov.uk/ons/dcp171778_292378.pdf [Accessed 28 March 2013].

Office for National Statistics (ONS, 2013). CPI indices. Available at: http://www.ons.gov.uk/ons/datasets-and-tables/data-selector.html?cdid=D7BZ&dataset=mm23&table-id=1.1 [Accessed 24 April 2013].

Olsson T, Achiron A, Alfredsson L, et al (2013). Anti-JC virus antibody prevalence in a multinational multiple sclerosis cohort. Mult Scler published online 4 March 2013.

Orme M, Kerrigan J, Tyas D, et al. (2007). The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health 2007 Jan;10(1):54-60.

Panitch H, Goodin DS, Francis G, et al. (2002). Randomized, comparative study of interferon beta-1a treatment regimens in MS: The EVIDENCE Trial. Neurology 2002 Nov 26;59(10):1496-506.

Parisé H, Laliberté F, Lefebvre P et al (2013). Direct and indirect cost burden associated with multiple sclerosis relapses: Excess costs of persons with MS and their spouse caregivers. J Neurol Sci. 2013 Jul 15;330(1-2):71-7.

Patel NN, Abraham P, Buscombe J, et al. (2006). The Cost Effectiveness of Treatment Modalities for Thyrotoxicosis in a U.K. Center. Thyroid 2006;16(6):593-598.

Patzold U, Pocklington PR (1982). Course of Multiple Scleroris - First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand 1982;65:248-66.

Payment by Results tariff 2012-13 (2013). Available at: https://www.gov.uk/government/publications/confirmation-of-payment-by-results-pbr-arrangements-for-2012-13 [Accessed 11 July 2013]

Pfleger CC, Flachs EM, Koch-Henriksen N, (2010). Social consequences of multiple sclerosis. Part 2. Divorce and separation: a historical prospective cohort study, Mult Scler,2010;16:878–82.

Phillips CJ. (2004). The cost of multiple sclerosis and the cost effectiveness of disease-modifying agents in its treatment. CNS Drugs. 18(9): 561-574.

Pickin, M, Cooper, C, Chater, T et al. (2009). The Multiple Sclerosis Risk Sharing Scheme Monitoring Study – early results and lessons for the future. BMC Neurology 9:1-8.

Pokorski RJ, (1997). Long-Term Survival Experience Of Patients With Multiple Sclerosis. Journal Of Insurance Medicine 1997;29(2):101-106.

Polman CH, Reingold SC, Edan G, et al. (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005 Dec;58(6):840-6.

Polman CH, O'Connor PW, Havrdova E, et al. (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006 Mar 2;354(9):899-910.

PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group (1998). Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998 Nov 7;352(9139):1498-504.

Personal Social Services Research Unit (PSSRU). Unit Costs of Health & Social Care 2012. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2012/ [Accessed 3 May 2013]. 2012.

Prosser LA, Kuntz KM, Bar-Or A, et al. (2004). Cost-effectiveness of interferon beta-1a, interferon beta-1b, and glatiramer acetate in newly diagnosed non-primary progressive multiple sclerosis. Value Health. 7(5): 554-568.

Pugliatti, M, Rosati G, Carton H, et al. (2006). "The epidemiology of multiple sclerosis in Europe." Eur J Neurol 13(7): 700-722

Ramagopalan SV, Byrnesa JK, Ortona S-M, et al. (2010). “Sex ratio of multiple sclerosis and clinical phenotype”. Eur J Neuro 2010 17:634–637.

Ramsaransing GS, De Keyser J. (2007). Predictive value of clinical characteristics for 'benign' multiple sclerosis. Eur J Neurol 2007; 14: 885-9.

Razvi S, Ingoe LE, McMillan CV et al. (2005). Health status in patients with sub-clinical hypothyroidism. European Journal of Endocrinology 152 713–717

Riazi A, Hobart C, Lamping DL, et al. (2003). Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson’s disease with normal population health profiles. J Neurol Neurosurg Psychiatry 2003;74:710–714.

