NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cladribine tablets for treating relapsing-remitting multiple sclerosis [ID64]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cladribine tablets for treating relapsing-remitting multiple sclerosis [ID64]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Cladribine for treating relapsing-remitting multiple sclerosis [ID64] – STA

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

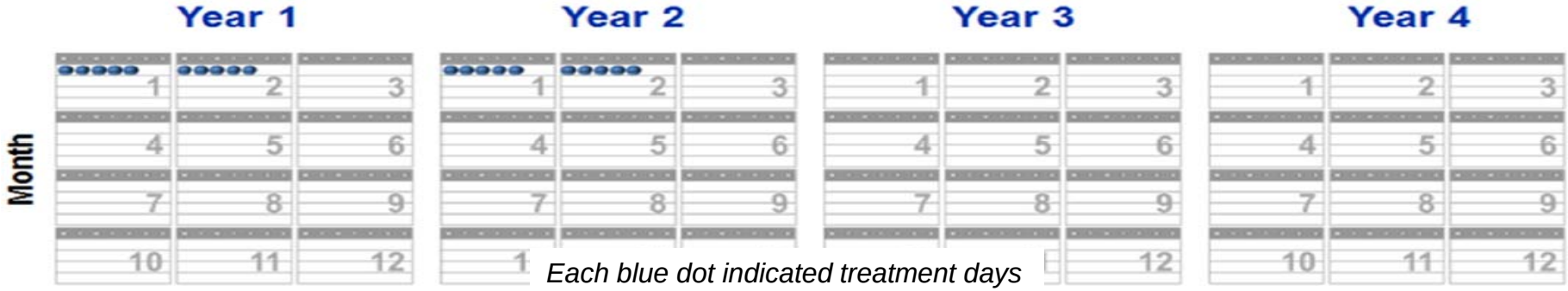
The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues

- Where does cladribine fit in the treatment pathway?
- Are the subgroups used by the company appropriate?
  - If not, does the committee prefer the combined highly active disease subgroup?
- Is cladribine clinically effective in all the relevant subgroups?
- What method of evidence synthesis is most appropriate (clinical trial, network meta-analysis, meta-regression or other?)
- Is the clinical evidence for cladribine robust enough to support an economic model?
  - If not, does the committee accept the ERG's assumption that cladribine has no effect on disability progression? Or the ERG assumption that comparators have equal effectiveness to cladribine?
- Innovation
- Equalities considerations

Cladribine (Mavenclad), Merck Serono

Marketing authorisation	• Adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features (June 2017) • Company do not intend to market cladribine in the UK for people with highly-active relapsing forms of secondary progressive MS
Mechanism of action	• 2-chloro-2'-deoxyadenosine, a purine analogue, activated selectively by lymphocytes, it inhibits adenosine deaminase. Used to treat hairy cell and chronic lymphocytic leukaemia (subcutaneous and intravenous respectively) • Cladribine targets CD19-positive B cells, CD8-positive and CD4-positive T-cells and is thought to interrupt the cascade of immune events central to MS (Leist 2011)
Dose / Admin	**Oral tablet**: 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. 1 course consists of 2 weeks of treatment (1st week of month 1&2). Daily dose 10-20mg



Each blue dot indicated treatment days

Multiple sclerosis

- Multiple sclerosis (MS) is a chronic, neurodegenerative disorder which affects the brain, optic nerves, and spinal cord
- It often results in progressive neurological impairment and severe disability
- Associated with symptoms such as pain, disturbance to muscle tone, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Approximately 93,000 people in England and Wales have MS, and about 4000 people are newly diagnosed each year
- Onset between 20 and 50 years for majority of people
- Twice as common in women as in men

Patient and professional feedback

- People with relapsing-remitting MS may not be able to take some or all current therapies either due to safety concerns or disease recurrence following prior therapy
- Patients may find current therapies too ‘intensive’ either in administration (e.g. regular hospital infusions) or monitoring (e.g. frequent blood testing)
- Cladribine has a lower degree of monitoring and administration intensity in comparison to other therapies
- MS Society survey found that 95% of people preferred pills, due to ease of use, convenience to everyday life and non-invasiveness
- Currently available oral treatments for MS (dimethyl fumarate, fingolimod and teriflunomide) are all taken daily (twice a day in the case of dimethyl fumarate)
- Cladribine is taken in two courses of tablets with relatively low side effect risks so would help to ensure some of the 44% of people who are potentially eligible for a DMT but not taking one can find a suitable treatment

Multiple sclerosis

Primary progressive MS
- Limited treatment options

Relapsing-remitting MS
- 85-90% of people at diagnosis
- Treatment strategy depends on patient choice, number of relapses, MRI, and response to previous treatment

~50% within 10 years

Secondary progressive MS
- Disease-modifying therapy not used for primary or secondary progressive MS, but some drugs licensed for secondary progressive disease *with relapses*

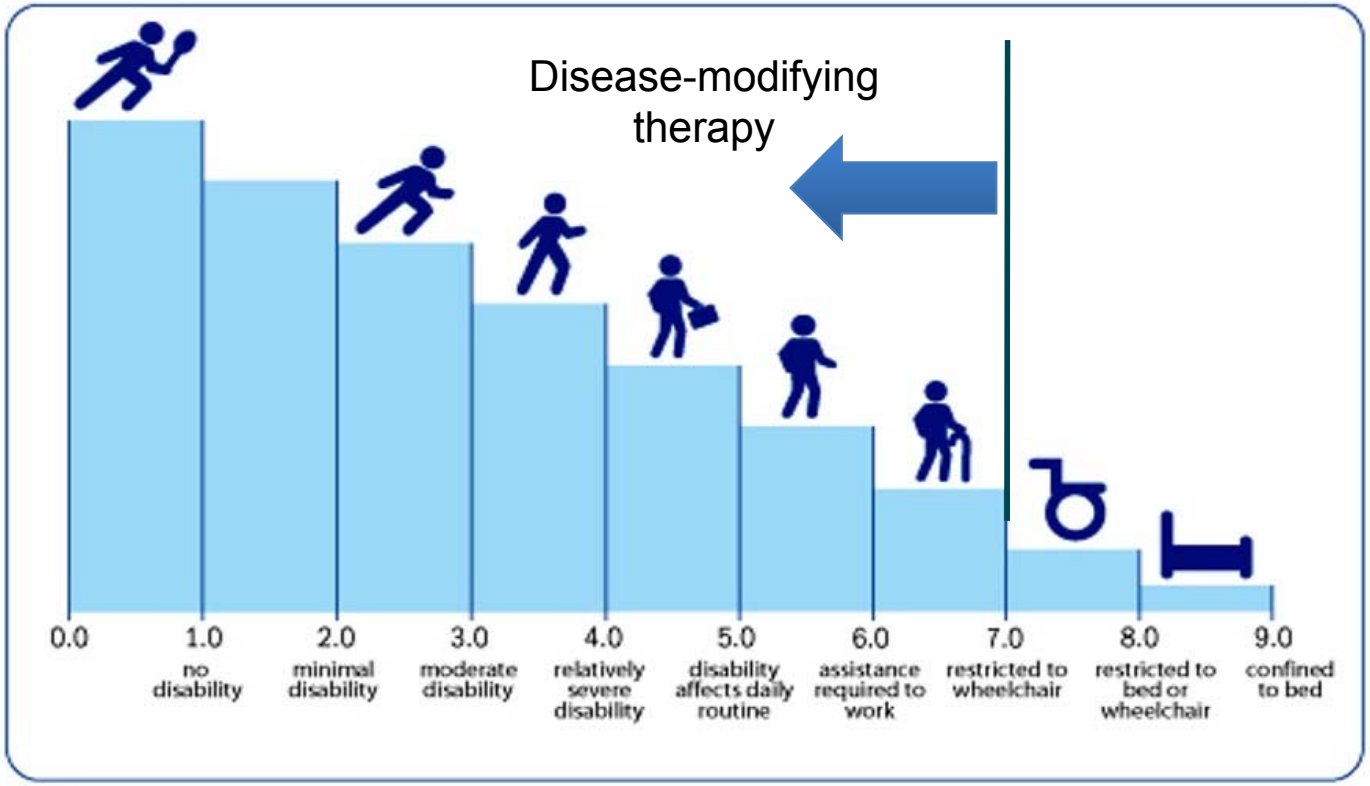
SUBGROUPS Definitions: see later..

High disease activity relapsing remitting MS, including:
- Rapidly evolving severe (RES) – RRMS
- Sub-optimally treated (SOT) - RRMS

Relapsing-remitting multiple sclerosis

Treatment aims to reduce frequency of **relapse** and slow **disability**

1. ***Relapses*** **–** symptoms lasting ≥24 hours without fever or infection
2. ***Disability*** *Expanded Disability Status Scale = EDSS*



http://caregivinglyyours.blogspot.co.uk/2011/04/whats-your-edss-score.html

Current management of relapsing-remitting multiple sclerosis

1st line

No previous treatment

- Interferon beta (Ongoing appraisal ID809)

(Avonex, Rebif, Plegridy, Betaferon/Extavia)

- Glatiramer acetate (Ongoing appraisal ID809)
- Teriflunomide (TA303)
- Dimethyl fumarate (TA320)
- Alemtuzumab (TA312)

Rapidly-evolving severe – 'RES'

- Natalizumab (TA127)
- Alemtuzumab (TA312)
- Daclizumab (TA441)
- Cladribine?

Change therapy – inadequate response/ adverse events

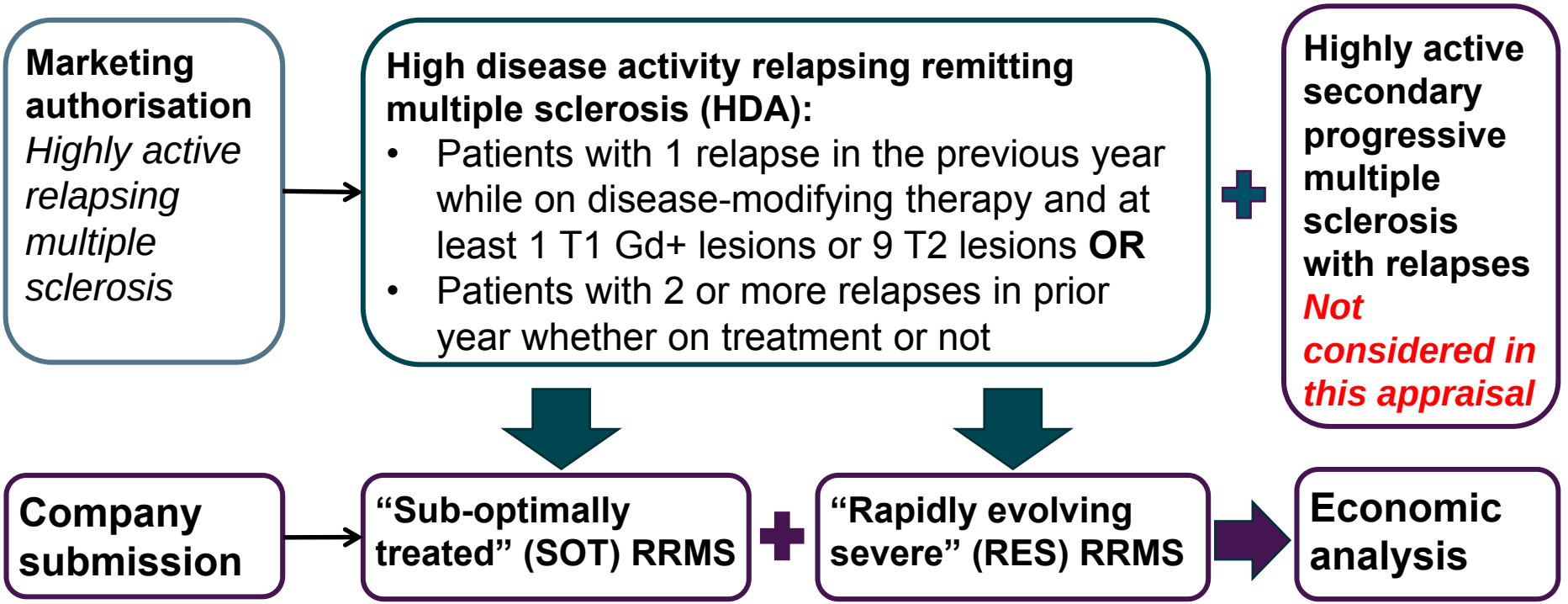
2nd line

Highly active despite previous treatment ("Sub-optimally treated" – 'SOT')

- Fingolimod (TA254)
- Alemtuzumab (TA312)
- Daclizumab (TA441)
- Cladribine?

⊙ Where does cladribine fit in the treatment pathway?

Subgroups in the company submission

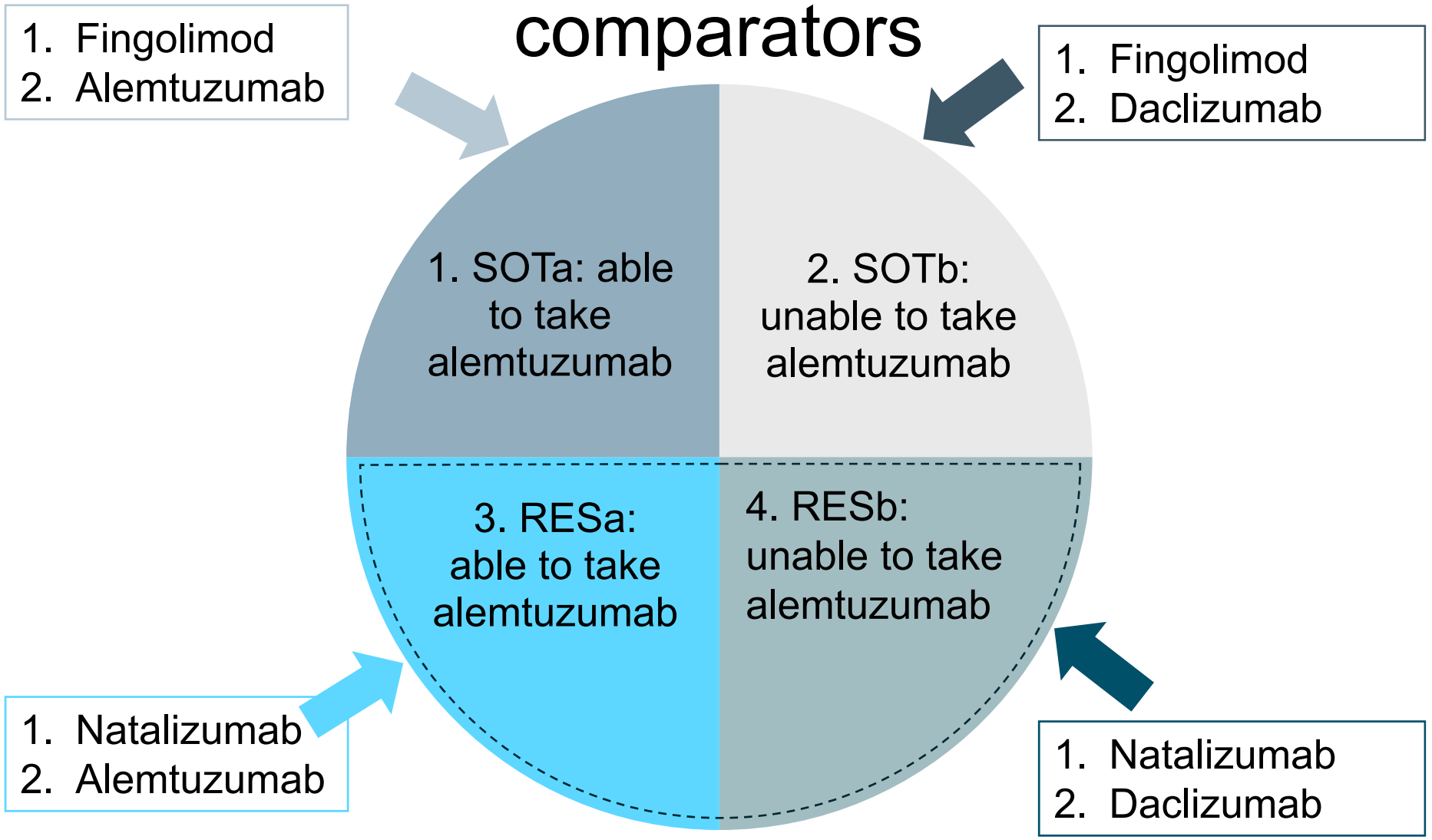


Subgroup criteria	HDA		RES	SOT
≥1 T1 Gd+ or ≥ 9 T2 lesions	✓			✓
≥1 T1 Gd+			✓	
Patients with ≥1 relapse while on treatment	✓			✓
Patients with ≥2 relapses regardless of treatment		✓	✓	

Company provided analyses only on RES-RRMS and SOT-RRMS and not on the additional subgroups of HDA-RRMS

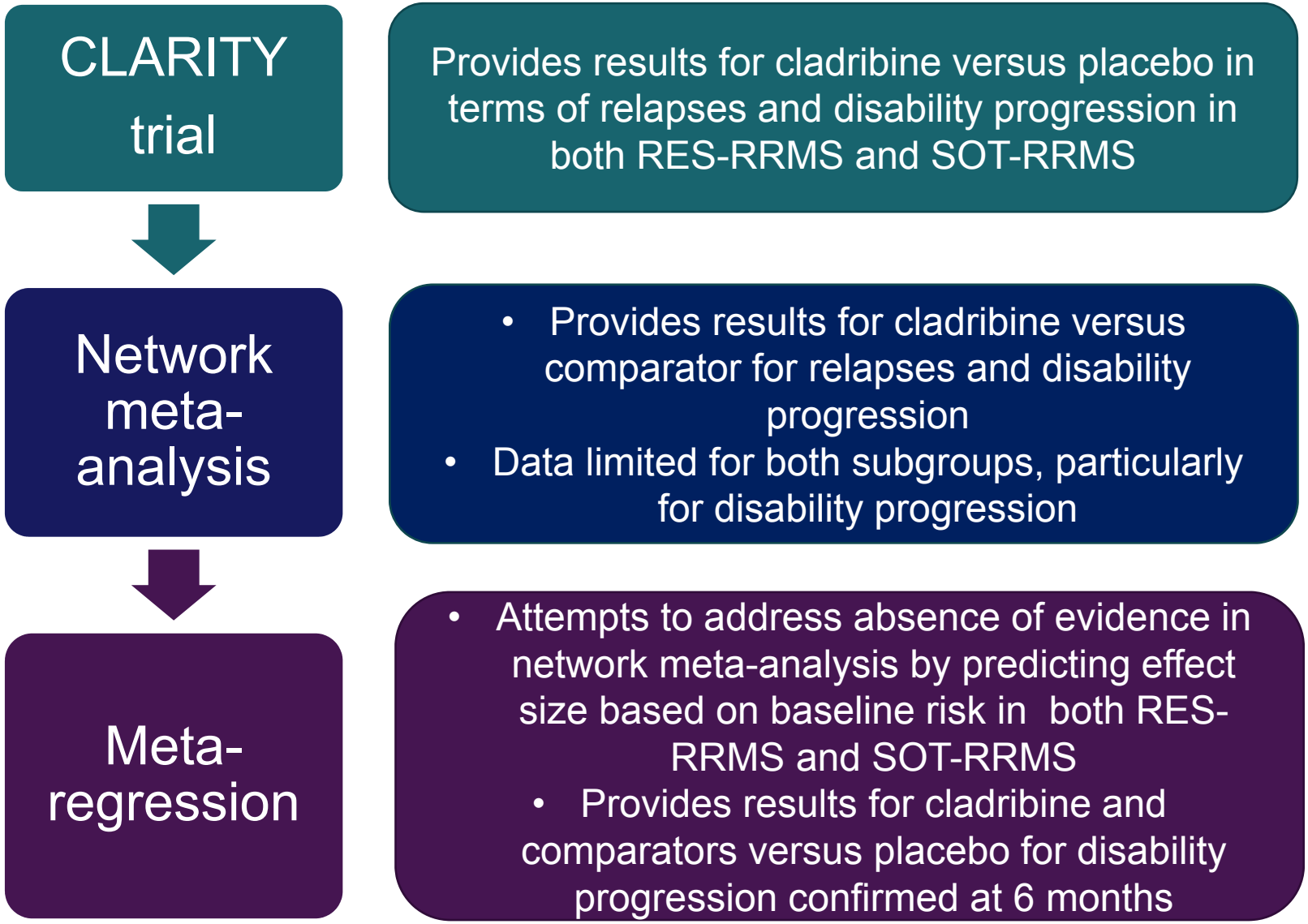
- Do the company subgroups (RES/SOT) represent the appropriate population for cladribine?

Decision problem: company comparators



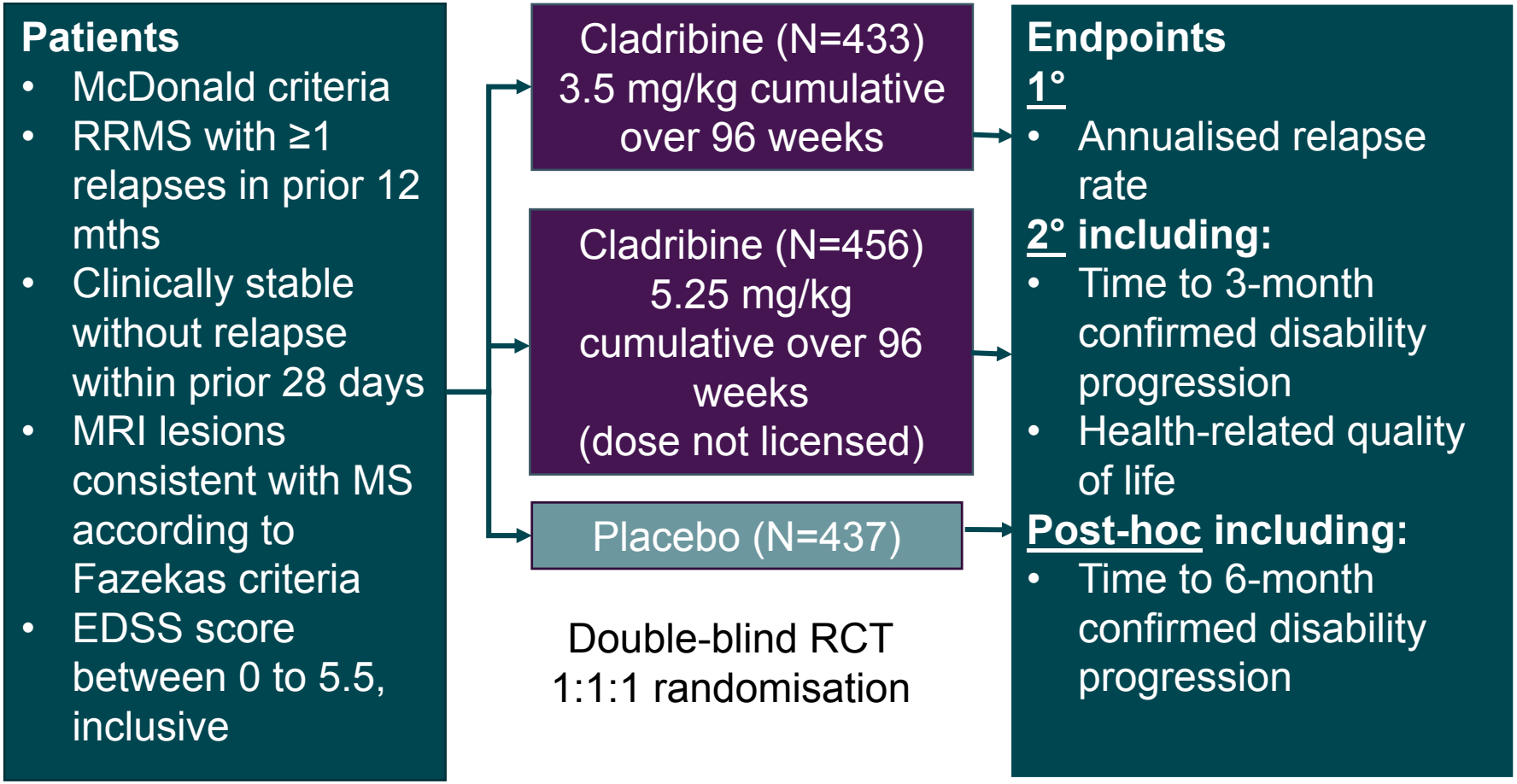
Abbreviations: RES, rapidly evolving severe; SOT, sub-optimally treated

Evidence base



Clinical evidence - CLARITY

Cladribine vs placebo (n=1326)



Extension study: CLARITY-EXT

- Patients enrolled in CLARITY who completed treatment and/or completed scheduled visits for full 96 weeks (N=98)
- Re-randomised to receive either 3.5 mg/kg cladribine or placebo

CLARITY analyses

	CLARITY	CLARITY EXT
Pre-planned subgroups	*Prior treatment* • Treatment-naïve • Treatment-experienced	*Prior treatment* • Treatment-naïve • Treatment-experienced *Treatment gap duration* • ≤4 weeks • >4 weeks to ≤43 weeks • >43 weeks
Post-hoc subgroups	• HDA-RRMS (licensed population) • RES-RRMS • SOT-RRMS	• HDA-RRMS (licensed population) • RES-RRMS

Abbreviations: HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT-RRMS: Sub-optimal therapy

Baseline characteristics – overall population

	CLARITY		CLARITY-EXT
	Placebo (n=437)	Cladribine 3.5 mg/kg (n=433)	Cladribine 3.5mg/kg [redacted]
Mean (SD) age, years	38.7 (9.9)	37.9 (10.3)	[redacted]
Female, %	65.9	68.8	[redacted]
Previous DMT use, %	30.2	25.4	[redacted]
Mean disease duration, years	5.2	4.7	[redacted]
Mean (SD) EDSS	2.9 (1.3)	2.8 (1.2)	[redacted]
Mean (SD) T1 Gd+ lesions	0.8 (2.1)	1.0 (2.7)	[redacted]
Mean (SD) T2 lesions	27.4 (17.7)	25.3 (16.3)	[redacted]

Abbreviations: DMT=disease-modifying therapy; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; SD=standard deviation

Baseline characteristics – subgroups

	Placebo			Cladribine 3.5mg/kg		
	HDA-RRMS (n=149)	RES-RRMS (n=41)	SOT-RRMS (n=32)	HDA-RRMS (n=140)	RES-RRMS (n=50)	SOT-RRMS (n=19)
Mean (SD) age, years	37.1 (10.2)	33.3 (8.2)	38.0 (8.8)	36.3 (9.5)	33.4 (7.9)	34.7 (8.0)
Female, %	63.1	58.5	68.8	72.9	72.0	73.7
Previous DMT use, %	37.6	24.4	100.0	32.9	34.0	100.0
Mean disease duration, years	4.8	3.9	7.6	3.9	2.9	5.8
Mean (SD) EDSS	3.0 (1.4)	2.9 (1.4)	3.6 (1.6)	2.9 (1.3)	2.8 (1.4)	3.2 (1.5)
Mean (SD) T1 Gd+ lesions	1.0 (2.8)	3.5 (4.6)	1.2 (2.1)	1.3 (3.5)	3.6 (5.6)	0.5 (0.8)
Mean (SD) T2 lesions	29.9 (19.8)	36.8 (24.4)	35.7 (21.1)	25.2 (17.2)	31.6 (16.8)	26.6 (18.1)

Abbreviations: DMT=disease-modifying therapy; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; HDA= high disease activity; RES= rapidly evolving severe; RRMS= relapsing remitting multiple sclerosis; SD=standard deviation; SOT=sub-optimally treated

Key outcome definition: disability progression

- Trial outcomes = ‘confirmed disability progression’ sustained for 3 or 6 months
- More sensitive measure of disease progression for EDSS states above 5 used than in previous appraisals

Current appraisal

- *Patients with baseline EDSS of 0: at least **1.5**-point EDSS increase, sustained for 3 months/6 months*
- *Patients with baseline EDSS between 0.5 and 4.5 (inclusive): at least **1.0**-point EDSS increase, sustained for 3 months/6 months*
- *Patients with baseline EDSS above 5: at least **0.5**-point EDSS increase, sustained for 3 months/6 months*

Previous appraisals (e.g. daclizumab, alemtuzumab)

- *Patients with baseline EDSS of 0: at least **1.5**-point EDSS increase, sustained for 3 months/6 months*
- *Patients with baseline EDSS above 0: at least **1.0**-point EDSS increase, sustained for 3 months/6 months*

- Time to sustained increase in EDSS score was reported using Kaplan-Meier survival curve
  - Gives results in terms of the proportion of patients progression-free at the end of follow up (96 weeks)

Key outcome definition: relapse rate

- Trial outcomes = annualised qualifying relapse rate
- Qualifying relapse defined differently from previous appraisals

Current appraisal

- *An increase of 2 points in at least one functional system of the EDSS*

or

- *An increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever*

lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement.