Richards, RG, Sampson FC, Beard SM, et al. (2002). "A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models." Health Technol Assess 6 (10): 1-73.

Rio J, Comabella M, Montalban X, et al. (2011). "Multiple sclerosis: current treatment algorithms." Curr Opin Neurol 24(3): 230-237.

Rodeghiero F, Stasi R, Gernsheimer T, et al. (2009). Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 113(11): 2386-2393.

Ross AP (2008) “Tolerability, adherence and patient outcomes” Neurology 71(24) suppl 3: S21-3

Rudick RA, Cutter GR, Baier M, et al. (2005). Estimating long-term effects of disease-modifying drug therapy in multiple sclerosis patients. Mult Scler 2005 Dec;11(6):626-34.

Rudick RA, Stuart WH, Calabresi PA, et al. (2006). Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med 2006 Mar 2;354(9):911-23.

Saida T, Kikuchi S, Itoyama Y, et al (2012). A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler 2012 Sep;18(9):1269-77.

Sander B, Hayden FG, Gyldmark M, et al. (2006). Post-Exposure Influenza Prophylaxis with Oseltamivir: Cost Effectiveness and Cost Utility in Families in the UK. Pharmacoeconomics 2006; 24 (4): 373-386.

Sanofi. CSR Phase 3 - TEMSO. 2011.

Sanofi. CSR Phase 3 - TENERE. 2011.

Sanofi. CSR Phase 3 - TOWER. 2012.

Scalfari A, Neuhaus A, Degenhardt A et al. (2010). The natural history of multiple sclerosis, a geographically based study 10: relapses and long-term disability. Brain 2010:133;1914-1929.

Scott TF, Schramke CJ (2010). Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later. J Neurol Sci 2010; 15: 292(1-2): 52-6.

Scottish Medicines Consortium (2007). Natalizumab 300mg concentrate for solution for infusion (Tysabri®). Resubmission. Available at http://www.scottishmedicines.org.uk/files/natalizumab_300mg_concentrate_for_solution_for_infusion__Tysabri__Resubmission_FINAL_August_2007_for_website.pdf [Accessed 4 April 2013]. 2007.

Scottish Medicines Consortium (2012). Fingolimod (as hydrochloride), 0.5mg hard capsules (Gilenya®). Resubmission. Available at: http://www.scottishmedicines.org.uk/files/advice/fingolimod_Gilenya_RESUBMISSION_FINAL_August_2012_amended_30.08.12.pdf [Accessed 4 April 2013]. 2012.

Selmaj K, Arnold DL, Cohen JA, et al. for the CARE-MS I and II Investigators (2012). Alemtuzumab Improves Patient-Reported Quality of Life in Relapsing-Remitting Multiple Sclerosis: CARE-MS I and II Phase 3 Trials. P338. Poster presented at 22nd ENS, Prague, 2012.

Shirani A, Zhao Y, Karim ME, et al. (2012). Association Between Use of Interferon Beta and Progression of Disability in Patients With Relapsing-Remitting Multiple Sclerosis. JAMA. 2012;308(3):247-256.

SmPC (draft). Summary of Product Characteristics (2013). Genzyme, *alemtuzumab/Lemtrada*.

SmPC. Summary of Product Characteristics (2010). Biogen Idec, *Avonex*. Available at: http://www.medicines.org.uk/emc/medicine/15349/SmPC/AVONEX+30+micrograms+powder+and+solvent+for+solution+for+injection/ [Accessed 22 May 2013]. 2012 Aug 10.

SmPC. Summary of Product Characteristics (2012). Bayer, *Betaferon*. Available at: http://www.medicines.org.uk/emc/medicine/1809/SmPC/Betaferon/ [Accessed. 2012 Jun 19].