Alemtuzumab, daclizumab, natalizumab

New or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist.

Fingolimod

New or worsening of a previously stable or improving pre existing neurological abnormality, separated by at least 30 days from onset of a preceding relapse. The abnormality must be present for at least 24 hours and occur in the absence of fever or infection.

Results: overall population

		Cladribine (N=433)	Placebo (N=437)
ARR at 96 weeks	ARR (95% CI)	0.14 (0.12, 0.17)	0.34 (0.30, 0.38)
	Rate ratio (95% CI)	0.42 (0.33, 0.53)	
Time to first qualifying relapse	K-M estimate of relapse-free patients, % (95% CI)	80.3 (76.1, 83.8)	61.1 (56.2, 65.6)
	Hazard ratio (95% CI)	0.45 (0.34, 0.58)	
Time to 3 months CDP	K-M estimate of progression-free patients, % (95% CI)	85.1 (81.3, 88.2)	76.3 (71.9, 80.2)
	Hazard ratio (95% CI)	0.59 (0.43, 0.81)	
Time to 6 months CDP	K-M estimate of progression-free patients, % (95% CI)	90.6 (87.4, 93.1)	83.3 (79.3, 86.6)
	Hazard ratio (95% CI)	0.53 (0.36, 0.78)	

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression at 96 weeks; K-M, Kaplan-Meier

Results: High disease activity (HDA)

		Cladribine (N=140)	Placebo (N=149)
ARR at 96 weeks	ARR (95% CI)	0.16 (0.12, 0.22)	0.46 (0.38, 0.55)
	Rate Ratio (95% CI)	0.35 (0.24, 0.50)	
Time to first qualifying relapse	K-M estimate of relapse-free patients, % (95% CI)	77.1 (68.8, 83.5)	53.3 (44.7, 61.2)
	Hazard Ratio (95% CI)	0.40 (0.26, 0.61)	
Time to 3 months CDP	K-M estimate of progression-free patients, % (95% CI)	91.0 (84.7, 94.8)	71.7 (63.4, 78.5)
	Hazard Ratio (95% CI)	0.28 (0.15, 0.54)	
Time to 6 months CDP	K-M estimate of progression-free patients, % (95% CI)	95.5 (90.2, 97.9)	77.7 (69.8, 83.8)
	Hazard Ratio (95% CI)	0.18 (0.08, 0.44)	

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression at 96 weeks; CI, confidence interval; K-M, Kaplan-Meier

Results: Rapidly evolving severe (RES)

		Cladribine (N=[redacted])	Placebo (N=[redacted])
ARR at 96 weeks	ARR (95% CI)	[redacted]	[redacted]
	Rate Ratio (95% CI)	[redacted]	
Time to first qualifying relapse	K-M estimate of relapse-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]	
Time to 3 months CDP	K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]	
Time to 6 months CDP	K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard Ratio (95% CI)	[redacted]	

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression at 96 weeks; CI, confidence interval; K-M, Kaplan-Meier

Results: Sub-optimal therapy (SOT)

		Cladribine (N=[redacted])	Placebo (N=[redacted])
ARR at 96 weeks	ARR (95% CI)	[redacted]	[redacted]
	Rate ratio (95% CI)	[redacted]	
Time to first qualifying relapse	K-M estimate of relapse-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard ratio (95% CI)	[redacted]	
Time to 3 months CDP	K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard ratio (95% CI)	[redacted]	
Time to 6 months CDP	K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
	Hazard ratio (95% CI)	[redacted]	

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression at 96 weeks; CI, confidence interval; K-M, Kaplan-Meier; NE, not estimable

Results: Subgroup summary

	HDA-RRMS	RES-RRMS	SOT-RRMS
ARR at 96 weeks Rate ratio (95% CI)	0.35 (0.24, 0.50)	[redacted]	[redacted]
Time to first qualifying relapse Hazard ratio (95% CI)	0.40 (0.26, 0.61)	[redacted]	[redacted]
Time to 3 months CDP Hazard ratio (95% CI)	0.28 (0.15, 0.54)	[redacted]	[redacted]
Time to 6 months CDP Hazard ratio (95% CI)	0.18 (0.08, 0.44)	[redacted]	[redacted]

Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression at 96 weeks; CI, confidence interval; HDA, high disease activity; K-M, Kaplan-Meier; NE, not estimable; RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; SOT, sub-optimally treated

CLARITY adverse events in overall population - summary

Adverse event (AE)	Cladribine n=430	Placebo n=435
Any AE leading to discontinuation, patients (%)	15 (3.5)	9 (2.1)
Most common treatment emergent adverse events, patients (%)		
Headache	104 (24.2)	75 (17.2)
Lymphopenia	93 (21.6)	8 (1.8)
Nasopharyngitis	62 (14.4)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	42 (9.7)
Nausea	43 (10.0)	39 (9.0)
Serious treatment emergent adverse events (% of patients)		
Infections and infestations	2.3%	1.6%
Hepatobiliary disorders	0.7%	0.7%
Gastrointestinal disorders	0.9%	0.5%
Injury, poisoning and procedural complications		
Neoplasms		
Blood and lymphatic system disorders		
Psychiatric disorders		
Cardiac disorders		
Respiratory, thoracic and mediastinal disorders		

Health related quality of life (HRQoL)

- Change from baseline in HRQoL of patients in CLARITY was captured by the disease-specific HRQoL measure, MSQoL-54
  - Questionnaire was only applied to sites in the UK, US, Australia, Canada and Italy
- Secondary HRQoL measures included the use of the EQ-5D visual analogue scale (VAS) and index
- No statistically significant differences in any of the domains of the MSQoL-54 were observed with cladribine compared to placebo
  - Company suggest this may be due to small sample size and patients tending to have a good level of HRQoL when entering the CLARITY trial, leaving little room for improvement
- Statistically significant improvements in the EQ-5D VAS ($p=0.001$) and EQ-5D-3L index scores ($p<0.001$) were observed in patients receiving cladribine
- Limited information provided in the company submission

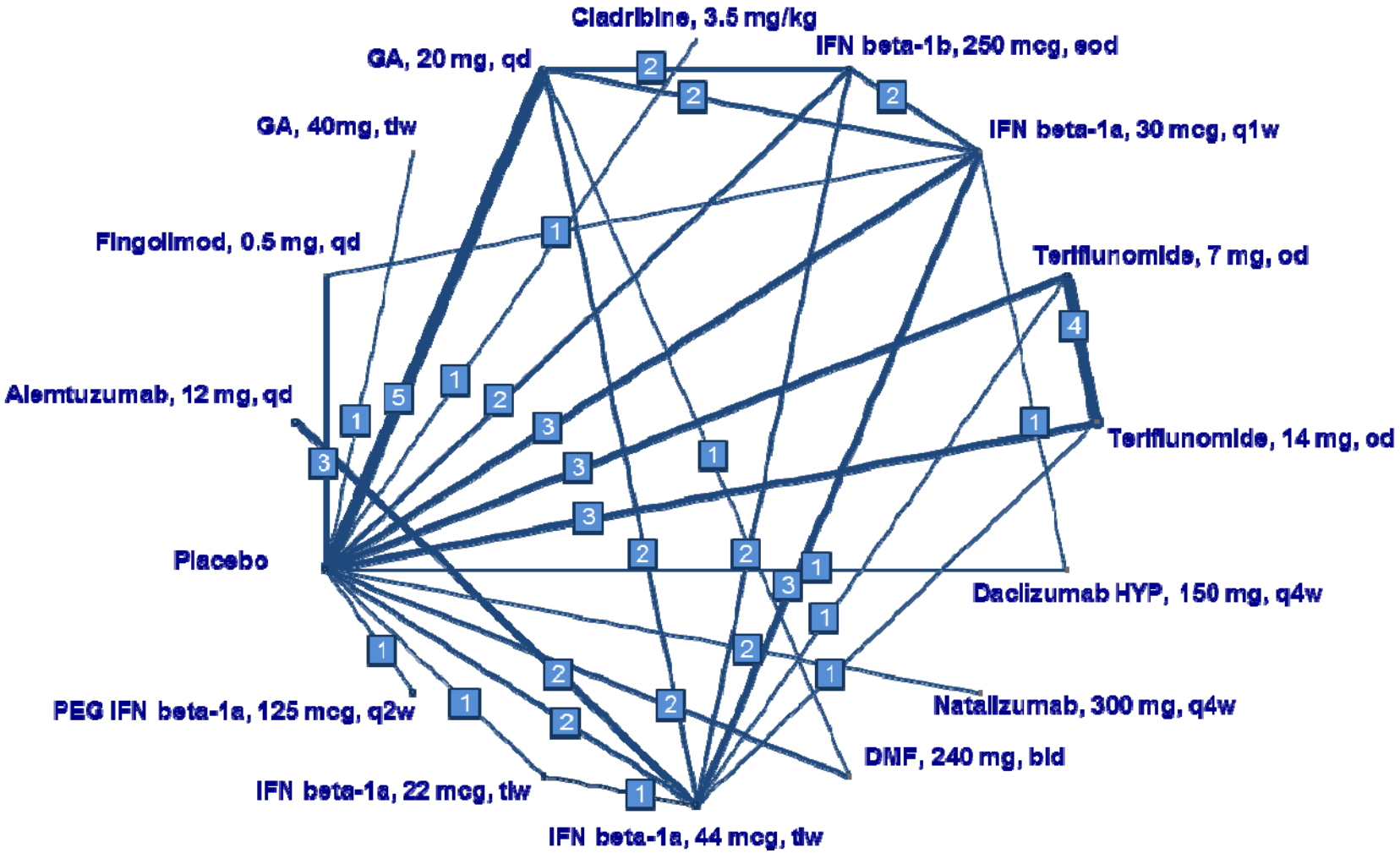
ERG critique of CLARITY

- Good quality and well conducted; participant characteristics balanced across treatment groups and pre-planned statistical methods generally appropriate
- Population included in CLARITY trial representative of people with MS likely to be treated in UK clinical practice
- Subgroup analyses were not pre-specified and the analyses are based on small number of participants with decreased statistical power
  - ERG encourages caution when interpreting the results, particularly for SOT-RRMS subgroup (19 and 32 participants for cladribine tablets and placebo respectively)
- Some patients may be included in both subgroups, resulting in double counting
- Analysis uses Cox regression which assumes proportional hazards to interpret estimated hazard ratios
  - Assumption holds for ITT population and HDA-RRMS subgroup, but plots for subgroups difficult to interpret, due to the small numbers of participants
- CLARITY EXT not critiqued by ERG as it is only used in the economic model to provide evidence for waning assumptions (see slide 57)

Network meta-analysis - summary

- Company conducted systematic literature review to identify RCTs which assessed efficacy, health-related quality of life, safety and tolerability outcomes associated with key interventions for RRMS
- Identified RCTs were included in the company's network meta-analyses
- Company performed NMAs using a hierarchical Bayesian approach
- Both fixed-effects (FE) and random-effects (RE) models were considered for NMAs; the choice was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC)
- The model with lowest DIC and/or the closest total residual deviance to the number of data points in the model was considered the best fitting model
- Results for key efficacy outcomes are presented on the following slides
- Company validate results by using a range of methodological approaches (e.g. frequentist), the findings of which were in line with the Bayesian NMA
- A further meta-regression was conducted to address shortcomings of the evidence in the relevant subgroups

Evidence network for annualised relapse rate in the overall patient population



ARR: Annualised relapse rate; bid: Twice a day; DMF: Dimethyl fumarate; eod: Every other day; GA: Glatiramer acetate; HDA: High disease activity relapsing-remitting multiple sclerosis; IFN: Interferon; ITT: Intention-to-treat; kg: Kilogram; µg: Microgram; mg: Milligram; od: Once daily; q1w: Once a week; q2w: Every 2 weeks; q4w: Every 4 weeks; qd: Per day; RES: Rapidly-evolving severe; SOT: Sub-optimal therapy; tiw: Three times a week

Company's network meta-analysis –
cladribine relative to other treatments in overall population

Cladribine vs…	ARR (RR) Median (95% CrI)	CDP3M (RR) Median (95% CrI)	CDP6M (RR) Median (95% CrI)
Placebo	**0.42 (0.32, 0.54)**	**0.61 (0.38, 0.96)**	0.54 (0.28, 1.06)
Alemtuzumab	1.31 (0.95, 1.82)	2.32 (0.82, 6.59)	1.37 (0.54, 3.70)
Daclizumab	0.92 (0.67, 1.26)	0.91 (0.41, 2.04)	1.08 (0.37, 2.98)
Dimethyl Fum.	0.79 (0.58, 1.08)	0.96 (0.54, 1.69)	0.85 (0.38, 1.97)
Fingolimod	0.91 (0.68, 1.23)	0.78 (0.45, 1.37)	0.79 (0.35, 1.78)
GA 20mg	**0.64 (0.49, 0.85)**	0.84 (0.49, 1.48)	0.82 (0.35, 1.90)
GA 40mg	**0.62 (0.44, 0.88)**		
Rebif 22mcg	**0.58 (0.43, 0.81)**	0.92 (0.47, 1.78)	
Avonex	**0.52 (0.40, 0.69)**	0.77 (0.39, 1.53)	0.79 (0.34, 1.78)
Rebif 44mcg	**0.64 (0.48, 0.84)**	0.94 (0.47, 1.80)	0.76 (0.32, 1.73)
Betaferon/Extavia	**0.62 (0.47, 0.84)**	0.68 (0.39, 1.27)	1.78 (0.59, 5.08)
Natalizumab	1.24 (0.89, 1.71)	1.11 (0.58, 2.06)	1.22 (0.47, 3.07)
Plegridy	**0.63 (0.44, 0.92)**		
Teriflunomide 7mg	**0.63 (0.47, 0.84)**	0.82 (0.46, 1.43)	0.66 (0.29, 1.50)
Teriflunomide14mg	**0.55 (0.40, 0.73)**	0.67 (0.38, 1.16)	0.57 (0.25, 1.29)

Notes-Bold text represents statistically significant results in favour of cladribine 3.5mg/kg

Abbreviations: ARR (RR), Annualised relapse rate (rate ratio); CDP3M, confirmed disability progression sustained for 3 months (hazard ratio); CDP6M, confirmed disability progression sustained for 6 months; GA, glatiramer acetate; HR, hazard ratio; mcg, microgram; RR, rate ratio.

Company's network meta-analysis – CDP

cladribine relative to other treatments in subgroups

	CDP6M (RR) Median (95% CrI)		CDP3M (RR) Median (95% CrI)
	HDA	RES	HDA
Placebo	**0.18 (0.08, 0.42)**	[redacted]	[redacted]
Alemtuzumab	0.50 (0.16, 1.59)	[redacted]	
Daclizumab	-	-	-
Dimethyl fumarate	-	-	[redacted]
Fingolimod	-	-	[redacted]
GA 20mg	-	-	[redacted]
Rebif 44mcg	**0.32 (0.12, 0.83)**	-	-
Natalizumab	-	[redacted]	[redacted]
Teriflun.14mg	-	[redacted]	-

No data available for disability progression in the SOT-RRMS subgroup

Notes – Bold text represents statistically significant results in favour of cladribine 3.5mg/kg

Abbreviations: ARR (RR), Annualised relapse rate (rate ratio); CDP3M, confirmed disability progression sustained for 3 months (hazard ratio); CDP6M, confirmed disability progression sustained for 6 months; GA, glatiramer acetate; HR, hazard ratio; RR, rate ratio; RES, rapidly evolving severe; SOT, sub-optimally treated

Company's network meta-analysis – ARR

cladribine relative to other treatments in subgroups

	ARR (RR) Median (95% CrI		
	HDA	RES	SOT
Placebo	**0.35 (0.24, 0.51)**	[redacted]	[redacted]
Alemtuzumab	0.99 (0.59, 1.66)	[redacted]	-
Daclizumab	-	[redacted]	-
Dimethyl fumarate	0.66 (0.41, 1.06)	-	-
Fingolimod	0.95 (0.58, 1.54)	[redacted]	[redacted]
GA 20mg	0.44 (0.25, 0.76)	-	-
Avonex	0.49 (0.27, 0.89)	[redacted]	[redacted]
Rebif 44mcg	0.49 (0.31, 0.78)	[redacted]	-
Natalizumab	1.14 (0.70, 1.84)	[redacted]	-
Teriflun. 7mg	**0.63 (0.38, 1.05)**	[redacted]	-
Teriflun.14mg	**0.51 (0.31, 0.84)**	[redacted]	-

No data available for disability progression in the SOT-RRMS subgroup

Notes – Bold text represents statistically significant results in favour of cladribine 3.5mg/kg

Abbreviations: ARR (RR), Annualised relapse rate (rate ratio); CDP3M, confirmed disability progression sustained for 3 months (hazard ratio); CDP6M, confirmed disability progression sustained for 6 months; GA, glatiramer acetate; HR, hazard ratio; RR, rate ratio; RES, rapidly evolving severe; SOT, sub-optimally treated

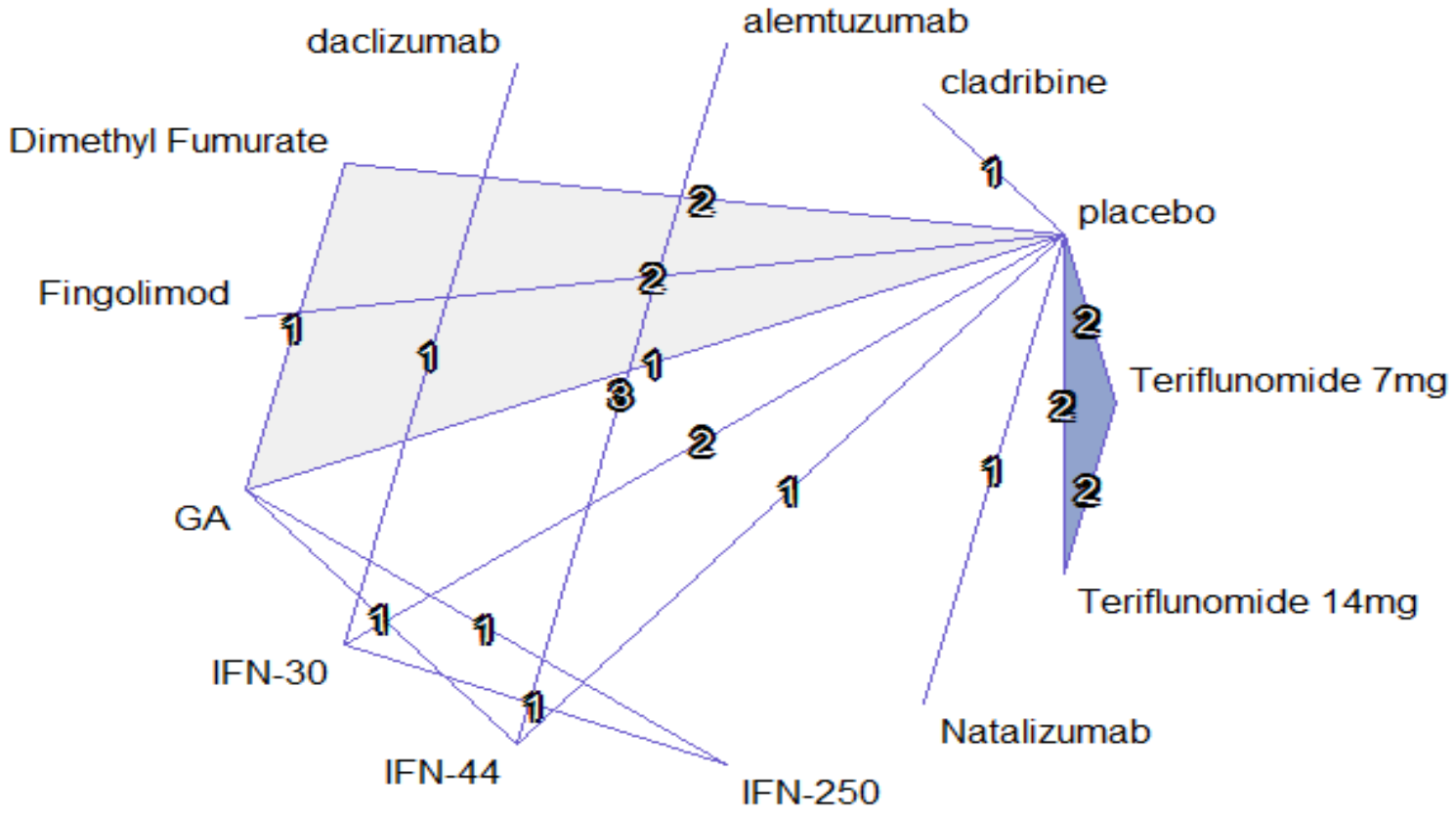
ERG critique – network meta-analysis

- General approach to identification of trials and inclusion of comparators appropriate; statistical approach generally appropriate
- Five trials included progressive MS (up to 12.3% of participants in each) and did not report results separately for RRMS
- Choices between fixed effects and random effects models within an NMA should be made taking into account consistency of trial designs, populations and evidence sources, rather than solely on model fit
- Company did not provide information about the number of participants for most analyses making it difficult to fully interpret NMA results from the subgroups
  - ERG assessments of NMA results based on relative precision of summary results provided for subgroups (i.e. standard errors of rate ratios or HRs)
- Results should be interpreted with caution due to heterogeneity in the network
- Analyses for inconsistency and heterogeneity due to trial or participant characteristics only conducted within the ITT population
  - Unclear if inconsistency or heterogeneity present in subgroup analyses
- Paucity of data available for key efficacy outcomes a “major limitation”
  - This was company rationale for meta-regression

Company meta-regression

- Company conducted a meta-regression, because of paucity of data available for the key efficacy outcomes in subgroups via a classic NMA approach
  - Including alemtuzumab: no published data linking control arm of alemtuzumab studies (IFN-β1a) to the network
- Meta-regression analysis conducted for the outcome of 6-month confirmed disability progression
- Uses differences in baseline risk between treatment groups to estimate efficacy
  - Assumes that baseline risk predicts efficacy and that observed differences between subgroups are explained by the relationship between baseline risk and effect size
- Efficacy results for disease progression from the meta-regression are included in the company's economic model

Evidence network for the meta-regression of 6-month confirmed disability progression at 24 months



GA: glatiramer acetate; IFN, interferon

Meta-regression results

- Company presented numerical results from four meta-regression models
- In terms of model fit, there is not one clearly favoured model (model DICs ranging from [redacted])
- All four models generated equally plausible effect estimates based on these model fit statistics
  - company preferred the simpler common covariate model to an exchangeable model
  - while fixed and random effects models equally plausible, as heterogeneity is expected, the random-effect with common covariate model was preferred

Treatment versus placebo	CDP6M Normalised HR (derived from log-HR and baseline risk) and 95% credible intervals	
	Centered on RES-RRMS	Centered on SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]
Fingolimod	Not applicable	[redacted]
Natalizumab	[redacted]	Not applicable

Abbreviations: CDP6M, confirmed disability progression sustained for 6 months; HR, hazard ratio; RES= rapidly evolving severe; RRMS= relapsing remitting multiple sclerosis; SOT=sub-optimally treated

Validation of meta-regression (1)

- Model has two assumptions:

1. Baseline risk predicts effect size (on a linear scale, given that the meta-regression model is expressed on a complimentary log-log scale)
   - Company validates this by plotting log HR of each comparator compared to placebo versus baseline risk complimentary log-log scale
   - Concludes that there is evidence of a consistent linear relationship between baseline risk and effect size and that the comparable slopes of these trend lines indicate that the relationship between effect size and baseline risk may also be consistent across drugs
   - ERG agrees in principle but notes that evidence of a linear relationship is not consistent for all comparators

Validation of meta-regression (2)

2. Relationship between baseline risk and effect size explains the effects observed in the different subgroups (i.e. that any differences across subgroups are not due to other known or unknown factors).
   - Company validates by considering whether results produced by meta-regression are sufficiently predictive of effect sizes observed in trials
   - As the meta-regression under-estimates effect size for natalizumab, the relationship between baseline risk and effect size does not explain differences observed across subgroups, and the ERG suggests the meta-regression approach may be invalid

- Company suggests that under-estimation may be due to the relationship between baseline risk and effect size estimate in AFFIRM differing from that in other studies, including CLARITY and PRISMS
- ERG argue that his suggestion contradicts the company's interpretation of their first validation

Therapy (vs placebo)	Cladribine	Natalizumab	Rebif 44
Study	CLARITY	AFFIRM	PRISMS
Baseline risk in placebo group	[redacted]	[redacted]	[redacted]
Predicted effect size (mean HR)	[redacted]	[redacted]	[redacted]
Observed effect size (mean HR)	[redacted]	[redacted]	[redacted]

ERG critique of meta-regression - summary

- The meta-regression methodology employed by the company was appropriate in principle with regards to modelling of the interaction term (independent, exchangeable or common effects) and choice of fixed or random-effects meta-regression model
- Uncertain whether the approach is valid for the company's objectives
- ERG agrees in principle that baseline risk predicts effect size but notes that evidence of a linear relationship is not consistent for all comparators
- Evidence may indicate relationship between baseline risk and effect size does not explain the differences observed across subgroups, → the meta-regression approach may be invalid
- ERG encourages caution when interpreting the results of this meta-regression

Summary – confirmed disability progression at 6 months in RES-RRMS

Treatment versus placebo	Trial result [HR (95% CI)]	Network meta-analysis [RR (95% CrI)]	Normalised meta regression [HR (95% CrI)]
Cladribine	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]

Comparison not possible for daclizumab and fingolimod due to data availability
Alemtuzumab trial results N/A as all trial data is in comparison with Rebif (IFN beta-1a)

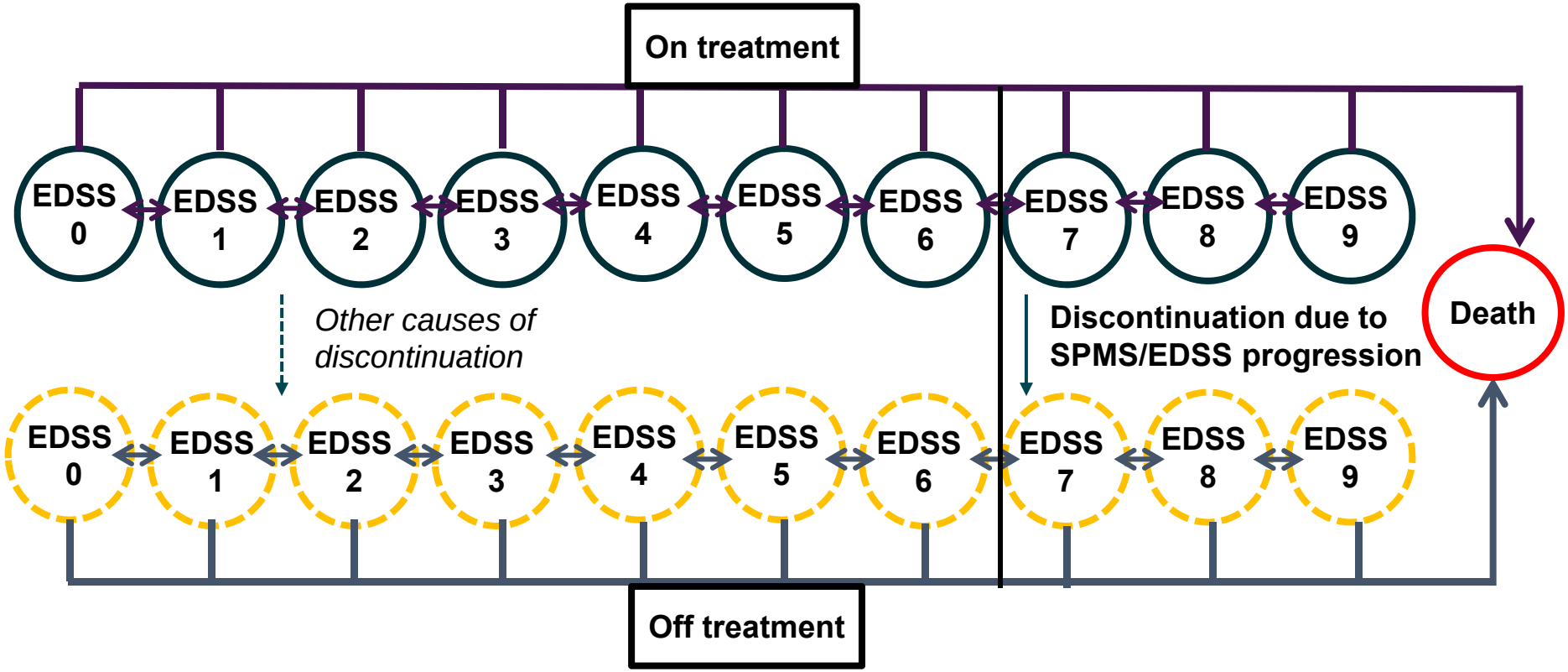
Abbreviations: CI, confidence interval; CrI, credible interval HR, hazard ratio; N/A, not applicable; RR, rate ratio.

- Company caution against naive cross comparisons of different models as they may have an effect on inference.
- Meta-regression “normalised” to risk of progression in RES population of CLARITY placebo arm, while NMA is un-centered and does not include any data adjustment
- Meta-regression effect sizes intend to predict outcomes in RES population of CLARITY, while NMA analysis assumes study-level effect estimates are exchangeable between studies

⊙ What method of evidence synthesis is most appropriate: clinical trial, network meta-analysis, meta-regression or other?

Cost effectiveness

Model structure



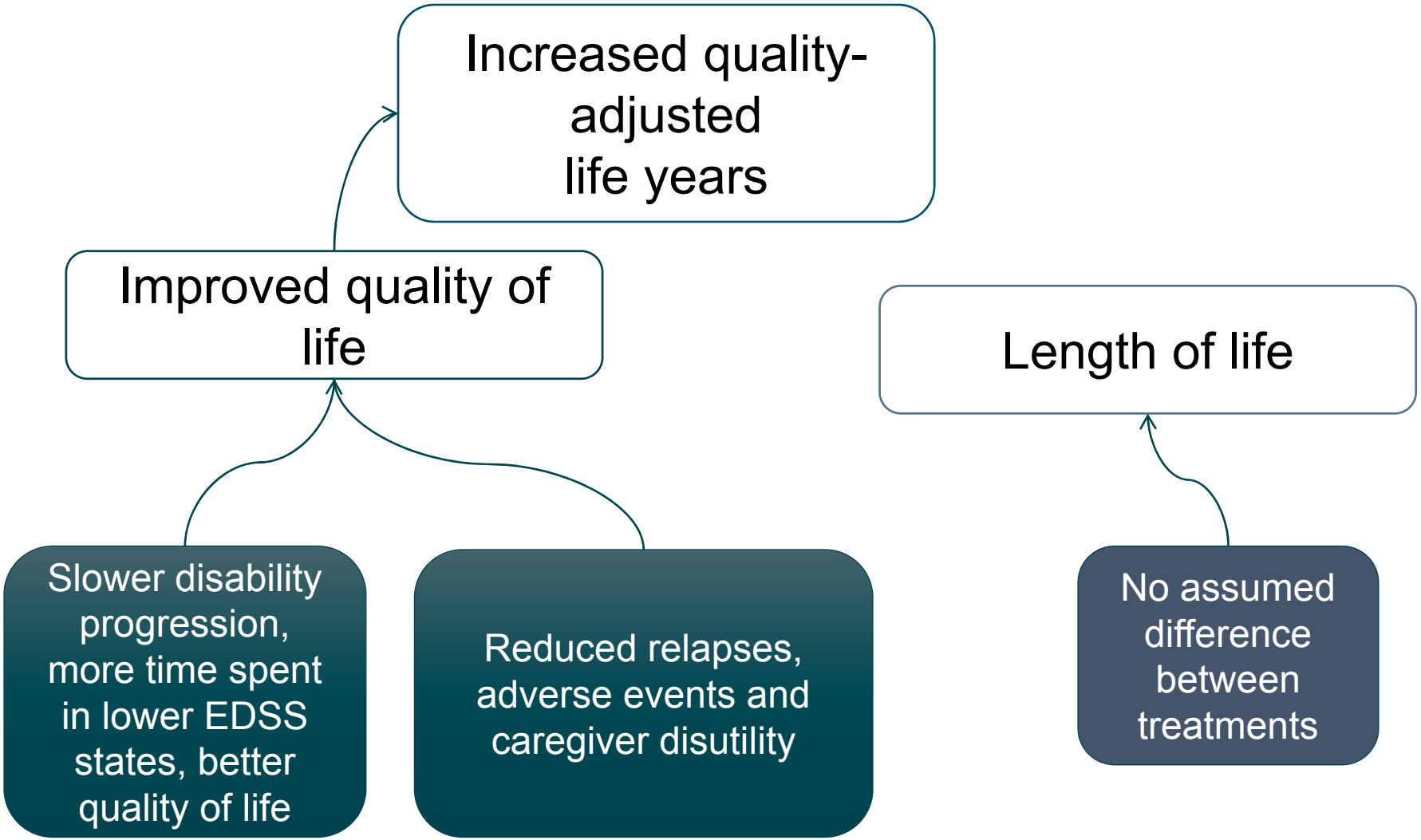
Model Assumptions

- Cycled yearly
- 50-year time horizon
- No distinction made between relapsing-remitting and secondary progressive forms of MS
- Discontinue therapy upon progression to EDSS 7.0
- Health benefits accrued up to point of discontinuation maintained, with future progression rates modelled based on a natural history data set

Model assumptions - summary

- Off treatment improvements and progression in EDSS as modelled using the preferred natural history data set from British Columbia
- A faster rate of progression in those with SOT-RRMS or RES-RRMS when compared to less active disease
- Inclusion of the long-term waning in drug efficacy for all therapies including cladribine
- Use of the committee preferred endpoint of 6 month confirmed disability progression
- Use of health state utility values from the CLARITY study
- Treatment with alemtuzumab and cladribine can be reinitiated following relapse

How treatments increase QALYs in model



ERG critique - model

- Satisfied with rationale for using simplified 11 health-state model rather than a 21 health-state model
  - Clinical advice to the ERG is that SPMS subtype does not significantly impact on costs or health-related quality of life
- Excel model frequently crashed when undertaking standard formula checking processes
  - Checks that the ERG was able to perform suggest model results are generated by accurate algorithms; however, the ERG is unable to guarantee this for all algorithms in the model

Summary of model inputs

Parameters	Manufacturer's source of evidence
Baseline characteristics	CLARITY
Natural history model: EDSS progression	Palace 2014 transition matrices (based on observed British Columbia MS dataset progressions)
Natural history model: annualised relapse rate	• Year 1 based on placebo arm of CLARITY • Subsequent years modelled using the annual change in relapse rate from Tremlett 2010 (analysis of British Columbia MS data)
Mortality	Office for National Statistics (all cause mortality); Jick 2014 (excess MS-related mortality)
Treatment effect: relapses	Company NMA. Duration of relapse from CLARITY
Treatment effect: disability progression	Company meta-regression
Utility data	EQ-5D in CLARITY for EDSS 0-5; Hawton et al 2016 for EDSS 6 to 8; Orne et al 2007 for EDSS 9
Costs	Hawton 2016b, Joint Formulary Committee 2015, Curtis 2015
Treatment discontinuation	Network meta-analysis
Adverse events	Clinical trial data identified in the systematic literature review

Baseline characteristics

Characteristic	RES-RRMS	SOT-RRMS
Mean age (se)	[redacted]	[redacted]
Female to male ratio:	[redacted]	[redacted]
Relapse in prior 12 months 0 1 2 >3	[redacted]	[redacted]
EDSS 0	[redacted]	[redacted]
EDSS 1.0	[redacted]	[redacted]
EDSS 2.0	[redacted]	[redacted]
EDSS 3.0	[redacted]	[redacted]
EDSS 4.0	[redacted]	[redacted]
EDSS 5.0	[redacted]	[redacted]
EDSS 6.0	[redacted]	[redacted]

Abbreviations: EDSS=expanded disability status scale; RES= rapidly evolving severe; RRMS= relapsing-remitting multiple sclerosis; se=standard error; SOT= sub-optimally treated

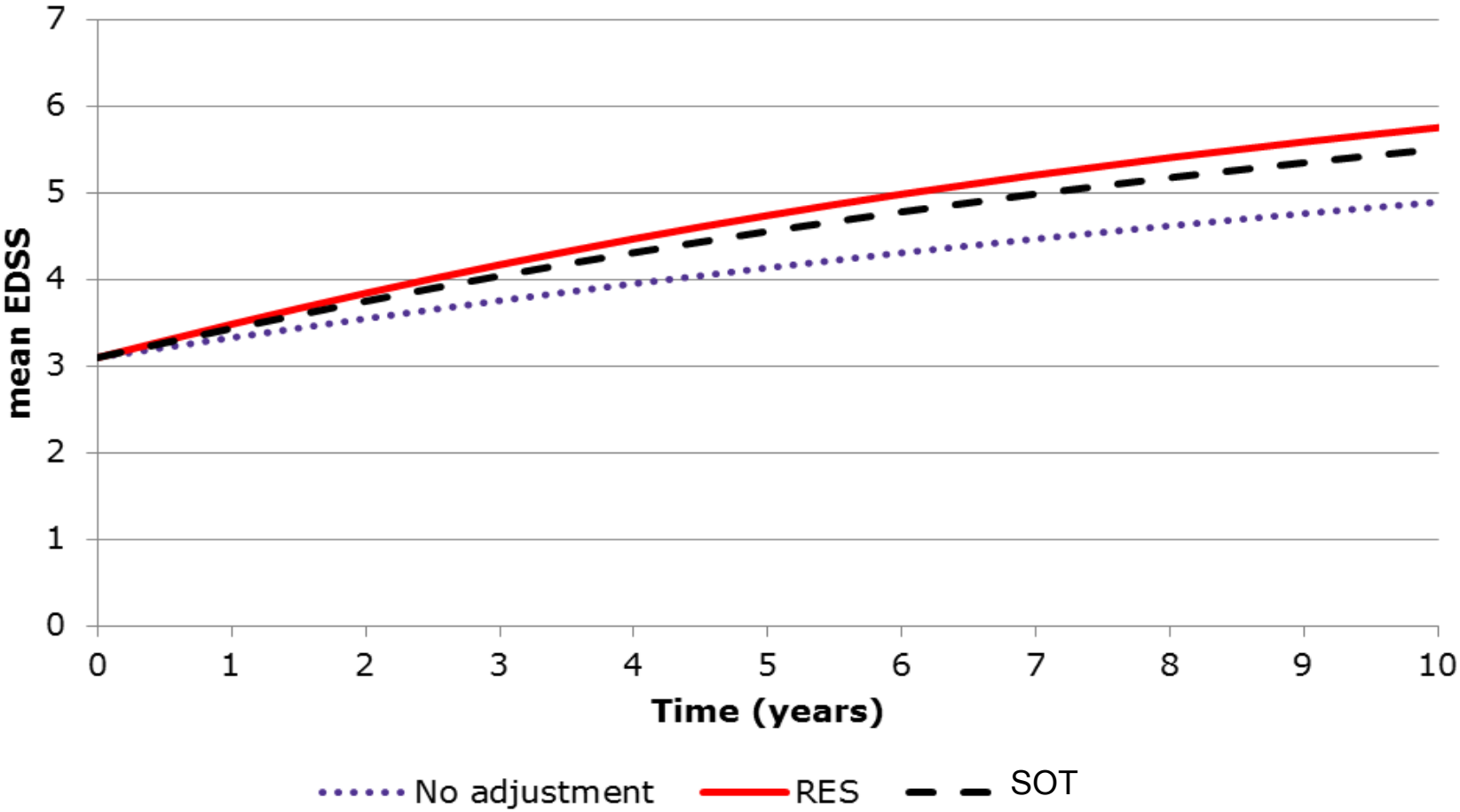
Natural history model disability progression rates – adjustment for subgroups

- Natural history model of MS (from British Columbia database analysis) was based on a cohort of people with active RRMS
- People considered by the company in this appraisal (RES-RRMS and SOT-RRMS) are likely to **progress at a faster rate** than people with less active disease
- TA441 (daclizumab) used sub-group specific transition matrices derived from the placebo arms of clinical studies to account for this
  - uncertainty of performing lifetime extrapolation using 2-year trial data
- To account for faster progression in RES-RRMS and SOT-RRMS, company includes an “acceleration parameter”
  - used to increase the probability of EDSS progression in the natural history model, prior to adjustment for the effect of disease modifying therapies
  - sub-group adjustments estimated from ratio of hazards for 6 month confirmed EDSS progression at week 96 in the placebo arm of CLARITY comparing each subgroup with its complement (i.e. non-subgroup)
- This adjustment retains EDSS “trends” observed in British Columbia MS analysis, and enables sensitivity analyses of sub-group progression rates

Natural history model - disability progression rates adjustment

	Hazard rate adjustment EDSS 0-6	Hazard rate adjustment EDSS 7+	Note
RES-RRMS	[redacted]	[redacted]	[redacted] progress by week 96 in RES-RRMS versus [redacted] progress in non-RES-RRMS groups of the placebo arm of CLARITY
SOT-RRMS	[redacted]	[redacted]	In the absence of data, the hazard rate adjustment for SOT-RRMS was assumed equal to the ratio of annualised relapse rates in the placebo group comparing SOT-RRMS [redacted] versus the active population [redacted]

Natural history model - disability progression rates adjustment



ERG critique – natural history of EDSS progression

- Although there is no clear alternative, use of acceleration factors simplistic
- Reliant on hazards being proportional for 6-month CDP between the RES-RRMS and non RES-RRMS, and between the SOT-RRMS and non SOT-RRMS subgroups
- If the hazards are not proportional then the approach may over or underestimate the rate of disease progression in the model
- Failure to test the validity of the proportional hazards assumption further adds to the uncertainty around the validity of the submitted model results

⊙ Is the company's use of an acceleration factor appropriate?

Natural history model - relapse rates

- Relapse rate for those not on treatment was modelled as a function of time as opposed to EDSS state as in previous appraisals
  - Company justification that relapse rates were modelled as a function of EDSS state rely on data from UK MS surveys conducted over 10 years ago, which may not reflect current relapse rates given trend towards lower annualized rates in placebo arms of recent clinical trials (Steinvorth 2013)
  - Previous approach also incorporated additional indirect effect of disease-modifying therapy on relapse rate through its effect on progression rate, which leads to double-counting of the benefits of DMT
- Annualised relapse rate (ARR) calculated by estimating the ARR during the first year of the simulation (from placebo arm of CLARITY) then using estimated change in ARR over time from the literature:
  - Tremlett et al (2010) reported longitudinal relationship between annualised relapse rate and characteristics of sex, age at onset, current age and disease duration using patient-level data from British Columbia MS dataset
  - Showed that the annualised relapse rate in the British Columbia MS dataset decreased by an average of 17% every 5 years

Natural history model – annualised relapse rates over time for best supportive care population

Treatment effect – disability progression

Treatment versus placebo	Normalised hazard ratio for 6 month disability progression comparing treatment versus placebo	
	RES-RRMS	SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]
Fingolimod	Not applicable	[redacted]
Natalizumab	[redacted]	Not applicable
Population risk	[redacted]	[redacted]

Normalised hazard ratio derived from log-hazard ratio and baseline risk from the company meta-regression

Abbreviations: RES= rapidly evolving severe; RRMS= relapsing remitting multiple sclerosis; SOT=sub-optimally treated

Treatment effect - relapses

Treatment versus placebo	Median ratio of annualised relapse rates comparing treatment versus placebo [95% crl]			
	RES-RRMS	**Source**	SOT-RRMS	**Source**
Cladribine	[redacted]	Company NMA	[redacted]	Company NMA
Alemtuzumab	[redacted]		[redacted]	CARE MS-II study
Fingolimod	Not in scope		[redacted]	Company NMA
Natalizumab	[redacted]		Not in scope	Company NMA
Daclizumab	[redacted]		[redacted]	Assumed same as cladribine

Abbreviations: crl, credible interval; NMA, network meta-analysis; RES= rapidly evolving severe; RRMS= relapsing remitting multiple sclerosis; SOT=sub-optimally treated

ERG critique – treatment effect (1)

- Results of company's network meta-analyses and meta-regressions should be treated with caution. In summary:
  - RES-RRMS and SOT-RRMS effectiveness data for cladribine in the NMAs based on post-hoc subgroup analyses
  - RES-RRMS and SOT-RRMS were post-hoc classifications of patients in the CLARITY trial
  - Definitions of RES-RRMS and SOT-RRMS may have differed between included trials in the network
  - Definition for RES-RRMS used in the CLARITY trial does not specify that people had to have had a *disabling* relapse, a term that was used in definitions of RES-RRMS in previous NICE MS TA submissions
  - ERG unable to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS
- Results from the company's statistical analyses not robust for both RES-RRMS and SOT-RRMS subgroups

ERG critique – RES-RRMS alternative treatment effect assumptions

- Credible intervals for 6-month CDP for all DMTs overlap and point estimates are similar (see slide 34)
- Estimates of annualised relapse rate compared to placebo for cladribine, alemtuzumab and daclizumab also reside in each other's credible intervals (see slide 53)
- Point estimate of ARR for natalizumab (which has a risk ratio compared to placebo of 0.19) only residing in the alemtuzumab credible interval (see slide 53)
- The ERG have therefore assumed, either:
  - For 6-month CDP, cladribine has no effectiveness compared to placebo. For qualifying ARR, the effectiveness of comparators excluding natalizumab is set equal to the effectiveness of cladribine (i.e., risk ratio 0.31)
  - **OR**
  - For 6-month CDP, the effectiveness of comparators is set equal to the effectiveness of cladribine. For qualifying ARR the effectiveness of comparators excluding natalizuamb is set equal to the effectiveness of cladribine

⊙ Does committee agree that clinical evidence for RES-RRMS is not robust enough for economic modelling? If so, which of ERG assumptions does committee prefer?

ERG critique – SOT-RRMS alternative treatment effect assumptions

- Credible intervals for 6-month CDP for all DMTs overlap and point estimates are similar (see slide 34)
- ARR results for the SOT-RRMS subgroup shows that point estimates are close and within the credible intervals of every other DMT (see slide 53)
- The ERG have therefore assumed that:
  - For qualifying ARR and 6-month CDP, the effectiveness of comparators is set equal to the effectiveness of cladribine

- Does committee agree that the clinical evidence for RES-RRMS is not robust enough for economic modelling?
- If so, does the committee agree with the ERG's assumption of equal effectiveness?

Treatment waning effect

- Company assess whether there is a waning effect for cladribine by using CLARITY EXT
- As placebo patients from CLARITY were re-randomised in CLARITY EXT, there is no data for placebo over the full 4 years
- Company estimate the effect of such patients switching from cladribine to placebo in CLARITY EXT, giving a hazard ratio for progression for cladribine relative to a group receiving placebo for 4 years
    - The rank preserving structural failure time (RPSFT) model and the iterative parameter estimation (IPE) algorithm were used, giving hazard ratios ranging from [redacted]
    - In CLARITY, point estimate of hazard ratio was [redacted] and so is largely comparable
- Company say this shows a constant effect of cladribine over 4 years → they assume a 4-year constant effect of cladribine in the model, using the waning effect from previous appraisals thereafter due to uncertainty
    - 25% waning after 2 years, 50% after 5 years as used in TA320 (dimethyl fumarate) and TA441 (daclizumab)

Year	Proportion of DMT effect	
	Cladribine	All comparators
0-2	100%	100%
2-4	100%	75%
4-5	75%	75%
5+	50%	50%

ERG critique – treatment waning effect

- Evidence provided by company not strong enough to support a different waning effect for cladribine
- For RES-RRMS (10 or fewer patients in trial arms), confidence intervals for the HRs used to support no waning between years 2 and 4 are wide and include a reduction in effectiveness between years 2 and 4 of 75% (i.e. the assumption previously used)
  - There is therefore evidence that waning for cladribine tablets is the same as assumed for DMTs in previous appraisals
- No evidence on the waning of effectiveness of cladribine in SOT-RRMS due to small patient numbers (2patients in intervention/placebo arm)
- Setting equal waning effect has no effect on the company's base case cost effectiveness results (i.e. cladribine remains dominant)

⊙ What is the most appropriate treatment waning effect?