SmPC. Summary of Product Characteristics (2009). Teva, *Copaxone* 20mg/ml, Solution For Injection, Pre-Filled Syringe. Available at: http://www.medicines.org.uk/emc/medicine/17516/SmPC/Copaxone+20mg+ml%2c+Solution+For+Injection%2c+Pre-Filled+Syringe/ [Accessed 22 May 2013]. 2009 Apr 17.

SmPC. Summary of Product Characteristics (2013). Novartis, *Extavia*. Available at: http://www.medicines.org.uk/emc/medicine/21659/SPC/Extavia/ [Accessed 5 June 2013]. 2013

SmPC. Summary of Product Characteristics (2013). Novartis, *fingolimod/Gilenya* 0.5mg hard capsules. Available at: http://www.medicines.org.uk/emc/medicine/24443/SmPC/Gilenya+0.5mg+hard+capsules/ [Accessed 14 February 2013]. 2013

SmPC. Summary of Product Characteristics (2013). Merck Serono, *Rebif*. Available at: http://www.medicines.org.uk/emc/medicine/22368/SmPC/Rebif+solution+for+injection+in+cartridges/ [Accessed 22 May 2013]. 2013 Mar 27.

SmPC. Summary of Product Characteristics (2006). Biogen Idec, *natalizumab/Tysabri*. Available at: http://www.medicines.org.uk/emc/medicine/18447/SmPC/TYSABRI+300+mg+concentrate+for+solution+for+infusion/ [Accessed 4 April 2013]. 2006.

Sorgalla S, Bernsen S, Gerbershagen K, et al. (2011). Efficacy and safety of natalizumab and jc-antibody prevalence following 36 months of treatment and more. Posters II Mult Scler 2011 17: S277 P987.

Stolp-Smith KA, Atkinson EJ, Campion ME, et al. (1998). Health care utilization in Multiple Sclerosis: A Population based study in Olmsetd County, MN. Neurology June 1998;50:1594-1600.

Sullivan PW and Ghushchyan V (2006). Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. Med Decis Making 2006; 26(4):410-420.

Tan H, Cai Q, Agarwal S, et al. (2011). "Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis" http://link.springer.com/article/10.1007%2Fs12325-010-0093-7 Advances in Therapy 2011:28(1):51-61

Trapp BD and Nave KA (2008). "Multiple sclerosis: an immune or neurodegenerative disorder?" Annu Rev Neurosci 2008;31:247-69.

Tremlett HL and Oger J. (2003). "Interrupted therapy. Stopping and switching of theß-interferons prescribed for MS". Mult Scler 2012 18: 1412.

Tremlett H, Yousefi M, Devonshire V, et al (2009). Impact of multiple sclerosis relapses on progression diminishes with time. Neurology 2009 Nov 17;73(20):1616-23.

Tremlett H, Zhao Y, Rieckmann P, et al. (2010). New perspectives in the natural history of multiple sclerosis. Neurology 2010 Jun 15;74(24):2004-15.

Tremlett H, Zhu F, Petkau J, et al. (2012). "Natural, innate improvements in multiple sclerosis disability". Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/22736751. Mult Scler. 2012 Oct;18(10):1412-21. Epub 2012 Jun 26. [Accessed 5 June 2013)

Trojano M, Pellegrini F, Fuiani A, et al. (2007). New natural history of interferon-beta-treated relapsing multiple sclerosis. Ann Neurol 2007 Apr;61(4):300-6.

Twyman CL, Group CS (2010). Durable efficacy of alemtuzumab treatment: clinical efficacy at four years. CMSC. 2010:Ab. S136.

Twyman CL (2011). More alemtuzumab relapsing-remitting multiple sclerosis patients are free of clinical disease activity at five years. Paper presented at: AAN 2011; Honolulu, Hawaii.

Twyman C, Montalban X, Arnold DL et al. (2013). Relapse Outcomes With Alemtuzumab Vs. Ifnb-1a In Active Relapsing-Remitting Multiple Sclerosis Patients Who Experienced Disease Activity While On Prior Therapy (CARE-MS II). P07.098. Poster presented at 65th AAN, San Diego 2013.