Treatment discontinuation

- Annualised discontinuation rates are based on all cause discontinuation rates over the whole included trial periods
- Due to the administration of cladribine and alemtuzumab, discontinuation probabilities are only applied to the first cycle to capture discontinuations between first and second courses
- Probabilities for alemtuzumab and fingolimod are weighted based on patient numbers in the respective trials
- In TA312 the company's model assumed that no patient who received alemtuzumab ever discontinued treatment

	Annual discontinuation probability	Data sources (trials)
Cladribine	4.854%	CLARITY
Alemtuzumab	2.266%	CAMMS223, CARE-MS I, CARE-MS II
Daclizumab	11.609%	Decide
Fingolimod	13.595%	FREEDOMS, FREEDOMS II
Natalizumab	6.4%	AFFIRM

ERG critique – treatment discontinuation

- In TA441 (daclizumab): all cause discontinuation rates taken from trials and applied to the whole time horizon
  - Criticised as unrealistic by ERG and committee because discontinuation rates associated with any DMT are as likely to be higher during the 1st year than subsequent years
  - ERG and committee for TA441 considered it more appropriate to apply discontinuation rates from last year of trial
- However, with only one line of treatment, clinical advice to the ERG suggested that treatment would only stop when there no further clinical benefit to a patient even if they were still having relapses
- ERG: a more realistic approach is to use trial treatment discontinuation rates where available (i.e. for cladribine and alemtuzumab) & assume treatment would continue whilst the patient receives benefit for the other treatments (in the company model until a patient reaches EDSS state 7)
- This change increases both costs and QALYs associated with treatment with daclizumab, fingolimod and natalizumab

⊙ What is the most appropriate way of modelling treatment discontinuation?

Treatment re-initiation

- Company assumed that treatment with cladribine and alemtuzumab could be reinitiated after relapse:
  - Re-initiation with cladribine modelled using expected proportion of patients who experience their 1st relapse between years 2-6 from CLARITY data
  - Model incorporates rates of re-exposure to alemtuzumab that are equal to those used in TA441 and TA312
- After year 6, no further re-initiation given uncertainty over the rate of relapse
- All patients who relapse will be re-initiated on a single course of cladribine, regardless of lymphocyte status or other factors that may preclude re-initiation
- Company says this is a conservative assumption that likely overestimates re-initiation costs for cladribine

Year	Eligible patients treated with cladribine	Eligible patients treated with alemtuzumab
1&2	100%	100%
3	[redacted]	28%
4	[redacted]	11%
5	[redacted]	1%
6	[redacted]	0%

ERG critique – treatment re-initiation

- Clinical advice to ERG is that patients may be re-exposed to alemtuzumab after relapse but there is no published effectiveness evidence
- Company modelling means that re-initiation increases the costs of treatment and administration as well as the costs and QALY losses that arise from adverse events
  - However, reflecting the absence of effectiveness evidence on re-exposure, this approach does not influence rates of qualifying ARR or 6-month CDP
- ERG considers it more appropriate to remove re-exposure to cladribine and alemtuzumab from base case analyses, which reduces costs and increases QALYs associated with both cladribine and alemtuzumab
  - No effect on the company's base case cost effectiveness results – cladribine remains dominant

⊙ Should cladribine/alemtuzumab treatment re-initation be included?

Utility values

- CLARITY only collected EQ-5D data up to EDSS state 5
- Hawton et al (2016) the preferred literature source, but data not available for EDSS state 9
  - Orne et al 2007 therefore used for EDSS state 9
- Values are not specifically for patients with RES-RRMS or SOT-RRMS
  - ERG considers that the primary driver of utility would be the EDSS state and so is satisfied that the values implemented in the company model are reasonable
- Company also included disutility to carers, as in all recent MS appraisals
  - ERG considered this not to be in accordance with NICE reference case and removed from ERG analysis
  - Suggest only the direct health effects of an intervention should be included in the analysis and that carers only benefit indirectly

⊙ Should disutility to carers be included?

Utility values

	Mean EQ-5D utility (se)	Source	Caregiver utility (se)	Source
EDSS state				
0	[redacted]	CLARITY	-0.002 (0.053)	Acaster et al 2013
1			-0.002 (0.053)	
2			-0.002 (0.053)	
3			-0.045 (0.057)	
4			-0.142 (0.062)	
5			-0.16 (0.055)	
6	0.496 (0.012)	Hawton et al 2016	-0.173 (0.054)	
7	0.392 (0.032)		-0.03 (0.038)	
8	0.025 (0.038)		-0.095 (0.075)	
9	-0.195 (0.119)	Orne et al 2007	-0.095 (0.075)	
Relapses				
Relapse (with our without hospitalisation)	-0.071 (0.013)	Orne et al 2007	-	

Abbreviations: EDSS=expanded disability status scale; EQ-5D=Euroqol 5 dimensions; se=standard error

Costs - summary

- Drug costs comprise three different components: acquisition, administration and monitoring
- The costs of treatment with alemtuzumab and cladribine also include treatment reinitiation (see slide 61)
- EDSS health state costs, the costs of relapses and the costs of adverse events were also included in the model

EDSS health state costs (2015/16 prices)

EDSS State	Annual direct medical costs	Annual direct non-medical costs	Total	ID809 values
0	£1,020	£1,675	£2,695	£949
1	£910	£1,675	£2,585	£987
2	£716	£1,675	£2,391	£724
3	£668	£1,675	£2,343	£3,958
4	£1,002	£8,569	£9,571	£1,917
5	£1,006	£8,569	£9,575	£3,253
6	£1,304	£8,569	£9,873	£4,342
7	£1,316	£35,592	£36,908	£11,429
8	£3,320	£35,592	£38,912	£27,838
9	Not reported	£35,592	-	£22,274

- Company identified three sources via systematic literature review:
- Hawton et al 2016 preferred as most recent but only included medical costs
- Karampampa 2012 preferred for non-medical costs, as insufficient detail in Tyas 2007 to adjust non-medical costs to include costs covered by NHS and PSS
- As in TA441, for non-medical costs, 80% of social and community care and 47% of investment costs were considered in the analysis

ERG critique – EDSS state costs

- Company says 80% of informal and professional care costs should be included as previous appraisals have suggested that 80% of non-medical care would be paid for by PSS
- Details of how 80% was derived not provided; ERG considers it likely to represent the % of professional domiciliary and personal care generally funded by PSS
  - Professional domiciliary and personal care is not the same as informal care
  - Karampampa costed informal care by multiplying hours of care provided by the average hourly wage rate in UK. But professional care was costed via unit costs reported by the PSSRU
- ERG: only professional care costs should be included because the costs of informal care are not met by PSS and not relevant to the NICE Reference Case
- Excluding these informal care costs brings the costs of being in each EDSS state in line with those in previous STAs and in the ongoing MTA (rev of TA32)
- ERG considers it appropriate to use the EDSS state costs used in the ongoing MTA updated to 2015/16 prices

⊙ What EDSS health state costs are appropriate (Hawton, MS MTA, other?)

Treatment costs

Therapy	Acquisition cost		Admin costs		Monitoring costs	
	Year 1	Year 2+	Year 1	Year 2+	Year 1	Year 2+
Cladribine: RES-RRMS patients		£25,917	£0	£0	£584	£215
Cladribine: SOT-RRMS patients		£26,373	£0	£0	£584	£215
Alemtuzumab	£35,225	£21,135	£2,782	£1,681	£444	£267
Daclizumab		£19,160	£204	£0	£349	£187
Fingolimod		£19,176	£551	£0	£821	£169
Natalizumab		£14,690	£7,159	£7,159	£540	£547
Relapse costs						
With hospitalisation		£3,463				
Without hospitalisation		£526				

Sources:

- Acquisition costs: British National Formulary (NB: list price, not including patient access schemes where applicable)
- Administration and monitoring costs: Company submissions from relevant appraisals
- Relapse costs: Hawton et al 2016

Adverse events

Adverse event	Utility	Duration (days)	QALY loss	Cost
Infusion site reaction	-0.011	5	-0.0002	£0
Injection site reaction	-0.011	13	-0.0004	£6.79
PML	-0.200	93.1	-0.0510	£1,268.11
Severe infection	-0.190	14	-0.0073	£3,287.62
Macular oedema	-0.040	84	-0.0092	£245.46
Gastrointestinal	-0.240	8	-0.0053	£707.28
Hypersensitivity	-1.000	7	-0.0192	£156.68
Autoimmune thyroid-related event	-0.110	365.25	-0.1100	£543.63
Influenza-like symptoms	-0.210	7	-0.0040	£6.79
Malignancy	-0.116	365.25	-0.1160	£11,427.59
Immune thrombocytopenic purpura	-0.090	28	-0.0069	£939.54

Abbreviations: QALY = quality-adjusted life year; PML= progressive multifocal leukoencephalopathy

- Systematic review failed to identify studies reporting adverse event utility in MS
- Additional ad-hoc searches were therefore performed to identify relevant data from previous RRMS appraisals and from other chronic conditions
- These data were supplemented with estimates of the duration of adverse events to provide estimates of the QALY loss from each event.

ERG's exploratory analysis

For RES-RRMS
R1a) For 6-month CDP, cladribine has no effectiveness compared to placebo. For qualifying ARR, the effectiveness of comparators is set equal to the effectiveness of cladribine
R1b) For qualifying ARR and 6-month CDP, the effectiveness of comparators is set equal to the effectiveness of cladribine
For SOT-RRMS
R1) For 6-month CDP and qualifying ARR the effectiveness of comparators is set equal to the effectiveness of cladribine
For SOT-RRMS and RES-RRMS
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4
R3) No re-exposure to cladribine
R4) Treatment discontinuation only at EDSS 7 after 2 years for comparators
R5) ID809 EDSS costs
R6) No carer disutility
R7) 2-year time horizon
R8) 4-year time horizon
In isolation only assumptions R1a, R7 and R8 are able to change company's base case results of cladribine dominating (depending on comparator)

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators (daclizumab, fingolimod)

Innovation

Company

- “Considerable step-change in the current treatment pathway”
- Short course, oral treatment with low monitoring requirements
- Fewer restrictions on family planning

Patient and professional feedback

- “Cladribine…avoids the infusion reaction caused by cell lysis experienced during alemtuzumab treatment. The components of the immune system involved with fighting infections are largely spared, reducing the risk of infections after treatment.”
- “No other currently available oral DMT requires such infrequent administration in MS making this genuinely innovative for people with MS. “

ERG

- “An oral MS treatment only given in two cycles that are 12 months apart, with no treatment in between or after, and with no unique monitoring above the standard, represents a step change and innovative treatment for people with MS.”

Equality issues

No equality issues have been identified during scoping or evidence submission

Authors

- **Thomas Palmer**
  Technical Lead
- **Jasdeep Hayre**
  Technical Adviser
- with input from the Lead Team (Mark Glover Miriam McCarthy, Nigel Westwood)

Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Cladribine tablets for treating relapsing-remitting multiple sclerosis

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of cladribine tablets within its marketing authorisation for treating relapsing-remitting multiple sclerosis.

Background

Multiple sclerosis is a chronic, disabling neurological disease. It occurs when the body's immune system destroys myelin, a protective sheath around nerve cells in the brain and spinal cord. People with multiple sclerosis experience symptoms which can include: pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

Approximately 89,000 people in England have multiple sclerosis, and about 4,000 people are diagnosed each year.[1] The relapsing-remitting form of multiple sclerosis affects approximately 85–90% of people at the time of diagnosis.[2-4] It is characterised by periods of remission (when symptoms are mild or disappear altogether) followed by relapses (which may or may not result in residual disability). Some people with relapsing-remitting multiple sclerosis can progress to develop secondary progressive multiple sclerosis. This is characterised by more persistent or gradually increasing disability.

Current pharmacological management of relapsing-remitting multiple sclerosis includes disease-modifying agents to reduce the frequency and severity of relapses. These agents include beta interferon and glatiramer acetate which are not currently recommended by NICE (technology appraisal guidance 32, currently under review by NICE), but are available in the NHS through a risk-sharing scheme arranged by the Department of Health. NICE technology appraisal guidance 127 recommends natalizumab as a possible treatment for people with rapidly evolving severe relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 254 recommends fingolimod as an option for treating adults with highly active relapsing–remitting multiple sclerosis despite treatment with beta interferon. NICE technology appraisal guidance 312 recommends alemtuzumab as an option for treating adults with active relapsing–remitting multiple sclerosis. NICE technology appraisal guidance 320 and 303 recommend dimethyl fumarate or teriflunomide respectively as options for treating people with relapsing-remitting multiple sclerosis who have had 2 clinically significant relapses in the previous 2 years, and not for people who have highly active or rapidly evolving severe relapsing-remitting multiple sclerosis.

Appendix B

The technology

Cladribine tablets (brand name unknown, Merck Serono) is an orally administered deaminase-resistant deoxyadenosine analogue that targets CD19-positive B cells, CD8-positive and CD4-positive T-cells thought to be an important role in multiple sclerosis.

Cladribine does not currently have marketing authorisation in the UK for treating relapsing-remitting multiple sclerosis. It has been studied in clinical trials compared with placebo or beta-interferon for use in adults with relapsing forms of multiple sclerosis.

Intervention(s)	Cladribine tablets
Population(s)	Adults with relapsing-remitting multiple sclerosis
Comparators	For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • teriflunomide For people with rapidly-evolving severe relapsing-remitting multiple sclerosis • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • natalizumab For people with highly active relapsing-remitting multiple sclerosis despite previous treatment • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • fingolimod

Appendix B

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 from disease activity • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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 will 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.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation.Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator. If the evidence allows, the following subgroups of patients will be considered: • patients with relapsing-remitting multiple sclerosis whose disease has inadequately responded to treatment with disease modifying therapy • patients with relapsing-remitting multiple sclerosis for whom treatment with disease modifying therapy is not suitable because of intolerance of contraindication • patients with relapsing-remitting multiple sclerosis who are planning pregnancy
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis', January 2002. NICE Technology Appraisal 32. Update in progress. 'Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis', August 2007. NICE Technology Appraisal 127. 'Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis', April 2012. NICE Technology Appraisal 254. 'Teriflunomide for treating relapsing-remitting multiple sclerosis', January 2014. NICE Technology Appraisal 303. 'Alemtuzumab for treating relapsing-remitting multiple sclerosis', May 2014. NICE Technology Appraisal 312. 'Dimethyl fumarate for treating relapsing-remitting multiple sclerosis', August 2014. NICE Technology Appraisal 320. **Appraisals in development (including suspended appraisals):** 'Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32)'. NICE Technology Appraisal ID809. Expected publication TBC 'Daclizumab for treating relapsing-remitting multiple

	sclerosis'. NICE Technology Appraisal ID827. Expected publication April 2017 'Ocrelizumab for treating primary progressive multiple sclerosis' NICE Technology Appraisal ID938. Expected publication February 2018 'Ocrelizumab for treating relapsing multiple sclerosis' NICE Technology Appraisal ID937. Expected publication February 2018 'Biotin for treating progressive multiple sclerosis' NICE Technology Appraisal ID919. Expected publication March 2018 'Laquinimod for the treatment of relapsing-remitting multiple sclerosis' (suspended appraisal). NICE Technology Appraisal ID560 **Related Guidelines:** 'Multiple sclerosis in adults: management' (2014). NICE Clinical Guideline 186. Review date October 2018 **Related Interventional Procedures:** 'Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis' (2012). NICE Interventional Procedures guidance 420. **Related Quality Standards:** 'Multiple sclerosis' (2016). NICE quality standard 108. **Related NICE Pathways:** Multiple sclerosis pathway (2016): http://pathways.nice.org.uk/pathways/multiple-sclerosis
Related National Policy	NHS England (May 2014) Disease Modifying Therapies for Patients with multiple sclerosis (MS). Clinical commissioning policy reference D04/P/b. Department of Health, NHS Outcomes Framework 2016-2017, April 2016. Domains 1–4.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Cladribine for the treatment of relapsing-remitting multiple sclerosis [ID64]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Manufacturers/sponsors • Merck Serono (cladribine) Patient/carer groups • Brain and Spine Foundation • Disability Rights UK • Leonard Cheshire Disability • MS-UK • Multiple Sclerosis National Therapy Centres • Multiple Sclerosis Society • Multiple Sclerosis Trust • Muslim Council of Britain • Neurological Alliance • South Asian Health Foundation • Specialised Healthcare Alliance • Sue Ryder Professional groups • Association of British Neurologists • British Geriatrics Society • British Neuropathological Society • Institute of Neurology • Primary Care Neurology Society • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • Therapists in MS (TIMS) • UK Clinical Pharmacy Association • UK Multiple Sclerosis Specialist	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • Multiple Sclerosis Wales • National Association of Primary Care • National Pharmacy Association • Neurological Alliance of Scotland • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Wales Neurological Alliance Comparator companies • Bayer Pharma (beta-interferon) • Biogen Idec (dimethyl fumarate, natalizumab, daclizumab, interferon beta-1a) • Genzyme Therapeutics (alemtuzumab, teriflunomide) • Novartis (interferon beta-1b,fingolimod) • Teva UK (glatiramer acetate) Relevant research groups • Brain Research Trust • British Neurological Research Trust

Appendix C

Consultees	**Commentators (no right to submit or appeal)**
Others • Department of Health • NHS Leeds South and East CCG • NHS England • NHS Salford CCG • Welsh Government •	• Cochrane Multiple Sclerosis Group • MRC Clinical Trials Unit • National Institute for Health Research • National Hospital for Neurology and Neurosurgery Associated Public Health Groups • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland;; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Document A

Company evidence submission summary for committee

Merck confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

June 2017

File name	Version	Contains confidential information	Date
Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]		YES	October 2017

Contents

Tables

Figures

Submission summary

A.1. Health condition

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) resulting in inflammation, demyelination, development of plaque lesions and progressive disability (Zuvich 2009). MS is the most common debilitating neurological disease among young adults (MS Trust 2017). Approximately 85% of patients with MS initially present with relapsing-remitting MS (RRMS), which is characterised by periodic acute exacerbations of disease activity (relapses) followed by periods of remission (Zuvich 2009). Relapses in patients with RRMS are unpredictable and are associated with inflammation and development of new focal lesions, followed by periods of remission, leading to partial or complete recovery (Zuvich 2009). Over time (typically 15-20 years following disease onset) , most patients with RRMS will enter a phase of progressive neurodegeneration, with or without periodic relapses, associated with the accumulation of permanent disability, termed secondary-progressive MS (SPMS) (Compston 2002; Hauser 2006; Zuvich 2009; Tremlett 2010). In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. To date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual. This has limited the ability to study the imaging and biomarker characteristics that may distinguish this course.

Some patients with RRMS experience a more aggressive disease course. These patients can be categorised as having high disease activity (HDA-RRMS), although its definition is evolving and which can be associated with a constellation of clinical and imaging activities, including these defined by the European Medicines Agency (EMA) specifically for natalizumab and fingolimod (Novartis 2017; Biogen 2017):

- failure to respond to an adequate course of at least one disease-modifying therapy (DMT), presenting with at least one relapse in the previous year while on therapy and at least nine T2-hyperintense lesions or at least one gadolinium-enhancing lesion, or
- treatment naïve with at least two disabling relapses in the last 1 year and at least one gadolinium-enhancing lesion or significant increase in T2-lesion load

There is no cure for MS. The EMA has acknowledged that in spite of a number of recent approvals for disease-modifying therapies (DMT), there remains a high unmet need for effective and well-tolerated treatments especially for patients with HDA-RRMS (Merck 2017b). Most current DMTs for HDA-RRMS deliver their effect by continuous immunosuppression, and in turn, patients receiving these treatments require close monitoring. The implications can be considerable; many patients travel significant distances to reach services for regular treatment administration and for monitoring that, due to its frequency, can interfere with daily life. Additionally, some DMTs are associated with restrictions on family planning, requiring discontinuation if a woman becomes pregnant while on treatment.

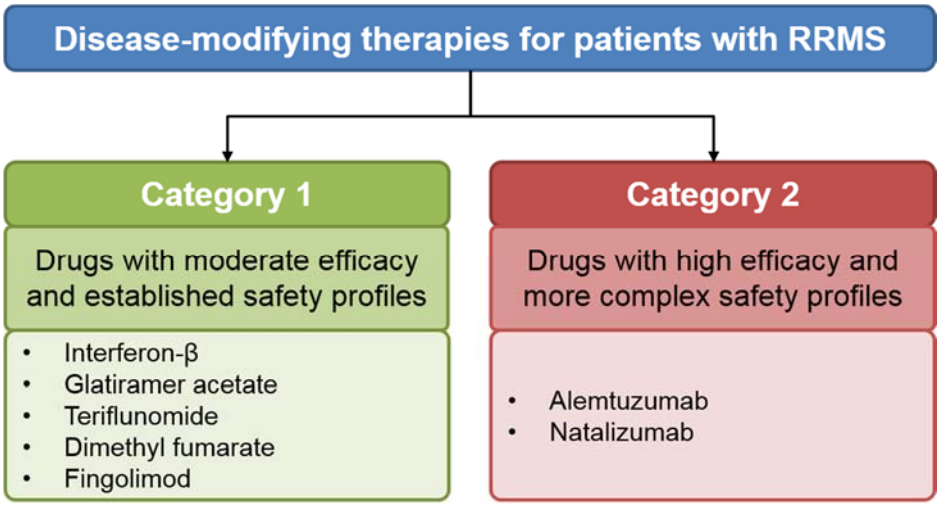
Of course, there are implications for the healthcare service too. MS specialist nurses are key health professionals managing the provision and monitoring of DMTs. They are under mounting pressure to deliver complex monitoring regimes for the DMTs. Recent documentation published by the MS Trust highlighted these concerns, which were supported by expert nurse feedback received by Merck. This commentary in the public domain (MS Trust 2016b; MS Trust 2016a; IOMSN 2004) highlights that there is a substantive need for treatments with reduced administration and monitoring burden than the currently available DMTs provide. In response to this advice, Merck has initiated a time and motion study in the MS area to quantify the burden that is presently faced by the National Health Service (NHS). Unfortunately, even though this is currently underway, results are not yet available. Merck would like to provide these data to the Committee as soon as they become available.

As described in detail in Section A.16, Cladribine Tablets is an efficacious DMT with a unique posology that can provide multiple benefits for patients, clinicians and healthcare providers.

A.2. Clinical pathway of care

Diagnosis and management of MS in adults is covered by NICE's CG186, although it does not directly address DMTs. There are a wide range of DMTs currently available in the UK providing patients and prescribing neurologists with alternative treatment options for RRMS. The Association of British Neurologists (ABN) have issued guidance on the prescribing of DMTs for MS and they classify the treatments into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles) (Scolding 2015) (Figure 1).

Figure 1: Categorisation of DMTs according to the ABN guidelines (2015)



SOURCE: Adapted from (Scolding 2015)

ABN: Association of British Neurologists; DMT: Disease-modifying treatment; RRMS: Relapsing-remitting multiple sclerosis

It is not currently known into which category Cladribine Tablets may fit or whether a separate category may be required.

A network meta-analysis (NMA) and a meta-regression analysis, undertaken by Merck for this submission, confirm Cladribine Tablet's comparable efficacy versus other high efficacy drugs for patients with HDA-RRMS on all outcomes of relevance to this decision problem. The safety and tolerability profile is characterised on the basis of 8 years of follow-up of treated patients, more than 3,000 patient years of exposure to Cladribine Tablets 3.5 mg/kg, and more than 8,000 patients years exposed to any dose of Cladribine Tablets, an extensive safety database in comparison to other high efficacy treatments on the market. In a Multi-Criteria Decision Analysis (MCDA), conducted by Merck in 2015 following advice from the EMA, leading MS physicians in Europe evaluated favourable (e.g. clinical efficacy, ease-of-use and durability) and unfavourable (e.g. AE & SAEs) attributes based on pivotal trial results has a favourable benefit:risk profile compared to fingolimod, natalizumab and alemtuzumab in patients with high disease activity.

A.3. Equality considerations

No equality issues have been identified for Cladribine Tablets.

A.4. The technology

Table 1: Technology being appraised – B.1.2 (page 17)

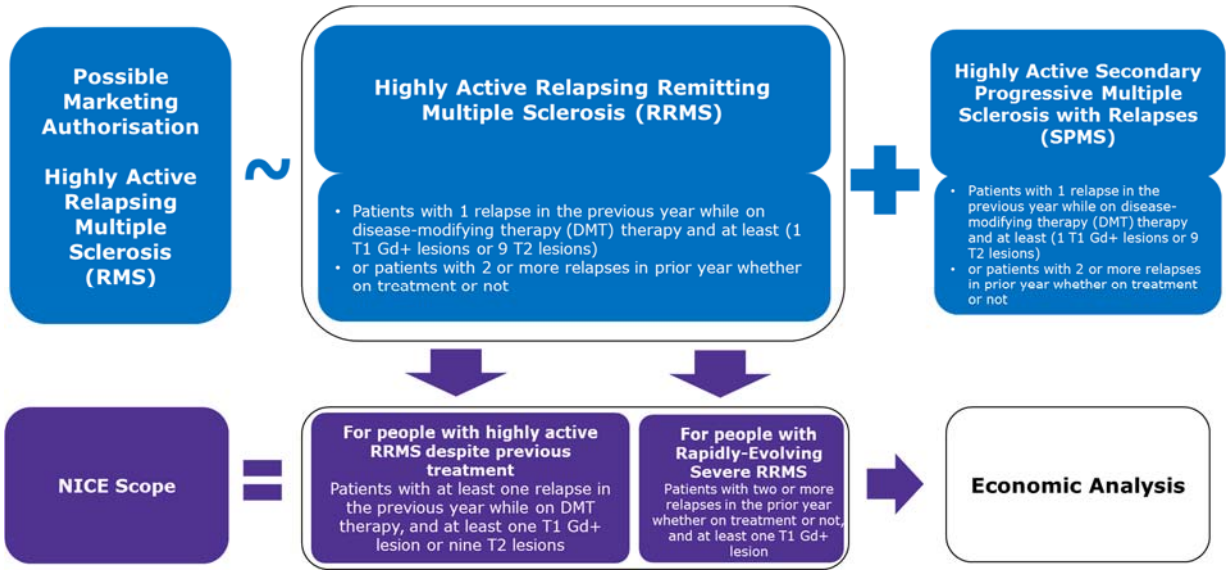
UK approved name and brand name	"Cladribine Tablets" (MAVENCLAD)
Mechanism of action	Cladribine is a deaminase-resistant nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells. The mechanism by which Cladribine Tablets exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS (Leist 2011). A distinguishing feature of Cladribine Tablets is discontinuous immunosuppression. Periods of lymphocyte depletion around treatment are followed by repopulation resulting in durable efficacy well beyond the period of treatment.
Marketing authorisation/CE mark status	Cladribine Tablets currently does not have marketing authorisation in the UK. An application for marketing authorisation was submitted to the European Medicines Agency in June 2016, and approval is expected in September 2017.
Indications and any restriction(s) as described in the summary of product characteristics	At present, Merck anticipates Cladribine Tablets to be indicated for the treatment of adult patients with either highly active *relapsing* MS (RMS) or the narrower indication highly active *relapsing-remitting* MS (RRMS), as defined by clinical or imaging features (see section 5.1 of the SmPC). This technology appraisal submission is based on the RRMS indication.
Method of administration and dosage	Cladribine Tablets is administered orally. The recommended cumulative dose of Cladribine Tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. No further treatment is required in years 3 and 4.
Additional tests or investigations	The introduction of Cladribine Tablets would not require additional tests, investigations or administration beyond those that are currently required for all patients with MS. In Section A.17, Merck presents the anticipated budget impact of Cladribine Tablets; as can be seen, treatment is anticipated to be cost-saving for the NHS because of the lower acquisition cost over 4 years and the considerable reduction in administration and monitoring burden for the healthcare service.
List price and average cost of a course of treatment	Confirmed list price (Department of Health 2017): • Cladribine Tablets 10mg x 1 tablet £2,047.24 • Cladribine Tablets 10mg x 4 tablets £8,188.97 • Cladribine Tablets 10mg x 6 tablets £12,283.46 Annual cost: approximately £13,000 per annum when the complete treatment cost of £52,000 is spread over a 4 year period
Patient access scheme (if applicable)	A Patient Access Scheme has not been included in the submission at this time

A.5. Decision problem and NICE reference case

At present, Merck anticipates Cladribine Tablets to be indicated for the treatment of adult patients with *either* highly active relapsing MS (RMS) - a highly active disease population including patients with RRMS and patients with *relapsing* forms of SPMS - or the narrower indication, highly active *relapsing-remitting* MS (RRMS), as defined by clinical or imaging features (see section 5.1 of the SmPC). This submission assumes a licence in the latter highly active RRMS (HDA-RRMS) population.

The NICE decision problem segments the HDA-RRMS population into patients with rapidly evolving severe (RES) RRMS and patients with highly active RRMS despite previous treatment (SOT). Therefore, Merck have undertaken further post hoc subgroup analyses to match NICE's scoping definitions. Figure 2 provides the definition of the patient populations relevant to the NICE decision problem and the patients from whom the evidence base relevant to this submission is derived. People with RRMS but without high disease activity are not within the marketing authorisation for Cladribine Tablets and therefore have not been included in this submission.

Figure 2: Relationship between the proposed marketing authorisation for Cladribine Tablets and the NICE scope subgroups



In Table 2, the final NICE scope is presented alongside the decision problem as addressed in this submission.

Table 2: The decision problem – B.1.1

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with RRMS	Adults patients with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for Cladribine Tablets	Active RRMS (as opposed to highly active RRMS) is not a part of the anticipated marketing authorisation for Cladribine Tablets.
Intervention	Cladribine Tablets	Cladribine Tablets	N/A
Comparator(s)	For people who have not had previous treatment: • alemtuzumab • beta-interferon • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment: • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • teriflunomide For people with rapidly-evolving severe RRMS: • alemtuzumab	For people with rapidly-evolving severe RRMS: • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment: • alemtuzumab • daclizumab • fingolimod	To align with the recent recommendation for daclizumab, the RES-RRMS and SOT-RRMS populations have been segmented into RES-RRMSa, RES-RRMSb, SOT-RRMSa and SOT-RRMSb. The comparators for Cladribine Tablets in this submission are therefore as follows: For people with rapidly-evolving severe RRMS and able to receive to alemtuzumab (RES-RRMSa): • natalizumab • alemtuzumab RES-RRMS and either contraindicated or otherwise unable to receive alemtuzumab (RES-RRMSb): • natalizumab • daclizumab For people with highly active RRMS despite previous

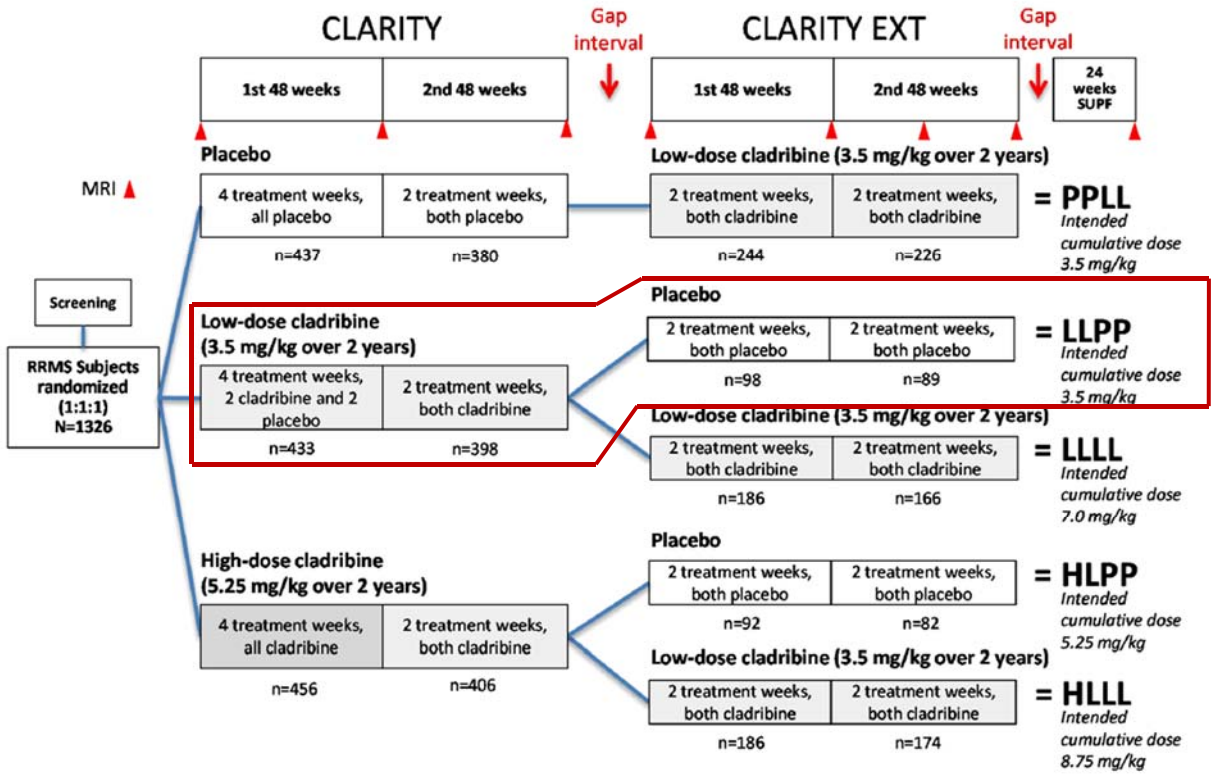
	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• daclizumab (subject to ongoing NICE appraisal) • natalizumab For people with highly active RRMS despite previous treatment: • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • fingolimod		treatment and able to receive to alemtuzumab (SOT-RRMSa) • fingolimod • alemtuzumab For people with highly active RRMS despite previous treatment and either contraindicated or otherwise unable to receive alemtuzumab (SOT-RRMSb) • fingolimod • daclizumab
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom from disease activity • mortality • adverse effects of treatment • HRQoL	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • MRI lesions • adverse effects of treatment • HRQoL	The outcome measures to be assessed as part of the decision problem are considered to be the most relevant for the target patient population. MRI lesions have been included as part of the decision problem given that MRI imaging techniques are commonly used to complement the diagnosis and prognosis of RRMS
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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 will 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.	As per reference case	N/A
Subgroups to be considered	The following subgroups of patients will be considered: • patients with RRMS whose disease has inadequately responded to treatment with disease modifying therapy • patients with RRMS whose disease is intolerant to treatment with disease modifying therapy • patients with highly active	All subgroup included in the NICE scope and included in the anticipated marketing authorisation for Cladribine Tablets have been included in the decision problem for Cladribine Tablets.	

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	RRMS • patients with rapidly evolving severe RRMS		
Perspective for outcomes	All health effects were modelled from a patient perspective	In-line with scope	
Perspective for costs	NHS and PSS perspective for costs were incorporated into the model	In-line with scope	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	50 years	This is in line with previous NICE appraisals
Synthesis of evidence on health effects	Based on systematic review	Health effects were based on a number of sources, including a systematic review and the CLARITY trial.	
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The health effects of treatment were modelled in terms of QALY and derived from EQ-5D questionnaires collected in CLARITY	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D questionnaires were completed by patients during the CLARITY trial	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Completed EQ-5D questionnaires in the CLARITY trial were mapped to health state utility (HSU) index values using the UK social tariff.	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There are no equity considerations	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Relevant cost and health resource use data were identified from various sources including previous NICE appraisals, a systematic review of published costing studies, the British National formulary, NHS reference costs, and PSS research unit reports, and from the summary of product characteristics for in-scope comparators.	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Both costs and health outcomes were discounted at a rate of 3.5% per annum.	

A.6. Clinical effectiveness evidence

Cladribine Tablets has been investigated in four main Phase II/III studies; CLARITY (Phase III), CLARITY EXT (Phase IIIb), ORACLE (Phase III), and ONWARD (Phase II). Additional safety data are being collected in an ongoing observational registry (PREMIERE), which captures 8 years of follow-up data on patients who participated in any of the Cladribine Tablets clinical trials. ORACLE and ONWARD utilised Cladribine Tablets for a different treatment population to that submitted for marketing authorisation, and therefore, their efficacy results have not considered here. CLARITY and CLARITY EXT are the pivotal trials for Cladribine Tablets which provide the evidence base for the efficacy, safety and tolerability of 3.5 mg/kg Cladribine Tablets in active and highly active RRMS over a 4-year period (Figure 3). Further, these studies provide the evidence for the posology of 3.5 mg/kg Cladribine Tablets, with 2 treatment weeks in year 1 and then again in year 2, and no further Cladribine Tablets treatment in years 3 and 4.

Figure 3: Summary of CLARITY and CLARITY EXT trial designs



SOURCE: (Merck 2017b)

NOTE: Red box indicates the licensed dose

H: High-dose Cladribine Tablets over 48 weeks; L: Low-dose Cladribine Tablets over 48 weeks; P; Placebo; SUPF: Supplemental follow-up

The pivotal CLARITY trial has been included in the comparative efficacy analyses and the economic model. The results of CLARITY EXT support the posology of Cladribine Tablets (2 years of treatment with no further Cladribine Tablets treatment required in years 3 and 4) and provide validation of the waning assumptions used in the economic model. The results from CLARITY EXT also form the basis of a simulated placebo extension analysis performed by Helen Bell-Gorrod and Nick Latimer (ScHARR) to support the waning assumptions. An overview of CLARITY and CLARITY EXT is provided in Table 3.

As mentioned above, a third study, ONWARD, is a trial that evaluated the efficacy and safety of Cladribine Tablets 3.5 mg/kg in combination with IFN-β; this regimen differs from the anticipated marketing authorisation and decision problem and as such, efficacy results from ONWARD are not included in this submission.

The additional study for Cladribine Tablets, ORACLE MS and PREMIERE registry, were identified in the systematic literature review. ORACLE is primarily focused on clinically isolated syndrome (CIS) population and PREMIER is a long-term safety dataset. As such, the safety outcomes from ORACLE MS and PREMIERE in addition to CLARITY and CLARITY EXT provide valuable data and have been incorporated into an integrated safety analysis.

Table 3: Clinical effectiveness evidence

Study title	CLARITY (NCT00213135)	CLARITY-EXT (NCT00641537)
Study design	Phase III double-blind, placebo-controlled, 96-week RCT	Phase IIIb double-blind, 96-week RCT; safety extension trial
Population	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study • Clinically stable and not had a relapse within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks
Intervention(s)	• Cladribine Tablets 3.5 mg/kg cumulative over 96 weeks (LL)* • Cladribine Tablets 5.25 mg/kg cumulative over 96 weeks (HL)	• Patients were randomised upon entry to receive either further doses of 3.5 mg/kg Cladribine Tablets or placebo, resulting in five reporting groups: • LLPP - cumulative 3.5 mg/kg* • LLLL- cumulative 7.0 mg/kg • PPLL - cumulative 3.5 mg/kg • HLLL - cumulative 8.75 mg/kg • HLPP - cumulative 5.25 mg/kg
Comparator(s)	Placebo	N/A
Outcomes specified in the decision problem	• Relapse rate • Severity of relapse • Disability • MRI lesions • Adverse effects of treatment • HRQoL	• Relapse rate • Disability (for example EDSS) • MRI lesions • Adverse effects of treatment
Reference to section in submission	B.2.6.1 (page 40)	B2.6.2 (page 45)

* Licensed dose for Cladribine Tablets

A.7. Key results of the clinical effectiveness evidence

The intention-to-treat (ITT) active RRMS patient population can be categorised into subgroups as determined by the patient experience with DMTs and by clinical and imaging features, the definitions of which are summarised in Table 4. Following the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice in December 2014, data from CLARITY were further analysed post-hoc to determine the benefits and risks of Cladribine Tablets in patient subgroups with HDA-RRMS (European Medicines Agency 2017). Cladribine Tablets are anticipated to be indicated for treatment of HDA-RRMS. The results of the post-hoc subgroups analyses, which are most relevant to this indication, are presented in this submission. For results of the ITT analyses, please see B.2.6.1 and B.2.6.2.

Table 4: Definitions of RRMS subgroups (CLARITY)

Subgroup	Subgroup definition	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS*	• Patients with one relapse in the previous year while on treatment and ≥1 T1 Gd+ lesion or ≥9 T2 lesions OR • Patients with ≥2 relapses in the prior year whether on treatment or not	N=140	N=149
RES-RRMS	• Patients with ≥2 relapses in the prior year whether on treatment or not AND • Patients with ≥1 T1Gd+ lesion	N=50	N=41
SOT-RRMS	• Patients with ≥1 relapse in the previous year while on treatment AND • Patients with ≥1 T1 Gd+ lesion or ≥9 T2 lesions	N=19	N=32

* The HDA-RRMS subgroup is the licensed indication according to the marketing approval application to the EMA

Gd+: Gadolinium-enhancing; HDA: High disease activity; RES: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT: Sub-optimal therapy

A.7.1 CLARITY – HDA-RRMS, RES-RRMS, and SOT-RRMS subgroups

A.7.1.1. Qualifying ARR and first qualifying relapse

The primary outcome of the CLARITY trial was qualifying annualised relapse rate (ARR). Patients treated with 3.5 mg/kg Cladribine Tablets across all treatment groups (HDA-RRMS, RES-RRMS and SOT-RRMS) demonstrated a reduction in qualifying ARR compared with placebo, consistent with the results for the ITT population. These reductions were shown to be statistically significant in patients with HDA-RRMS and RES-RRMS [redacted] (Merck 2017a).

Patients within the HDA-RRMS and RES-RRMS subgroups were at a significantly lower risk of experiencing a first qualifying relapse in the 3.5 mg/kg Cladribine Tablets groups compared with placebo (HDA-RRMS [HR: 0.40; p<0.0001], RES-RRMS [HR: [redacted] (Merck 2017a).

In addition to the ARR reduction and similar to the ITT analysis, patients treated with 3.5 mg/kg Cladribine Tablets in the HDA-RRMS subgroup analysis had a higher proportion of patients qualifying as relapse-free at 96 weeks compared with placebo (72.1% vs. 46.3%). This was also observed for the RES-RRMS [redacted] and SOT-RRMS treatment groups [redacted] (Merck 2017a).

A.7.1.2. 3-month confirmed disability progression

Results for 3-month confirmed disability progression in the HDA-RRMS subgroup were consistent with the results observed in the ITT population. Treatment with 3.5 mg/kg Cladribine Tablets in the HDA-RRMS subgroup was associated with a significant reduction in risk of 3-month confirmed disability progression of 72% compared with placebo (p=0.0001). However, a statistical difference was not

observed between 3.5 mg/kg Cladribine Tablets and placebo in the RES-RRMS or SOT-RRMS subgroups (Merck 2017a).

In the HDA-RRMS subgroup, 82% of patients who received 3.5 mg/kg Cladribine Tablets were reported to be 3-month CDP-free compared with 59.7% in the placebo treatment arm. In addition, [redacted] percentage of patients in the SOT-RRMS subgroup treated with 3.5 mg/kg Cladribine Tablets were 3-month CDP-free compared with those treated with placebo [redacted] However, there was [redacted] in the proportion of 3-month CDP-free patients in the RES-RRMS subgroup between the 3.5 mg/kg Cladribine Tablets and placebo treatment arms [redacted] (Merck 2017a).

A.7.1.3. 6-month confirmed disability progression

Results for the HDA-RRMS subgroup time to 6-month confirmed disability progression were similar to the ITT analysis. The risk of experiencing 6-month confirmed disability progression in the 3.5 mg/kg Cladribine Tablets group was significantly lower compared with placebo (HR: 0.18; p=0.0001). However, [redacted] between 3.5 mg/kg Cladribine Tablets and placebo in the RES-RRMS or SOT-RRMS subgroups (Merck 2017a).

For all subgroups analysed, the proportion of 6-month CDP-free patients was higher following treatment with 3.5 mg/kg Cladribine Tablets compared with placebo (Merck 2017a).

A.7.1.4. Endpoints associated with MRI lesions

Results for the HDA-RRMS subgroup in MRI lesion activity were similar to the ITT population. HDA-RRMS patients treated with 3.5 mg/kg Cladribine Tablets demonstrated a significant relative reduction in active T1 Gd+ lesions (90.5%), active T2 lesions (77.0%), CU lesions (79.7%) and T1 hypointense lesions (81.4%) compared with placebo (p<0.0001 for all) (Merck 2017a). Statistically significant reductions in active T1 Gd+ lesions, active T2 lesions, CU lesions and T1 hypointense lesions were also observed in the RES-RRMS and SOT-RRMS subgroups.

A.7.1.5. No Evidence of Disease Activity (NEDA-3)

The proportion of patients with NEDA-3 status was consistently higher following treatment with 3.5 mg/kg Cladribine Tablets compared with placebo in the HDA-RRMS, RES-RRMS, and SOT-RRMS subgroups. Furthermore, patients treated with 3.5 mg/kg Cladribine Tablets were significantly more likely to have no evidence of disease activity at 96 weeks compared with placebo in the HDA-RRMS (44% v 7%; p<0.0001), RES-[redacted]) and SOT-RRMS [redacted]) subgroups (Merck 2017a).

The full details of the CLARITY trial and CLARITY EXT are presented in Section B. Data from CLARITY EXT has been used primarily in safety analyses and to support assumptions of durable efficacy for the marketing authorisation for the economic modelling.

A.7.2 Safety analysis

The safety profile of Cladribine Tablets has not only been demonstrated through CLARITY and CLARITY EXT, but with t additional studies in Merck's clinical development programme (ORACLE and PREMIERE). Considerable data are available from the integrated safety analysis from CLARITY, CLARITY-EXT, ORACLE, and PREMIERE. Total treatment exposure in this analysis of 923 patients who had received 3.5mg/kg Cladribine Tablets is 3432 patient years, over a mean time of 194 weeks (compared with 2025 patient years for placebo). The number of AEs per 100 patient-years (PYs) based on the integrated safety analysis was marginally higher in the cohort exposed to Cladribine Tablets 3.5 mg/kg compared with the placebo cohort (103.29 and 94.26, respectively). Similarly, the number of severe and serious treatment-emergent adverse events (TEAEs) per 100 patient-years was similar between Cladribine Tablets (3.7 and 3, respectively) and placebo (4.0 and 3.6, respectively). Treatment discontinuations per 100 patient-years were generally low in both Cladribine Tablets and placebo cohorts (2.07 and 1.05, respectively) indicating that Cladribine Tablets is well tolerated.

Lymphopenia is expected with Cladribine Tablets treatment and is linked to its mode of action. During CLARITY, patients who experienced lymphopenia were able to recover and no serious opportunistic infections were reported in patients treated with Cladribine Tablets. The incidence of Grade 3 and 4

lymphopenia with treatment is low, and the integrated safety analysis indicated that by following a risk mitigation plan (applying strict haematological criteria in treatment years), Grade 3 lymphopenia in patients at the end of year 1 and 2 was reduced. In parallel, a reduction in herpes zoster infection, which was observed to be higher in patients with Grade 3 lymphopenia, is expected. Recommendations for screening for latent infections prior to initiation of therapy, and the second treatment course are advised given the slightly higher risk (herpes zoster per 100 PY: 0.83 v 0.20).

Based on the integrated safety analysis, while there are numerical differences in the number of reported malignancies between Cladribine Tablets and comparator groups, the safety data do not provide conclusive evidence that the malignancy risk is increased with Cladribine Tablets. Importantly, an independent meta-analysis of 11 trials (including CLARITY) of licensed DMTs concluded that there was no significant difference in the rate of cancer in actively treated patients in the CLARITY trial compared with trials of other DMTs (dimethyl fumarate, fingolimod, teriflunomide, natalizumab, alemtuzumab, and glatiramer acetate) (Pakpoor 2015).

Safety data are discussed in detail in Section B.2.10.

A.8. Evidence synthesis

A.8.1 Meta-analysis

A meta-analysis was not possible as only one study included Cladribine Tablets at the licensed dose (3.5 mg/kg as monotherapy) in the target patient population (HDA-RRMS).

A.8.2 Comparative effectiveness

In line with NICE recommended methodology a full clinical systematic review was undertaken to identify studies relevant to the decision problem. A conventional NMA was undertaken to establish the comparative efficacy and safety of Cladribine Tablets versus its relevant comparator treatments in all populations; the ITT, overall HDA-RRMS subgroup and constituent RES-RRMS and SOT-RRMS subgroups. The NMA is presented in full in Appendix D and summarised in Section B.2.9.1. It demonstrates that Cladribine Tablets is comparable to other DMTs evaluated in the HDA-RRMS population. However, in the sub-populations of patients who are relevant to this decision problem – RES-RRMS and SOT-RRMS – additional analyses were required to fully inform the inputs for the cost-effectiveness analysis (see Table 5). This was specifically the case for comparisons with alemtuzumab where, as noted in previous NICE appraisals (TA441), it is challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network.

Table 5: Summary of the comparators and availability of data for network meta-analysis in the HDA-RRMS, RES-RRMS and SOT-RRMS populations

Population	Term	Comparators in scope	Comparisons possible on the CDP6M endpoint	Comparisons possible on the CDP3M endpoint	Comparisons possible on the ARR endpoint
High disease activity	HDA NMA	Not specified in scope	Alemtuzumab† IFN-β-1a 44 µg	Dimethyl fumarate, fingolimod, GA	Alemtuzumab dimethyl fumarate, fingolimod, GA, IFN-β-1a 30 µg, natalizumab, teriflunomide 7 mg/14 mg
Rapidly evolving severe	RES NMA	Natalizumab Alemtuzumab Daclizumab*	Alemtuzumab† IFN-β-1a 44 µg Natalizumab	Natalizumab fingolimod, teriflunomide 7 mg/14 mg	Alemtuzumab, daclizumab fingolimod, GA, IFN-β-1a 30 µg, IFN-β-1a 44 µg Natalizumab, teriflunomide 7 mg/14 mg
Highly active RRMS despite treatment	SOT NMA	Fingolimod Alemtuzumab Daclizumab*	Not feasible as hazard ratio for Cladribine Tablets versus placebo is 0.00		IFN-β-1a 30 µg, Fingolimod

* Daclizumab is recommended in those unable to receive alemtuzumab; †comparisons to alemtuzumab made possible through the inclusion of unpublished data from PRISMS

ARR: Annualised relapse rate; CDP: Confirmed disability progression; GA: Glatiramer acetate; HDA: High disease activity; IFN: Interferon; NMA: Network meta-analysis; RES: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT: Sub-optimal therapy

In spite of post-hoc analyses performed on the Phase III PRISMS study (IFN-β1a 44 µg versus placebo) to address the gap in evidence linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network in the RES-RRMS group, analyses were still not possible in SOT-RRMS. This is because the majority of RRMS patients eligible for PRISMS were naïve to DMTs at the time the study was conducted.

The lack of publicly available efficacy data for daclizumab in RES-RRMS and SOT-RRMS also meant it was not possible to conduct a full range of comparisons with the conventional NMA. The comparisons that could be done were exclusively based on post-hoc analyses, the robustness of which is unclear in the absence of specific baseline characteristic data for the subgroups from comparator studies.

Given the importance of the comparison with alemtuzumab in the UK, Merck undertook a meta-regression analysis for key efficacy outcomes with adjustment for baseline risk (centred on the baseline risk for RES-RRMS/SOT-RRMS) on trials in the active RRMS population. We also discuss the results of the ITT NMA which provides evidence on the comparative efficacy of Cladribine Tablets versus all in-scope comparators.

The meta-regression analysis, conducted following advice from an independent NMA expert, aimed to extrapolate the effect size estimates from the active RRMS population to the RES-RRMS and SOT-RRMS subgroups, by relating efficacy to baseline risk, and centring baseline risk to the expected value in each group. This analysis allows the prediction of the effect size for Cladribine Tablets versus all in-scope comparators. Merck considers this to be a strength of the approach to this decision problem.