Tyas D, Kerrigan J, Russell N, et al. (2007). The Distribution of the Cost of Multiple Sclerosis in the UK: How Do Costs Vary by Illness Severity? Value in Health 2007; 10(5):386-389.

van Hoek AJ, Gay N, Melegaro A, et al (2009). Estimating the cost-effectiveness of vaccination against herpes zoster in England and Wales. Vaccine 2009;27:1454-1467.

Vermersch P, Czlonkowska A, Grimaldi LM, et al. (2012). A Multicenter, Randomized, Parallel-Group, Rater-Blinded Study Comparing the Effectiveness and Safety of teriflunomide and subcutaneous Interferon beta-1a in Patients with Relapsing Multiple Sclerosis. Presented at 4th CMSC and ACTRIMS, San Diego, 2012.

Vollmer T, Soelberg Sorensen P, et al. (2011). "A placebo-controlled and active comparator phase III trial (BRAVO) for relapsing-remitting multiple sclerosis". Mult.Scler (Abstract) 2011. 17(10): S507-S508.

Vukusic S, Passante N, Dufour M, et al. (2011). TYSEDMUS: Observational prospective follow-up study of patients with MS and treated with natalizumab in France using the French EDMUS (European Database for Multiple Sclerosis) network – Four-year results. Posters II Mult Scler 2011 17: S277 P970.

West T, Wyatt M, High A, et al. (2006). Are initial demyelinating event recovery and time to second event under differential control? Neurology 2006; 67: 809-13.

Wingerchuk DM, on behalf of CAMMS223 study group (2010). Efficacy of alemtuzumab in highly active relapsing-remitting multiple sclerosis patients in the CAMMS223 Trial. Presented at the 26th ECTRIMS & 15th RIMS,Sweden, 2010. Mult.Scler 2010(P49);S41-S196.

Wray S, Group CS (2011). Alemtuzumab reduces risk of sustained accumulation of disability and relapse rate at years 1 and 2 in CAMMS223. Presented at 25th Annual Meeting of the CMSC, Montreal, Canada, 2011. International Journal of MS Care. May 2011; 13(3); Ab. S44.

Wray S, Arnold DL, Cohen J (2012). Alemtuzumab improves disability on MSFC and visual function in CARE-MS I. Presented at the 4th Cooperative Meeting of CMSC and ACTRIMS, San Diego, California 2012). International Journal of MS Care. May 2012; 14(2):Ab. DX91.

Wynia K, van Wijlen AT, Middel B, et al. (2012). Change in disability profile and quality of life in multiple sclerosis patients: a five-year longitudinal study using the Multiple Sclerosis Impact Profile (MSIP). Mult Scler 2012 May;18(5):654-61.

Wynn D, (2010). Disability progression-free efficacy of alemtuzumab in relapsing-remitting multiple sclerosis patients in the CAMMS223 trial. Presented at 26th Congress of ECTRIMS and 15th RIMS. Mult Scler. 2010;16(10):S140.

Yorkston K, Johnson K, Klasner E, et al. (2003). Getting the work done: a qualitative study of individuals with multiple sclerosis. Available at: http://informahealthcare.com/doi/abs/10.1080/0963828031000090506 Disability and Rehabilitation, 2003; 25(8): 369-379. Online Publication Date: 22 April 2003 [Accessed 10 July 2013]

Zajicek JP, Ingram WM, Vickery J, et al. (2010). “Patient-orientated longitudinal study of multiple sclerosis in south west England (The South West Impact of Multiple Sclerosis Project, SWIMS) 1: protocol and baseline characteristics of cohort.” BMC Neurol 2010;10:88.

Zwibel HL, Smrtka J. (2011). Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 17 Suppl 5 Improving, S139-S145.