The results of the meta-regression analysis shows significant overlap in the credible intervals for the hazard ratios of confirmed disability progression at 6 months, with no therapy statistically dominating in terms of efficacy. At the point estimate level, Cladribine Tablets was predicted to be more efficacious than fingolimod (log hazard ratio relative to placebo of [redacted] for Cladribine Tablets versus [redacted] for fingolimod) and alemtuzumab [redacted] but marginally less efficacious than natalizumab [redacted]) and daclizumab [redacted]) for the RES-RRMS population. The corresponding normalised hazard ratios were [redacted] for treatment effect of Cladribine Tablets, [redacted] for alemtuzumab[redacted] for daclizumab, in the RES-RRMS and [redacted] for natalizumab versus placebo.

The log-hazard ratios were un-centred and transformed to produce an estimate of DMT effect in the SOT-RRMS subgroup. The corresponding normalised hazard ratios in this population were [redacted] for Cladribine Tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, and [redacted] for fingolimod versus placebo. Overall, the meta-regression predicted that DMTs would be less effective in the SOT-RRMS population than in RES-RRMS.

Overall, the results of the meta-regression suggest that Cladribine Tablets are of equivalent efficacy to these therapies on the endpoint of confirmed disability progression at 6 months.

When tolerability and safety were considered the NMA results indicated that Cladribine Tablets did not differ significantly from placebo for all-cause treatment discontinuations, discontinuations because of AEs, the incidence of AEs or grade 3 or 4 AEs. Cladribine Tablets were not significantly worse than any comparator DMT for any of these outcomes.

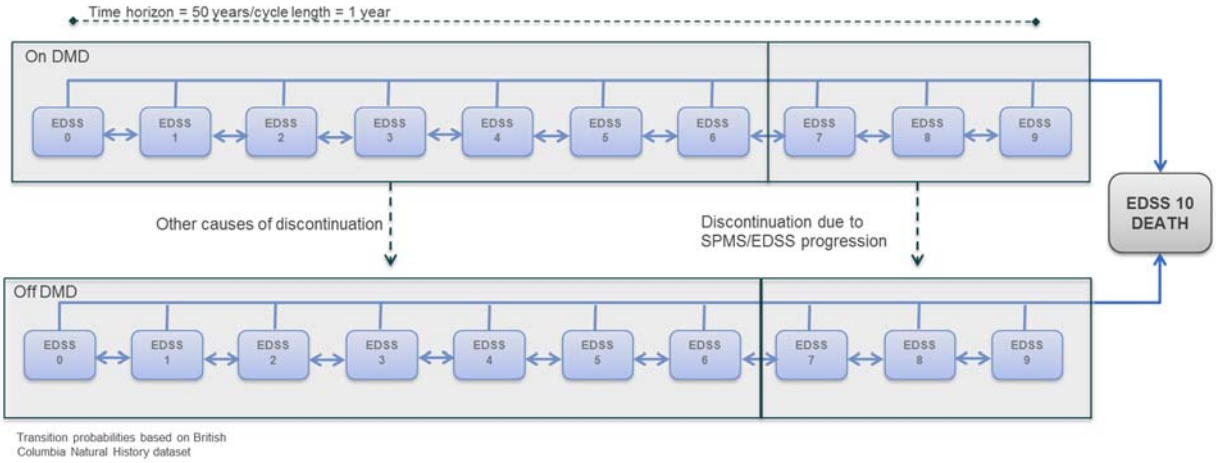
A.9. Key clinical issues

- Across the 4 years of study treatment, there was no continuous placebo arm. To address this, Merck conducted a treatment switching analysis in collaboration with ScHARR, the results of which are presented in section B.2.9.1.
- Due to the delay in the initiation of CLARITY EXT, some patients who completed CLARITY were not immediately enrolled into CLARITY EXT, resulting in a gap period of varying lengths of time to entry into CLARITY EXT for each patient. However, there was no consistent or meaningful relationship between the duration of the gap period and the majority of efficacy endpoints, suggesting that selection bias is not a concern.
- It was particularly challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network. To address this, Merck conducted a meta-regression analysis, utilising unpublished data from the PRISMS trial, to extrapolate the effect size estimates from the active RRMS population to the RES-RRMS and SOT-RRMS groups, by relating efficacy to baseline risk, and centring baseline risk to the expected value in each group

A.10. Overview of the economic analysis

A cohort-based multi-state Markov state transition model was developed to simulate the costs and effectiveness of treatment in people with RRMS. An annual cycle length was adopted with outcomes evaluated over a time horizon of 50-years. The model for Cladribine Tablets uses a simplified version of the model structures used in previous NICE submissions, summarised in the Figure below. In all other respects, the model was developed consistent with precedent in previous NICE appraisals in RRMS, following a substantial and in-depth analysis of previous NICE submissions (see Section B.3.1.). The economic analysis presented in this submission focuses on the use of Cladribine Tablets in people with RES-RRMS and SOT-RRMS. Results demonstrate that Cladribine Tablets is a cost-effective treatment alternative for patients with HDA-RRMS. It is dominant (i.e. cost-saving and more effective) versus alemtuzumab, daclizumab and natalizumab in RES, and dominant versus alemtuzumab, fingolimod and daclizumab in SOT. Considerable cost-savings for the NHS are predicted. The analyses were subject to a range of deterministic and probabilistic sensitivity analyses and PSA results are broadly consistent with those of the deterministic analysis, confirming they are robust and providing confidence in the base-case results.

Figure 4: Model diagram – B.3.2.2 (page 93)



A.11. Incorporating clinical evidence into the model

The structure of the 11-health state model is based on the natural history transition matrix reported by Palace et al and used in the UK risk sharing scheme and recent NICE MTA (GID-TAG529). The model also captures the independent effects of relapses on the costs and health related quality of life of people with MS.

The treatment-adjusted model combines the reference model with the comparative efficacy and safety of DMT versus placebo. As with the natural history model, the treated cohort was at risk of progressing, improving, or staying in the same EDSS state, or entering the death state.

Treatment with a DMT was assumed to alter the natural course of disease by:

- Decreasing the probability of progressing in EDSS state over time, versus current care
- Decreasing the annualised rate of relapse versus BSC
- Altering the incidence of drug-related adverse events

There was no assumed effect of DMT on the probability of improving in EDSS and the probability of death, which were fixed to the values used in the natural history model. The probability of remaining in the same EDSS state was increased to reflect that fewer patients progressed on DMT. This follows approaches accepted in all previous appraisals in RRMS.

The efficacy and safety inputs to the model were derived from meta-analyses of clinical data identified from the systematic literature review and clinical study reports for Cladribine Tablets.

As in previous appraisals, patients were assumed to benefit from treatment while “on DMT”. These effects were assumed to gradually wane over time. In each model cycle, patients “on DMT” were at risk of discontinuing treatment for reasons such as loss of efficacy and tolerability.

Patients who discontinued treatment were assumed to retain the cumulative benefits of DMT up to the point of discontinuation. Upon discontinuation, patients immediately switched to BSC, with progression and relapse rates based on the natural history model. No further treatment was given in line with models accepted in previous NICE appraisals.

Due to their posology, for both alemtuzumab and Cladribine Tablets, the usual concept of treatment “discontinuation” does not apply as most patients are expected to receive two short courses of treatment and to then undergo observation for disease progression. The probability of discontinuation for Cladribine Tablets and alemtuzumab was therefore applied to the first cycle only to capture discontinuations between the first and second courses. Patients who completed the two courses were assumed to remain “on DMT” without actively receiving drug, and hence were no longer considered at risk of discontinuation. The efficacy of Cladribine Tablets and alemtuzumab was assumed to wane over time in recognition that the full effect may not persist for a lifetime.

A.12. Key model assumptions and inputs

A summary of the key assumptions in the base case model is outlined in Table 6.

Table 6: Summary of basic structural assumptions

Aspect	Assumption	Justification
Health states	EDSS captures the main health problems associated with MS	Numerous studies have shown a strong correlation between EDSS and resource consumption and health related quality of life. EDSS is the preferred tool for measuring disability in people with MS as recommended by the European Medicines Agency
Lifetable/half-cycle correction	EDSS and drug-related costs and QALY are modelled based on midpoint estimates assuming patients, on average, transition mid-way through the model cycle. Exceptions are the drug costs of Cladribine Tablets and alemtuzumab which are assumed to accrue at the start of the model cycle as therapy is given as a fixed course at the beginning of each treated year.	Standard approach to mitigate the risk of under or over-estimating costs and effects
Natural history of MS – disability progression	Disability progression is modelled assuming a constant transition probability matrix over time	Consistent with approaches taken in previous economic models Constant transition probability matrix shown to accurately predict EDSS status over 10-years
Natural history of MS – relapse	In the base case, relapses are modelled independently from EDSS state , and assumed to vary over time	Consistent with approaches taken in previous economic models This is to avoid double counting of DMT effect
Effectiveness of DMT - application	Sustained accumulation of disability and relapses are modelled independently, with independent treatment effects applied.	Consistent with approaches taken in previous economic models Some treatments may be more effective in reducing relapses than slowing disease progression
Discontinuation of DMT or cessation of DMT benefits	People with MS are assumed to discontinue therapy upon progression to EDSS 7.0 People treated with alemtuzumab or Cladribine Tablets are also assumed to stop benefiting from therapy once progression to EDSS 7.0 or greater. The health benefits of DMT that are accrued up to the point of discontinuation or cessation of therapy benefits is maintained with future progression rates modelled based on a natural history data set	This is consistent with approaches taken in past economic models Clinical trials in RRMS have typically focused on patients who have non-ambulatory RRMS including patients with EDSS <6.5 in study enrolment. No data are available on the effects of DMT in people with EDSS 7.0 or greater
Effectiveness of DMT – waning over time	The effectiveness of DMT is assumed to wane over time	This is consistent with approaches taken in past economic models Long-term treatment with natalizumab can lead to the development of neutralising antibodies that can reduce the effectiveness of these therapies The effectiveness of fixed course therapies such as alemtuzumab or Cladribine Tablets will wane over time due to recovery of the immune system and other factors implicated in the pathogenesis of MS

Aspect	Assumption	Justification
No distinction made between RR and SP forms of MS	Any difference in the transition rate between RR and SP forms of MS is accounted for in the averaged transition rates used in the model	This is consistent with approaches taken in past economic models Transition rates used in the base case analysis were sourced from Palace et al (Palace 2014), which includes data from an RRMS cohort who are followed through to SPMS.
Inclusion of adverse events	Relevant drug related adverse events include infusion and injection site reactions, PML, macular oedema, malignancy, severe infections, autoimmune-thyroid events, hypersensitivity and allergic reaction	Infusion and injectable site reactions are commonly reported adverse events across the clinical trial literature and have been incorporated in previous models Natalizumab, and fingolimod has been associated with an increased risk of PML Fingolimod has been associated with an increased risk of macular oedema and skin cancer Cladribine Tablets, fingolimod, natalizumab, teriflunomide and alemtuzumab have been associated with an increased risk of severe infection Alemtuzumab has been associated with an increased risk of autoimmune-thyroid related events including immune thrombocytopenic purpura Natalizumab has been associated with an increased risk of hypersensitivity and allergic reaction

A.13. Base-case ICER (deterministic)

In line with the expected marketing authorisation for Cladribine Tablets and the final scope, the base-case results of the economic analyses are presented for the following four groups:

- RES-RRMSa: RES-RRMS and able to receive to alemtuzumab
- RES-RRMSb: RES-RRMS but unable to receive to alemtuzumab
- SOT-RRMSa: SOT-RRMS and able to receive to alemtuzumab
- SOT-RRMSb: SOT-RRMS but unable to receive to alemtuzumab

Comparators are as specified in

In Table 2, the final NICE scope is presented alongside the decision problem as addressed in this submission.

Table 2, and all analyses are presented for a lifetime horizon of 50 years.

A.13.1 RES-RRMSa

The results of the deterministic base case analysis for the RES-RRMSa population are provided in Table 7.

Table 7: Base-case results for RES-RRMSa at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	480,441	22.176	8.098					
Alemtuzumab	499,575	22.176	7.916	-19,134	0.000	0.182	Cladribine dominant	Cladribine dominant
Natalizumab	611,117	22.176	7.586	-130,676	0.000	0.512	Cladribine dominant	Cladribine dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the RES-RRMSa population, Cladribine Tablets was dominant (e.g. less costly and more effective) versus alemtuzumab and natalizumab in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets was the least costly treatment in the RES-RRMSa population with a total discounted lifetime cost of £480,441. The next most expensive strategies were alemtuzumab (£499,575) followed by natalizumab (£611,117). Cladribine Tablets was cost-saving versus both alemtuzumab and natalizumab, with incremental costs of -£19,134 (alemtuzumab) and -£130,676 (natalizumab).

Cladribine Tablets was the most effective strategy in the population with a total discounted QALY of 8.098, and compared with total QALYs of 7.916 for alemtuzumab and 7.586 for natalizumab. The incremental QALYs comparing Cladribine Tablets versus alemtuzumab was +0.182, and versus natalizumab was +0.512.

A.13.2 RES-RRMSb

The results of the deterministic base case analysis for the RES-RRMSb population are provided in Table 8.

Table 8: Base-case results for RES-RRMSb at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	480,441	22.176	8.098					
Daclizumab – at list price	569,623	22.176	7.174	-89,182	0.000	0.924	Cladribine dominant	Cladribine dominant
Natalizumab	611,117	22.176	7.586	-130,676	0.000	0.512	Cladribine dominant	Cladribine dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the RES-RRMSb population, Cladribine Tablets was dominant (e.g. less costly and more effective) versus alemtuzumab and natalizumab in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets was the least costly treatment in the population with a total discounted cost of £480,441. The next most expensive strategies were daclizumab (£569,623) followed by natalizumab (£611,117). Cladribine Tablets was cost-saving versus both alemtuzumab and natalizumab, with incremental costs of -£89,182 (daclizumab) and -£130,676 (natalizumab).

Cladribine Tablets was the most effective strategy in the population with a total discounted QALY of 8.098, and compared with total QALYs of 7.174 for daclizumab and 7.586 for natalizumab. The

incremental QALYs comparing Cladribine Tablets versus daclizumab was +0.924, and versus natalizumab was +0.512.

A.13.3 SOT-RRMSa

The results of the deterministic base case analysis for the SOT-RRMSa population are provided in Table 9.

Table 9: Base-case results for SOT-RRMSa at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	467,361	21.318	7.570					
Alemtuzumab	484,910	21.318	7.417	-17,549	0.000	0.153	Cladribine dominant	Cladribine dominant
Fingolimod – list price	539,427	21.318	6.626	-72,066	0.000	0.944	Cladribine dominant	Cladribine dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the SOT-RRMSa population, Cladribine Tablets was dominant (e.g. less costly and more effective) versus alemtuzumab and fingolimod in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets was the least costly and most effective treatment in the population with a total discounted cost of £467,361, and a total discounted QALY of 7.570. The next most expensive strategy was alemtuzumab (£484,910) with a total discounted QALY of 7.417. Fingolimod was the most expensive (£539,427) and least effective strategy with a total QALY of 6.626.

A.13.4 SOT-RRMSb

The results of the deterministic base case analysis for the SOT-RRMSb population are provided in Table 10.

Table 10: Base-case results for SOT-RRMSb at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	467,361	21.318	7.570					
Daclizumab	533,758	21.318	7.022	-66,397	0.000	0.548	Cladribine dominant	Cladribine dominant
Fingolimod	539,427	21.318	6.626	-72,066	0.000	0.944	Cladribine dominant	Cladribine dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In the SOT-RRMSb population, Cladribine Tablets was dominant (e.g. less costly and more effective) versus daclizumab and fingolimod in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets was the least costly and most effective treatment in the population with a total discounted cost of £467,361, and a total discounted QALY of 7.570. The next most expensive strategy

was daclizumab (£533,758) with a total discounted QALY of 7.022. Fingolimod was the most expensive (£539,427) and least effective strategy with a total QALY of 6.626.

A.14. Probabilistic sensitivity analysis

Separate probabilistic analyses were conducted in the four groups of interest; RES-RRMSa, RES-RRMSb, SOT-RRMSa, and SOT-RRMSb. For each analysis, a run of 1000 Monte Carlo simulations was performed. This number of iterations was judged to be sufficient to achieve convergence in the expected cost and QALY for each intervention. PSA results were consistent with results of the deterministic analysis and are summarised in Table 11.

Table 11: Base-case results (probabilistic) – B.3.8 (page 142)

Treatment	Costs Mean	Lower 95% limit	Upper 95% limit	QALY Mean	Lower 95% limit	Upper 95% limit	Incremental cost (mean)	Incremental QALY (mean)	Probabilistic ICER	Probability cost effective at £20,000 (Multi-way)	Probability cost effective at £30,000 (Multi-way)
RES-RRMSa at list price											
Cladribine Tablets	475,162	322,885	700,515	8.154	5.407	11.002				64.5%	63.7%*
Alemtuzumab	495,655	340,710	730,918	7.952	5.103	10.962	-20,492	0.202	Cladribine dominant	35.5%	36.3%
Natalizumab	604,411	467,522	808,947	7.663	5.243	10.148	-129,249	0.491	Cladribine dominant	0.0%	0.0%
RES-RRMSb at list price											
Cladribine Tablets	471,594	318,242	699,831	8.249	5.350	11.024				97.5%	96.9%
Daclizumab	559,064	405,457	775,105	7.329	4.875	9.658	-87,470	0.920	Cladribine dominant	2.3%	2.6%
Natalizumab	600,923	463,227	795,561	7.751	5.360	10.105	-129,328	0.498	Cladribine dominant	0.2%	0.5%
SOT-RRMSa at list price											
Cladribine Tablets	472,273	302,102	706,643	7.555	4.360	10.586				61.6%	60.8%
Alemtuzumab	491,914	316,157	731,764	7.357	4.305	10.600	-19,641	0.198	Cladribine dominant	35.3%	35.7%
Fingolimod	538,566	375,052	758,147	6.682	4.236	9.358	-66,293	0.873	Cladribine dominant	3.1%	3.1%
SOT-RRMSb at list price											
Cladribine Tablets	472,012	309,822	704,745	7.572	4.570	10.394				86.5%	84.5%
daclizumab	534,318	383,222	738,342	7.082	4.557	9.528	-62,306	0.489	Cladribine dominant	10.1%	11.9%
Fingolimod	538,296	379,940	763,761	6.727	4.485	9.011	-66,283	0.845	Cladribine dominant	3.4%	3.6%

* The probabilities of being cost-effective by threshold become stable over time. As most of the samples fall in either the dominant, or dominated quadrants, the variation in the willingness to pay threshold has a minimal effect. The proportion of samples that are cost-effective (e.g. in the dominant quadrant) remain similar.

A.14.1 Deterministic sensitivity analysis

The results of the deterministic sensitivity analyses are summarised via a series of tornado diagrams. Each parameter in the analysis was varied between its lower and upper 95% confidence or credible interval, or by 50% of its mean value if statistical measures of variance were not available. The tornado diagrams for all subgroups show that the analysis is sensitive to variation in the effect of DMT on confirmed disability progression.

Most scenarios showed that treatment with Cladribine Tablets was either cost-effective at a threshold of £30,000 versus it comparator or with positive net health effects in favour of Cladribine Tablets.

A.14.1.1. RES-RRMSa

The results of the deterministic sensitivity analyses for RES-RRMSa are summarised in the following tornado diagrams for comparisons versus alemtuzumab (Figure 5), and natalizumab (Figure 6).

Figure 5: Tornado diagram for RES-RRMSa, Cladribine Tablets versus alemtuzumab

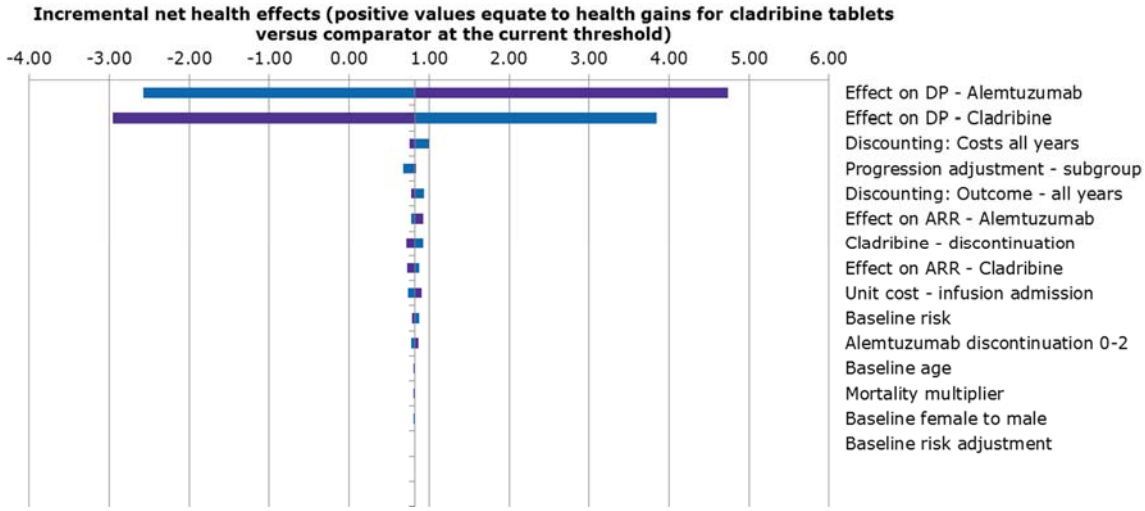
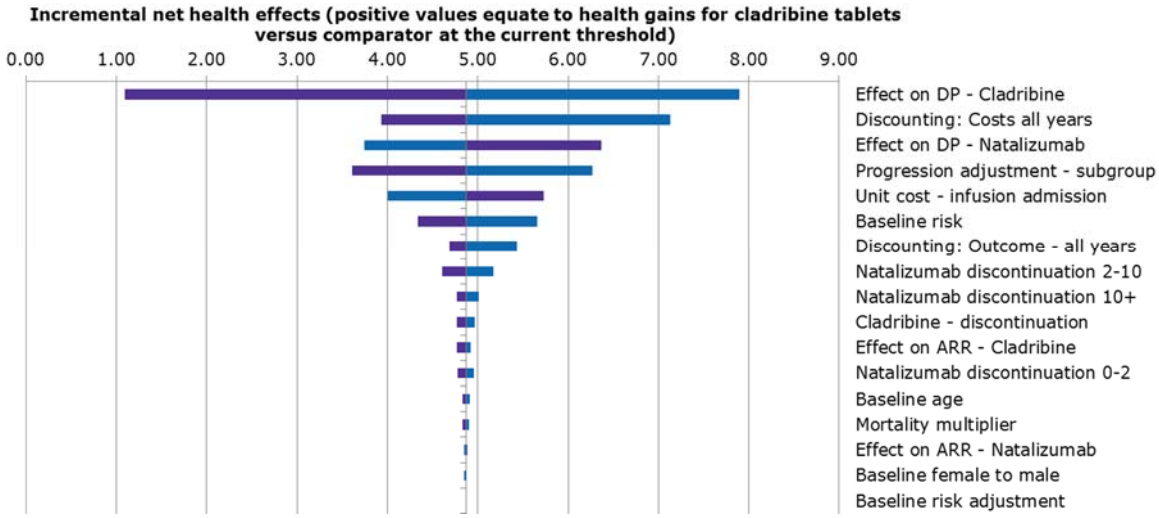


Figure 6: Tornado diagram for RES-RRMSa Cladribine Tablets versus natalizumab

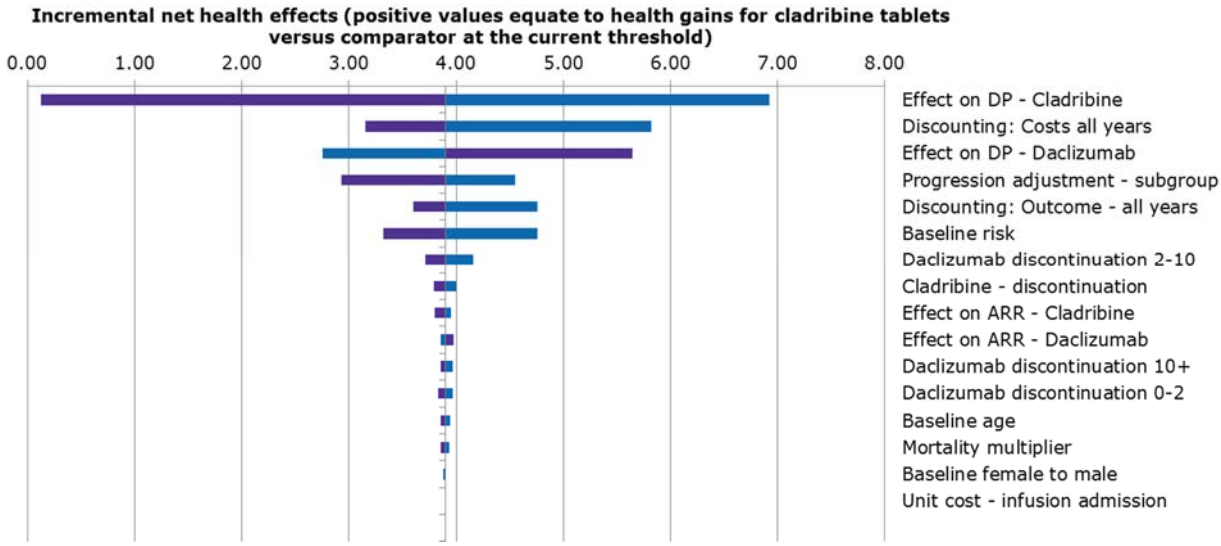


A.14.1.2. RES-RRMSb

The results of the deterministic sensitivity analyses for RES-RRMSb are summarised in Figure 7 for the comparison of Cladribine Tablets versus daclizumab, and in Figure 6 for the comparison to natalizumab.

The incremental net health effects of Cladribine Tablets versus daclizumab were positive in all scenarios. Cladribine Tablets was therefore judged to be cost-effective versus daclizumab at a threshold of £30,000 per QALY gained.

Figure 7: Tornado diagram for RES-RRMSb, Cladribine Tablets versus daclizumab



A.14.1.3. SOT-RRMSa

The results of the deterministic sensitivity analyses for SOT-RRMSa are summarised in the following tornado diagrams for comparisons versus alemtuzumab (Figure 8), and fingolimod (Figure 9). The tornado diagram for Cladribine Tablets versus fingolimod applies to both SOT-RRMSa and SOT-RRMSb as fingolimod is a comparator in both groups, and the same model inputs are used in both analyses.

Figure 8: Tornado diagram for SOT-RRMSa, Cladribine Tablets versus alemtuzumab

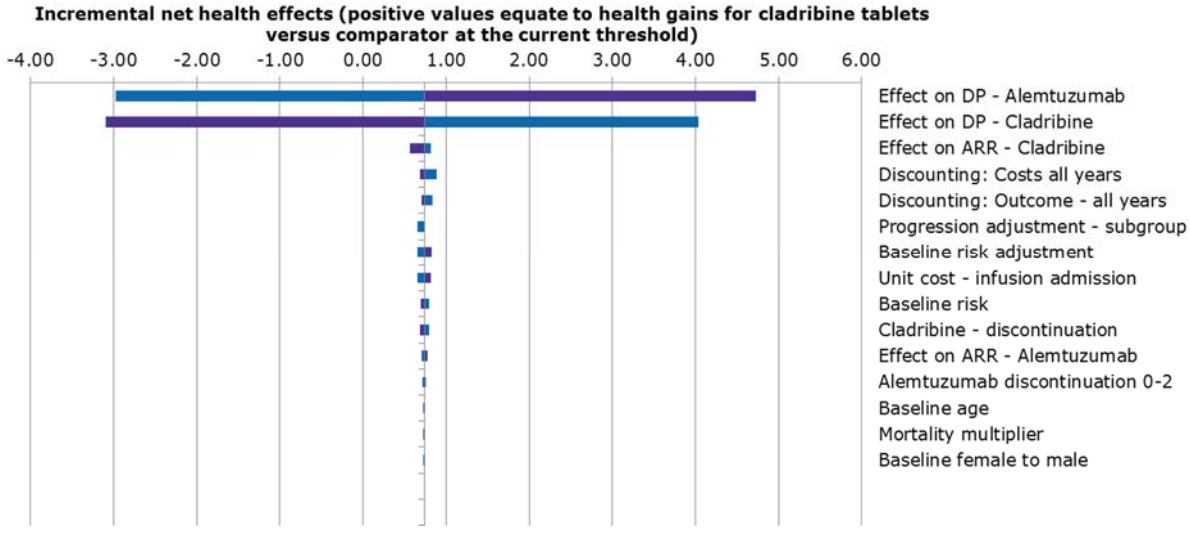
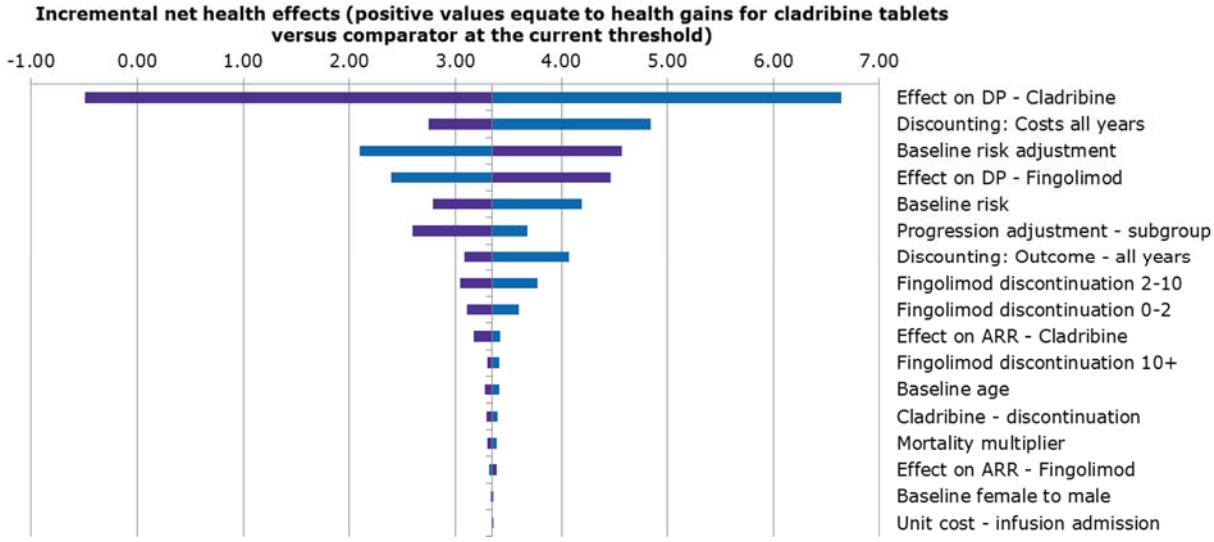


Figure 9: Tornado diagram for SOT-RRMSa, Cladribine Tablets versus fingolimod

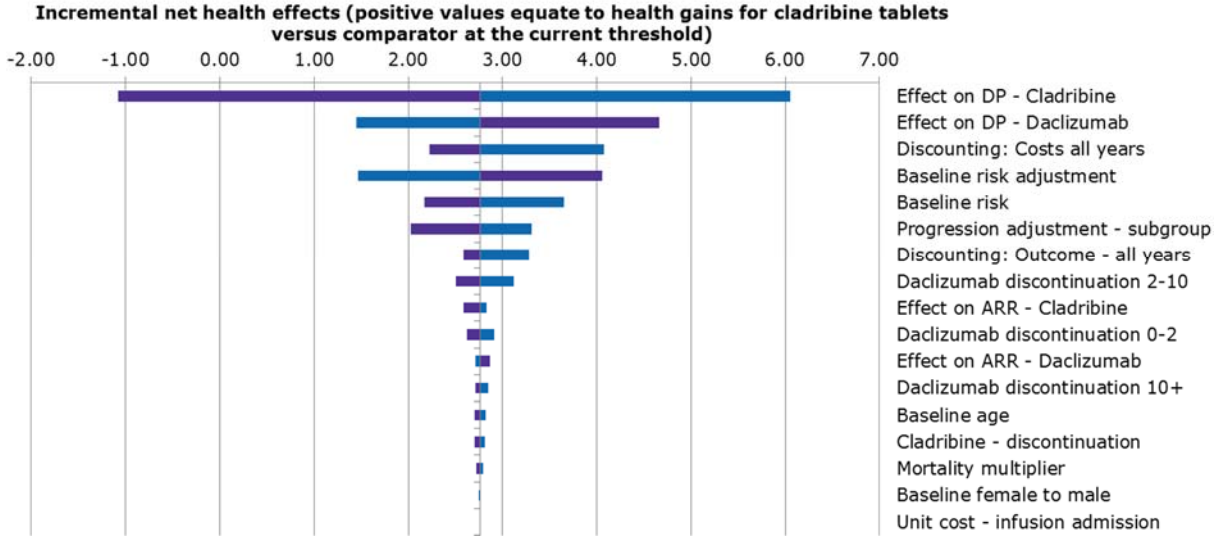


A.14.1.4. SOT-RRMSb

The results of the deterministic sensitivity analyses for SOT-RRMSb are summarised in Figure 10 for the comparison of Cladribine Tablets versus daclizumab, and in Figure 9 for the comparison to fingolimod.

The incremental net health effects comparing Cladribine Tablets versus daclizumab were positive in all but one scenario.

Figure 10: Tornado diagram for SOT-RRMSb, Cladribine Tablets versus daclizumab



A.15. Key sensitivity and scenario analyses

Scenario analyses were performed to test the robustness of the analysis to variations in underlying model assumptions and to the use of alternative input parameters (e.g. different utility sets or transition matrices for the natural history of disease). The incremental cost-effectiveness ratios were generated for each scenario and then compared against the base case results.

A.15.1 RES-RRMSa

Across the majority of scenario analyses, Cladribine Tablets was the dominant treatment strategy yielding cost-savings for additional QALYs when compared to natalizumab and alemtuzumab. Versus natalizumab, cost-savings ranged from £77,359 to £198,586 with QALY gains ranging from 0.073 to 1.075. The corresponding incremental costs and incremental QALYs for Cladribine Tablets versus alemtuzumab were more uncertain; incremental costs ranging from -£54,406 (savings) to +£43,513 and incremental QALY ranging from -1.217 to 0.944.

The only scenario where Cladribine Tablets was not the dominant strategy was in comparison to alemtuzumab in the scenario that used a conventional network meta-analysis and unpublished RES-RRMS subgroup data from PRISMS (interferon beta-1a versus placebo) to link alemtuzumab (alemtuzumab versus interferon beta-1a) trial data to the RES-RRMS subgroup data for CLARITY (Cladribine Tablets versus placebo). In this scenario, Cladribine Tablets was more costly (+£36,519) but less effective (-1.071) than alemtuzumab as a result of the alemtuzumab effect size (hazard ratio of [redacted] versus placebo) being numerically superior to the effect size for Cladribine Tablets (hazard ratio of [redacted] versus placebo). As with the meta-regression analysis, there was significant overlap in the 95% credible intervals of the conventional meta-analysis, and hence no individual DMT was statistically superior over its comparators in terms of 6 month confirmed disability progression.

Cladribine Tablets was dominant versus natalizumab in all scenarios tested, including when modelling the efficacy of therapy using the conventional network meta-analysis. In this scenario, natalizumab was more efficacious than Cladribine Tablets (hazard ratio of [redacted] for Cladribine Tablets versus placebo compared to [redacted] for natalizumab versus placebo) but required ongoing initiation of therapy to sustain a durable effect. Treatment with Cladribine Tablets is expected to yield sustained health benefits without the need for regular re-initiation of therapy. The discontinuation of natalizumab due to factors such as tolerability reduced the overall effectiveness of natalizumab, leading to fewer QALYs when compared to Cladribine Tablets.

A.15.2 RES-RRMSb

Across all scenarios tested, Cladribine Tablets was the dominant treatment strategy yielding cost-savings for additional QALYs when compared to daclizumab and natalizumab. In comparison to daclizumab, cost-savings ranged from £48,749 to £146,956 with QALY gains ranging from 0.585 to 1.789. This included scenarios where the list price for daclizumab was discounted at rates of 20 and 40%.

The results of the scenario analysis for natalizumab in RES-RRMSb are identical to those reported for RES-RRMSa as the same input parameters are used across RES-RRMS groups. The scenario analyses for natalizumab were summarised in the previous section.

A.15.3 SOT-RRMSa

Across all scenarios tested, Cladribine Tablets was the dominant treatment strategy yielding cost-savings for additional QALYs when compared to alemtuzumab and fingolimod. The cost-savings comparing Cladribine Tablets versus alemtuzumab ranged from £11,342 to £54,723, and from £30,081 to £117,023 versus fingolimod. This included scenarios where the list price for fingolimod was discounted at rates of 20% and 40%.

A.15.4 SOT-RRMSb

Across all scenarios tested, Cladribine Tablets was the dominant treatment strategy yielding cost-savings for additional QALYs when compared to daclizumab and fingolimod. The cost-savings comparing Cladribine Tablets versus daclizumab ranged from £28,685 to £105,811, and from £30,081 to £117,023 versus fingolimod. This included scenarios where the list price for fingolimod and daclizumab were discounted at rates of 20 and 40%.

A.16. Innovation

There remain significant unmet patient and healthcare service needs that new MS treatments can address. These are outlined in Section A.1. Cladribine Tablets is an efficacious DMT with a unique posology that can provide multiple benefits for the patient, clinician and healthcare providers.

The key innovations for patients relate to the drug's posology:

- Short course, oral treatment: Cladribine Tablets requires two short courses of oral treatment over 2 years, which could be self-administered at home, providing efficacy over a total of 4 years with no additional treatment required in years 3 and 4. This allows patients to be treated with minimal disturbance to their lives, with fewer medications to take and fewer hospital appointments compared with other DMTs.
- Monitoring burden: The contrast in monitoring requirements between Cladribine Tablets and other DMTs is significant and the impact on patients' daily life is likely to be considerable. Alemtuzumab, another annual treatment (for two years) for example, requires monthly blood monitoring during treatment years and for 48 months after the last dose, in contrast to the six that will be recommended for Cladribine Tablets during the first two years of treatment.
- Fewer restrictions on family planning: MS typically affects young adults between the age of 20 and 40 years and twice as many women than men. Patients receiving DMTs are recommended to stop treatment when they become pregnant, thereby increasing the risk of a relapse. The unique posology of Cladribine Tablets allows patients to be treated in Year 1 and Year 2 with no further treatment in Year 3 and Year 4 means that family planning can be considered from 6 months following the last dose of Cladribine Tablets in Year 2.
- Patient preference: The short course, oral nature of cladribine treatment was considered by the ABN as a potential motivator to some patients, preferred over the frequent administration and monitoring burden and adverse effects associated with infusions, a comment that was reflected in the responses from the MS Society and MS Trust in the NICE scope consultations.

Merck commissioned a Discrete Choice Experiment to establish patient requirement and preference for Cladribine Tablets. The study was independently executed by the Institute for Medical Technology Assessment (iMTA) and is currently being finalised and prepared for publication. It systematically investigated patient preferences for the characteristics of all available DMTs. Based on the responses of [redacted] RRMS patients from the UK, MS patients considered that the attributes of Cladribine Tablets would provide [redacted] options (overall) and [redacted] oral treatment option.

There are also key financial benefits for the healthcare system associated with Cladribine Tablets. The oral, short-course dosing of Cladribine Tablets results in considerably lower administration and monitoring cost burden compared with other DMTs:

- Administration: The ability to administer treatment outside of the acute care setting results in a low administrative burden for both patients, their carers and healthcare providers; only 20 days of oral dosing with Cladribine Tablets is required over 4 years, compared with 1,400 oral tablets for daily oral therapies, 8 days of infusion for alemtuzumab and approximately 52 infusions for natalizumab (over 4 years).
- Monitoring: In addition to lower administration costs, monitoring costs are also considerably reduced for Cladribine Tablets compared with other DMTs. During their 2 years of treatment, patients receiving Cladribine Tablets will only require a total of six blood tests. Patients receiving

natalizumab, fingolimod or alemtuzumab are expected to require multiple blood tests and additional analyses such as urinalysis, ophthalmological analyses, MRI and cardiovascular monitoring.

Merck is currently conducting the feasibility and pilot stage of a time and motion study which will quantify the burden on the NHS of the monitoring associated with the DMTs specified as comparators in this appraisal. This will enable a real world examination of the current pressures in the healthcare system which Cladribine Tablets can help to alleviate (see Section B.2.11). Initial results will become available during the course of this appraisal and will be provided to NICE. This study will consolidate the conclusion from our own budget impact analyses that Cladribine Tablets is the lowest cost high efficacy treatment for adults with HDA-RRMS, providing value to both payers and patients because of its short-course, oral posology. Merck believes there are additional system benefits from the innovative dosing regimen of Cladribine Tablets including improved treatment choice, equity of access no matter the geographical location and the opportunity to offer a different clinician-patient/carer experience through a self-management and increased patient accountability approach, leading to improved outcomes and QoL.

At no extra cost to NHS England, Merck will provide an innovative patient support program (PSP) for patients and healthcare professionals that fully integrates the support of a single service provider to enrol and manage patients who receive Cladribine Tablets. This PSP aims to further reduce the administrative and monitoring burden of hospitals and concomitantly accumulate and maintain a registry of patients on Cladribine Tablets to track performance and health-related outcomes.

The innovative aspects of the Cladribine Tablets highlighted in this section provide a considerable step-change in the current treatment pathway to potentially improve the overall management of highly-active RRMS and the lifestyle of affected patients.

A.17. Budget impact

The introduction of Cladribine Tablets as a treatment alternative for HDA-RRMS will result in a low or not significant increase in budget for years 1 and 2 that is followed by significant annual cost savings of approximately £1.35 million, £4.14 million and £3.03 million in years 3 through 5. The net cost savings predicted in years 3 through 5 are the result of reduced DMT use in people who complete two courses of Cladribine Tablets and are DMT free for up to 4 years post-initiation of treatment.

Table 12: Budget impact – Company budget impact analysis submission

	Company estimate	Cross reference
Number of people in England who would have treatment	[redacted]	Table 13, section 5.0 of Company budget impact analysis submission
Average treatment cost per person	Cladribine Tablets: £26,759 in year 1 £26,390 in year 2+	Table 8, section 4.0 of Company budget impact analysis submission
Estimated annual budget impact on the NHS in England	+£336,439 in year 1 +1,346,880 in year 2 -£1,352,520 in year 3 -£4,140,513 in year 4 -£3,034,979 in year 5	Table 17, section 7.0 of Company budget impact analysis submission

A.18. Interpretation and conclusions of the evidence

Despite current treatment options, there remains a substantial unmet need in HDA-RRMS for additional treatment options that, alongside high-efficacy, have a low treatment burden, improved adherence and reduced requirements for frequent switching. Cladribine Tablets has a well characterised efficacy and safety profile. The anticipated MAA will consolidate it as a treatment option with an optimal benefit:risk

profile in patients with highly active disease. Cladribine Tablets has demonstrated comparable efficacy versus the relevant comparators in, and has potential for health gains when allowing for a sustained effect over the first four years.

The innovations associated with its unique posology provide benefits for patients and for the healthcare service. The acquisition costs (approximately £13,000 per annum when the complete treatment cost of £52,000 is spread over a 4 year period) compare favourably with the annualised costs of daclizumab (£19,160 – list price), fingolimod (£19,176 – list price), natalizumab (£14,690 for acquisition), and alemtuzumab (£14,090 based on £56,360 for 2 courses). This, alongside the vastly reduced administration and monitoring costs, will lead to considerable cost savings for the NHS.

A robust, de novo economic analysis, closely following precedent set by Committee preferences in previous NICE appraisals, supports the conclusion that Cladribine Tablets is a cost-effective treatment in HDA-RRMS patients. It is dominant (e.g. cost-saving and more effective) versus alemtuzumab, daclizumab and natalizumab in RES-RRMS, and dominant versus alemtuzumab, fingolimod and daclizumab in SOT. Over a lifetime horizon, the model predicts discounted cost-savings with Cladribine Tablets that range from £130,676 versus natalizumab to £17,549 for alemtuzumab in SOT. In most scenarios, the cost-savings result from a lower lifetime drug acquisition cost for Cladribine Tablets due to its unique fixed course posology (versus continuously administered treatments), plus cost-savings from delaying EDSS progression and the additional care required at more severe EDSS states. The associated QALY gains from Cladribine Tablets ranged from +0.153 (alemtuzumab in SOT) to +0.944 (fingolimod in SOT). The analyses are robust and were performed using the best available evidence currently available on the costs, and clinical outcomes of treatment in RRMS.

In the probability sensitivity analysis, the probability that Cladribine Tablets is cost-effective at a threshold of £20,000 was in excess of 60% across all populations rising to 96% in comparison to fingolimod and daclizumab (both at list price) in SOT-RRMSb. The wide credible intervals surrounding the total costs and QALYs of each intervention in the PSA is due to the wide credible intervals around the efficacy of DMT in RRMS; no DMT treatment demonstrated statistical superiority over another.

Sensitivity analyses to test the robustness of the economic analysis were comprehensive and addressed the various concerns raised about assumptions and model inputs used in previous NICE appraisals (summarised in B.3). A variety of analyses are presented: excluding direct non-medical costs, applying the same waning assumption across all comparators and considering alternative input parameters. In all but one scenario analysis, Cladribine Tablets remained dominant (less costly and more effective) versus its comparators in RES-RRMS and SOT-RRMS. This demonstrates the overall robustness of the economic analysis.

The Committee can be confident that a robust set of clinical and economic analyses have demonstrated that Cladribine Tablets is a cost-effective treatment alternative for people with HDA-RRMS. In an over-burdened NHS system with no additional capacity, it is rare to have the opportunity to recommend an innovative product such as Cladribine Tablets that aligns with NHS priorities around place-based care, patient accountability, cost avoidance and equity of access to innovation in a complex and chronic, long-term condition like MS.

A.19. References

Biogen. (2017) NATALIZUMAB [Summary of Product Characteristics].

Compston A, Coles A. (2002) Multiple sclerosis. Lancet. 359(9313): 1221-1231.

Department of Health. (2017) Price application for MAVENCLAD.

European Medicines Agency. (2017) Data on file: Scientific Advice from the CHMP.

Hauser SL, Oksenberg JR. (2006) The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron. 52(1): 61-76.

IOMSN. (2004) Multiple Sclerosis: Key Issues in Nursing Management.

Leist TP, Weissert R. (2011) Cladribine: mode of action and implications for treatment of multiple sclerosis. Clin Neuropharmacol. 34(1): 28-35.

Merck. (2017a) Data on file: CLARITY GEVD subgroup analyses.

Merck. (2017b) Data on file: Clinical overview.

MS Trust. (2016a) MS Forward View: a consensus for the future of MS services.

MS Trust. (2016b) MS Specialist Nursing in the UK 2016: Report on progress towards equitable provision.

MS Trust. (2017) Introduction to MS. https://www mstrust org uk/understanding-ms/what-ms/introduction-ms.

Novartis. (2017) FINGOLIMOD [Summary of Product Characteristics].

Pakpoor J, Disanto G, Altmann DR, Pavitt S, Turner BP, et al. (2015) No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. Neurol Neuroimmunol Neuroinflamm. 2(6): e158.

Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, et al. (2014) UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open. 4(1): e004073.

Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, et al. (2015) Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol. 15(4): 273-279.

Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. (2010) New perspectives in the natural history of multiple sclerosis. Neurology. 74(24): 2004-2015.

Zuvich RL, McCauley JL, Pericak-Vance MA, Haines JL. (2009) Genetics and pathogenesis of multiple sclerosis. Semin Immunol. 21(6): 328-333.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Document B

Company evidence submission

June 2017

File name	Version	Contains confidential information	Date
Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]		**YES**	**October 2017**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Grey highlighted text in the footer does not work as an automatic form field, but serves the same purpose – as prompt text to show where you need to fill in relevant details. Replace the text highlighted in [grey] in the header and footer with appropriate text. (To change the header and footer, double click over the header or footer text. Double click back in the main body text when you have finished.)

Table of Contents

List of figures

List of tables

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The final NICE scope identifies the relevant patient population as adult patients with relapsing-remitting multiple sclerosis (RRMS). At present, Merck anticipates Cladribine Tablets to be indicated *either* for the treatment of adult patients with either highly active *relapsing* MS (RMS) - a highly active disease population including patients with RRMS and patients with relapsing forms of SPMS - or the narrower indication, highly active *relapsing-remitting* MS (RRMS), as defined by clinical or imaging features (see section 5.1 of the SmPC). This submission assumes a licence in the latter highly active RRMS (HDA-RRMS) population.

The NICE scope segments the HDA-RRMS population into patients with rapidly evolving severe (RES) RRMS and patients who are sub-optimally treated (SOT). Table 1 and Figure 1 provide the definitions of the patient populations relevant to the NICE decision problem, the patient population included in the Cladribine Tablets marketing authorisation and the patients from whom the evidence base relevant to this submission is derived.

Figure 1: Relationship between the proposed marketing authorisation for Cladribine Tablets and the NICE scope subgroups

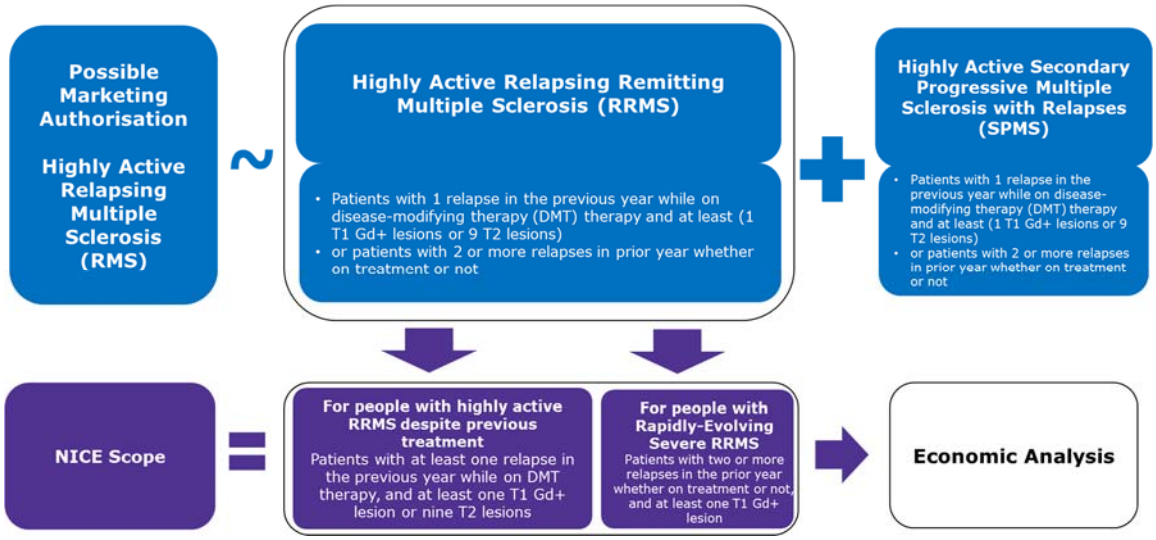


Table 1: Definitions of patient populations relevant to the NICE decision problem

Active RRMS	HDA-RRMS	
	RES-RRMS	SOT-RRMS
Patients with RRMS and at least one relapse in the previous year	Patients with two or more relapses in the prior year whether on treatment or not, and at least one T1 Gd+ lesion	Patients with at least one relapse in the previous year while on DMT therapy, and at least one T1 Gd+ lesion or nine T2 lesions

DMT: Disease-modifying therapy; Gd: Gadolinium; HDA: High disease activity; RES: Rapidly evolving severe; SOT: Sub-optimal therapy

Note that the NICE decision problem also applies to patients with RRMS who are treatment-naïve and treatment-experienced but without disease activity. These populations are not anticipated to be a part of the marketing authorisation for Cladribine Tablets and are therefore not relevant to the NICE decision problem.

In line with the final recommendation for daclizumab, the RES and SOT populations are further divided into those who are able to receive alemtuzumab and those who are unable to receive alemtuzumab. This is described fully in the cost-effectiveness section (Section B.3). Within the cost-effectiveness section, there are therefore four populations of interest:

- RESa: RES and able to receive to alemtuzumab
- RESb: RES but unable to receive to alemtuzumab
- SOTa: SOT and able to receive to alemtuzumab
- SOTb: SOT but unable to receive to alemtuzumab

presents the final NICE scope and the decision problem addressed in this submission.

Table 2: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with RRMS	Adults patients with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for Cladribine Tablets	Active RRMS (as opposed to *highly* active RRMS) is not a part of the anticipated marketing authorisation for Cladribine Tablets.
Intervention	Cladribine Tablets	Cladribine Tablets	N/A
Comparator(s)	For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • dimethyl fumarate • teriflunomide For people with rapidly-evolving severe RRMS. • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab (subject to ongoing NICE appraisal) • fingolimod	For people with rapidly-evolving severe RRMS • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab • fingolimod	To align with the recent recommendation for daclizumab, the RES and SOT populations have been segmented into RESa, RESb, SOTa and SOTb. The comparators for Cladribine Tablets in this submission are therefore as follows: For people with rapidly-evolving severe RRMS and able to receive to alemtuzumab (RESa): • natalizumab • alemtuzumab RES and either contraindicated or otherwise unable to receive alemtuzumab (RESb): • natalizumab • daclizumab For people with highly active RRMS despite previous treatment and able to receive to alemtuzumab (SOTa) • fingolimod • alemtuzumab For people with highly active RRMS despite previous treatment and either contraindicated or otherwise unable to receive alemtuzumab (SOTb) • fingolimod • daclizumab

Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom from disease activity • mortality • adverse effects of treatment • HRQoL	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • MRI lesions • adverse effects of treatment • HRQoL	The outcome measures to be assessed as part of the decision problem are considered to be the most relevant for the target patient population. MRI lesions have been included as part of the decision problem given that MRI imaging techniques are commonly used to complement the diagnosis and prognosis of RRMS
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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 will 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.	As per reference case	N/A
Subgroups to be considered	The following subgroups of patients will be considered: • patients with RRMS whose disease has inadequately responded to treatment with disease modifying therapy • patients with RRMS whose disease is intolerant to treatment with disease modifying therapy • patients with highly active RRMS • patients with rapidly evolving severe RRMS	All subgroup included in the NICE scope and included in the anticipated marketing authorisation for Cladribine Tablets have been included in the decision problem for Cladribine Tablets.	
Perspective for outcomes	All health effects were modelled from a patient perspective	In-line with scope	
Perspective for costs	NHS and PSS perspective for costs were incorporated into the model	In-line with scope	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	50 years	This is in line with previous NICE appraisals

Synthesis of evidence on health effects	Based on systematic review	Health effects were based on a number of sources, including a systematic review and the CLARITY trial.	
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The health effects of treatment were modelled in terms of QALY and derived from EQ-5D questionnaires collected in CLARITY	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D questionnaires were completed by patients during the CLARITY trial	
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Completed EQ-5D questionnaires in the CLARITY trial were mapped to health state utility (HSU) index values using the UK social tariff.	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	There are no equity considerations	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Relevant cost and health resource use data were identified from various sources including previous NICE appraisals, a systematic review of published costing studies, the British National formulary, NHS reference costs, and PSS research unit reports, and from the summary of product characteristics for in-scope comparators.	
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Both costs and health outcomes were discounted at a rate of 3.5% per annum.	

EDSS: Expanded disability status scale; EMA: European Medicines Agency; HRQoL: Health-related quality of life; MRI: Magnetic resonance imaging; RRMS: Relapsing-remitting multiple sclerosis

B.1.2 Description of the technology being appraised

A summary of the technology to be appraised is presented in Table 3 and detailed in the following subsections. In addition to the summary, the following documents are included in the Appendix C in support of this appraisal:

- The draft Summary of Product Characteristics (SmPC)
- The European public assessment report produced by the regulatory authorities.

Table 3: Technology being appraised

UK approved name and brand name	"Cladribine Tablets" (MAVENCLAD)
Mechanism of action	Cladribine is a deaminase-resistant nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells. The mechanism by which Cladribine Tablets exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS (Leist 2011). A distinguishing feature of Cladribine Tablet is discontinuous immunosuppression. Periods of lymphocyte depletion around treatment are followed by repopulation resulting in durable efficacy well beyond the period of treatment.
Marketing authorisation/CE mark status	Cladribine Tablets currently does not have marketing authorisation in the UK. An application for marketing authorisation was submitted to the European Medicines Agency in June 2016, and approval is expected in September 2017.
Indications and any restriction(s) as described in the summary of product characteristics	At present, Merck anticipates Cladribine Tablets to be indicated for the treatment of adult patients with *either* highly active *relapsing* MS (RMS) or the narrower indication highly active *relapsing-remitting* MS (RRMS), as defined by clinical or imaging features (see section 5.1 of the SmPC). This technology appraisal submission is based on the RRMS indication.
Method of administration and dosage	Cladribine Tablets is administered orally. The recommended cumulative dose of Cladribine Tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. No further treatment is required in years 3 and 4.
Additional tests or investigations	The introduction of Cladribine Tablets would not require additional tests, investigations or administration beyond those that are currently required for all patients with MS. In Section A.17, Merck presents the anticipated budget impact of Cladribine Tablets; as can be seen, treatment is anticipated to be cost-saving for the NHS because of the considerable reduction in administration and monitoring burden for the healthcare service.
List price and average cost of a course of treatment	Confirmed list price (DH, 2017): • Cladribine Tablets 10mg x 1 tablet £2,047.24 • Cladribine Tablets 10mg x 4 tablets £8,188.97 • Cladribine Tablets 10mg x 6 tablets £12,283.46 Annual cost: approximately £13,000 per annum when the complete treatment cost of £52,000 is spread over a 4 year period
Patient access scheme (if applicable)	A Patient Access Scheme has not been included in the submission at this time

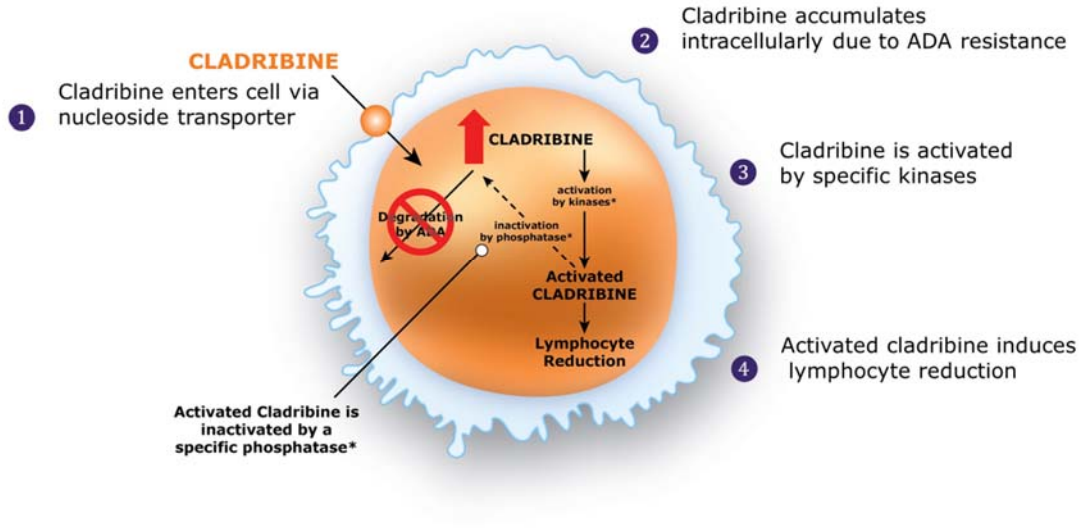
B.1.2.1. Mechanism of action

Cladribine is a deaminase-resistant nucleoside analogue of deoxyadenosine that is activated by intracellular phosphorylation in specific cell types, resulting in preferential and sustained reduction of dividing and non-dividing T and B lymphocyte, with less effect on other immune cells. The selectivity of cladribine for lymphocytes is dependent on a higher deoxycytidine kinase/5'-nucleotidase ratio than other cell types, which allows activation of cladribine by sequential phosphorylation (Figure 2). Cladribine can penetrate the intact blood-brain barrier (BBB) as shown by a cerebrospinal fluid (CNS)-plasma concentration ratio of approximately 0.25 in patients without BBB compromise. This, together

with its sustained effects on circulating lymphocytes, may affect the recruitment of inflammatory cells into nascent inflammatory foci in the CNS in MS patients (Leist 2011).

Cladribine is also believed to have effects on pro- and anti-inflammatory cytokines; reducing the pro-inflammatory cytokines (e.g. fibroblast growth factor, TGF-β1, TNF-α) and enhancing anti-inflammatory cytokines (e.g. IL-4, IL- 5 and IL-10) (Leist 2011).

Figure 2: Mechanism of action for cladribine



SOURCE: Adapted from (Leist 2011)

* Cladribine is inactivated by 5'-nucleotidase

MS pathology involves a complex chain of events in which different immune cell types, including autoreactive T and B cells play a key role (Merck 2017j). The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated but its depletive effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS (Merck 2017j).

Although cladribine has a short half-life, the observed effect is due to the immediate selective depletion of both T and B cell lymphocytes, followed by repopulation to normal levels over time thereby giving this treatment a unique posology that consists of a short treatment course followed by a prolonged period of sustained drug efficacy for at least 4 years (Section B.2). This posology allows patients who have RMS with highly active disease the opportunity to maintain a low impact treatment regimen and continue with normal daily activities.

B.1.2.2. Marketing authorisation/CE mark status

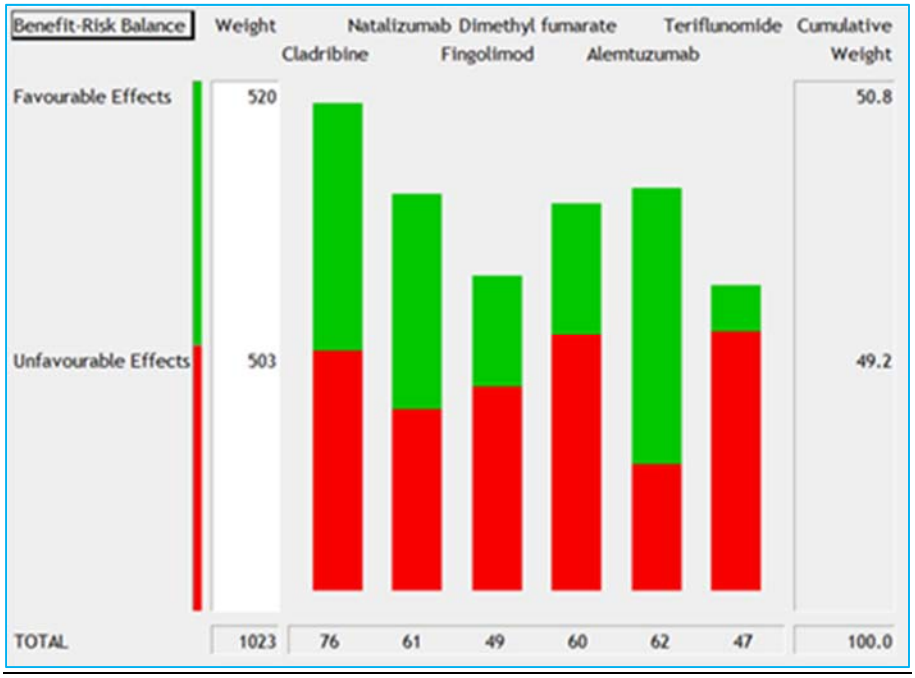
A marketing authorisation application (MAA) for MAVENCLAD (Cladribine Tablets) was submitted to the EMA in June 2016 with the expected approval date of September 2017; CHMP opinion is expected in July 2017. At present, Merck anticipates Cladribine Tablets to be indicated for the treatment of adult patients with *either* highly active relapsing MS (HDA-RMS) or the narrower indication highly active relapsing-remitting MS (HDA-RRMS), as defined by clinical or imaging features (see section 5.1 of the SmPC).

Merck has previously submitted a MAA for Cladribine Tablets to the EMA for the treatment of patients with RRMS. The history of the EMA regulatory submissions is summarised in Figure 3.

Figure 3: Timeline summary of the marketing authorisation history of Cladribine Tablets

During the initial review, the CHMP highlighted the clinical benefits of Cladribine Tablets, but asked Merck to focus on a population with an optimal benefit:risk profile. Based on the Scientific Advice from the EMA, a multiple-criteria decision analysis (MCDA) was performed to determine the benefit:risk profile of Cladribine Tablets compared with other disease-modifying treatments (DMTs). The MCDA concluded the greatest overall benefit:risk profile was observed in the patients with HDA (Figure 4).

Figure 4: Benefit:risk profile of Cladribine Tablets vs. other DMTs in patients with HDA-RRMS



NOTE: The larger the size of the green bars indicates more benefit; the larger the size of the red bars indicates better safety (i.e. less risk)

Following on from the MCDA results and as part of the marketing authorisation application, a conditional approval was requested by Merck in September 2010, for patients with HDA-RRMS and/or at high risk of disease progression or patients who were intolerant to interferon-β (IFN- β) or glatiramer acetate (GA) therapies. However, at the time of re-examination, no new clinical evidence on the safety of Cladribine Tablets was available in the RRMS-HDA population and a negative opinion was issued. Despite initial concerns regarding safety, the CHMP highlighted that the efficacy of Cladribine Tablets was sufficiently demonstrated among the intention-to-treat (ITT) population (active RRMS) and the subgroups analysed. It was also suggested that the potential safety concerns (namely lymphopenia, infection risk and malignancy risk) could be mitigated by the introduction of a risk management plan proposed by Merck.

After receiving a negative opinion from the CHMP and a Complete Response Letter from the US FDA in 2011, Merck announced in June 2011, as a precautionary measure, not to pursue further the worldwide approval process of Cladribine Tablets. Subsequently, the product was withdrawn from the markets in Australia and Russia, and all ongoing applications in other countries were withdrawn. Merck continued their Phase II and Phase III trials that were ongoing at the time, including the collection of long-term safety data to support a thorough characterisation of the safety profile of cladribine and which has helped to establish the updated benefit/risk assessment for the treatment of RRMS.

Since the initial MAA in 2009, the clinical evidence package for Cladribine Tablets has considerably expanded. The inclusion of results from three additional RCTs and a prospective observational safety registry has increased patient experience from 2,000 patient-years (PYs) in 2009 to over 10,000 PYs to date. This additional data has substantiated the positive clinical efficacy of Cladribine Tablets while also mitigating safety concerns previously identified by the CHMP. Following the availability of new clinical data, Merck has filed new submissions in the EU (June 2016) and Canada (December 2016), as well as a variation submission in Australia (January 2017). Filings in other jurisdictions are ongoing.

B.1.2.3. Method of administration and dosage

Cladribine Tablets is an oral medication where the recommended cumulative dose is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year (Merck 2017j). Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight (Table 4) (Merck 2017j). Cladribine Tablets are recommended to be administered at approximately 24-hour intervals. If one of the daily doses consists of two tablets, both tablets are taken together as a single dose (Merck 2017j).

Table 4: Dose distribution of Cladribine Tablets per treatment week in each treatment year

Weight range, kg	Dose, mg (number of 10 mg tablets) per treatment week	
	Treatment week 1	Treatment week 2
40 to <50	40 (4)	40 (4)
50 to <60	50 (5)	50 (5)
60 to <70	60 (6)	60 (6)
70 to <80	70 (7)	70 (7)
80 to <90	80 (8)	70 (7)
90 to <100	90 (9)	80 (8)
100 to <110	10 (10)	90 (9)
100 and above	10 (10)	10 (10)

SOURCE: (Merck 2017j)

Lymphocyte counts must be normal before Cladribine Tablets initiation in Year 1, and patients should have at least 800 cells/mm^3 before initiation of Cladribine Tablets in Year 2. In the absence of this, a treatment course could be delayed for up to 6 months to allow lymphocyte counts to recover (Merck 2017j).

Following completion of the two treatment courses, no further treatment with Cladribine Tablets is required in years 3 and 4 (Merck 2017j). Subsequent re-initiation of Cladribine Tablets after year 4 has not been assessed. Figure 5 illustrates the full 4-year treatment course for Cladribine Tablets.

Figure 5: Dosing regimen for Cladribine Tablets

NOTE: The blue dots represent the number of days on which treatment should be administered

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) resulting in inflammation, demyelination, development of plaque lesions and progressive disability (Zuvich 2009). MS is the most common debilitating neurological disease among young adults (MS Trust 2017). Approximately 85% of patients with MS initially present with relapsing-remitting MS (RRMS), which is characterised by periodic acute exacerbations of disease activity (relapses) followed by periods of remission (Zuvich 2009). Relapses in patients with RRMS are unpredictable and are associated with inflammation and development of new focal lesions, followed by periods of remission, leading to partial or complete recovery (Zuvich 2009). Over time (typically 15-20 years following disease onset) , most patients with RRMS will enter a phase of progressive neurodegeneration, with or without periodic relapses, associated with the accumulation of permanent disability, termed secondary-progressive MS (SPMS) (Compston 2002; Hauser 2006; Zuvich 2009; Tremlett 2010). In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course. To date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual. This has limited the ability to study the imaging and biomarker characteristics that may distinguish this course.

Some patients with RRMS experience a more aggressive disease course. These patients can be categorised as having high disease activity (HDA-RRMS), although its definition is evolving and which can be associated with a constellation of clinical and imaging activities, including these defined by the European Medicines Agency (EMA) specifically for natalizumab and fingolimod (Novartis 2017; Biogen 2017):

- failure to respond to an adequate course of at least one disease-modifying therapy (DMT), presenting with at least one relapse in the previous year while on therapy and at least nine T2-hyperintense lesions or at least one gadolinium-enhancing lesion, or
- treatment naïve with at least two disabling relapses in the last 1 year and at least one gadolinium-enhancing lesion or significant increase in T2-lesion load

There is no cure for MS. The EMA has acknowledged that in spite of a number of recent approvals for disease-modifying therapies (DMT), there remains a high unmet need for effective and well-tolerated treatments especially for patients with HDA-RRMS (Merck 2017b). Most current DMTs for HDA-RRMS deliver their effect by continuous immunosuppression, and

in turn, patients receiving these treatments require close monitoring. The implications can be considerable; many patients travel significant distances to reach services for regular treatment administration and for monitoring that, due to its frequency, can interfere with daily life. Additionally, some DMTs are associated with restrictions on family planning, requiring discontinuation if a woman becomes pregnant while on treatment.

Of course, there are implications for the healthcare service too. MS specialist nurses are key health professionals managing the provision and monitoring of DMTs. They are under mounting pressure to deliver complex monitoring regimes for the DMTs. Recent documentation published by the MS Trust highlighted these concerns, which were supported by expert nurse feedback received by Merck. This commentary in the public domain (MS Trust 2016b; MS Trust 2016a; IOMSN 2004) highlights that there is a substantive need for treatments with reduced administration and monitoring burden than the currently available DMTs provide. In response to this advice, Merck has initiated a time and motion study in the MS area to quantify the burden that is presently faced by the National Health Service (NHS). Unfortunately, even though this is currently underway, results are not yet available. Merck would like to provide these data to the Committee as soon as they become available.

B.1.3.2. Diagnosis and measurement of disease state

Consensus clinical and magnetic resonance imaging (MRI) criteria are used for the diagnosis of MS, in the absence of a definitive diagnostic test.

The clinical outcome of disability progression is measured though the accumulation of permanent disability according to the Expanded Disability Status Scale (EDSS) (Kurtzke 1983). The EDSS score ranges from 0, which indicates no disability, to 10, which indicates death, in increments of 0.5 (after EDSS 1) (Kurtzke 1983). The time course for disease progression in RRMS is variable. The time it takes to reach an EDSS score of 6, noted as disability requiring assistance to walk, is reported to range between 15 years and 32 years from disease onset although there are multiple factors that can impact the time course of disease progression in RRMS including the age of the patient at disease onset, the initial disease course, and frequency of relapses (Tremlett 2010).

In addition to clinical symptoms, patients with RRMS may present with subclinical disease activity, in particular plaque lesions in the brain detected by MRI, which often occur during remission. These lesions are indicative of active inflammatory disease activity and may predict disability and MS prognosis (Fisniku 2008). The current criteria for the diagnosis of MS are known as the McDonald criteria and are summarised in Table 5 (Polman 2011).

Table 5: The McDonald criteria for MS diagnosis

Clinical presentation	Additional data needed for MS diagnosis
• Two or more attacks[a] • Objective clinical evidence of two or more lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	• None
• Two or more attacks[a] • Objective clinical evidence of one lesion	DIS, demonstrated by: • One or more T2 lesion in at least two MS-typical regions of the CNSb Or • Await a further clinical attack[a] implicating a different CNS site

Clinical presentation	Additional data needed for MS diagnosis
• Two or more attacks[a] • Objective clinical evidence of two or more lesions	DIT, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time Or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan Or • Await a second clinical attack[a]
• One attack[a] • Objective clinical evidence of one lesion (CIS)	DIS and DIT, demonstrated by: • For DIS: o One or more T2 lesion in at least two MS-typical regions of the CNSb or o Await a second clinical attacka implicating a different CNS site • For DIT: o Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time or o A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan or o Await a second clinical attack[a]
• Insidious neurological progression suggestive of PPMS	1 year of disease progression (retrospectively or prospectively determined) plus two of three of the following criteria[b]: • Evidence for DIS in the brain based on one or more T2 lesion(s) in the MS-characteristic regions • Evidence for DIS in the spinal cord based on two or more T2 lesions in the spinal cord • Positive CSF

SOURCE: (Polman 2011)

a: An attack is defined as an episode of neurological disturbance typical of MS

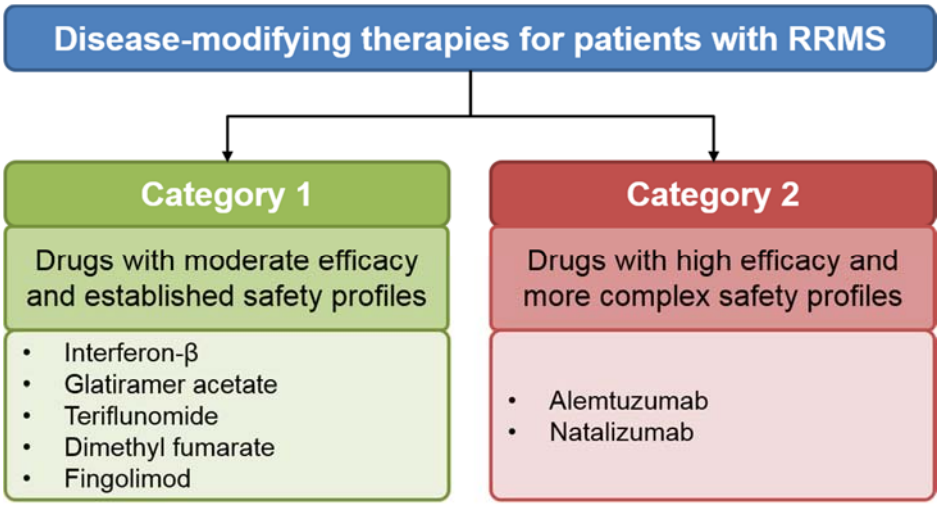
b: Gadolinium-enhancing lesions are not required

CIS: Clinically isolated syndrome; CNS: Central nervous system; CSF: Cerebrospinal fluid; DIS: Dissemination in space; DIT: Dissemination in time; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; PPMS: Primary progressive multiple sclerosis

B.1.3.3. Clinical pathway of care

Diagnosis and management of MS in adults is covered by NICE's CG186, although it does not directly address DMTs. There are a wide range of DMTs currently available in the UK providing patients and prescribing neurologists with alternative treatment options for RRMS. The Association of British Neurologists (ABN) have issued guidance on the prescribing of DMTs for MS and they classify the treatments into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles) (Scolding 2015) (Figure 6).

Figure 6: Categorisation of DMTs according to the ABN guidelines (2015)



SOURCE: Adapted from (Scolding 2015)

ABN: Association of British Neurologists; DMT: Disease-modifying treatment; RRMS: Relapsing-remitting multiple sclerosis

It is not currently known into which category Cladribine Tablets may fit or whether a separate category may be required.

A network meta-analysis (NMA) and a meta-regression analysis, undertaken by Merck for this submission, confirm Cladribine Tablet's comparable efficacy versus other high efficacy drugs for patients with HDA-RRMS on all outcomes of relevance to this decision problem. The safety and tolerability profile is characterised on the basis of 8 years of follow-up of treated patients, more than 3,000 patient years of exposure to Cladribine Tablets 3.5 mg/kg, and more than 8,000 patients years exposed to any dose of Cladribine Tablets, an extensive safety database in comparison to other high efficacy treatments on the market. In a Multi-Criteria Decision Analysis (MCDA), conducted by Merck in 2015 following advice from the EMA, leading MS physicians in Europe evaluated favourable (e.g. clinical efficacy, ease-of-use and durability) and unfavourable (e.g. AE & SAEs) attributes based on pivotal trial results and determined that Cladribine Tablets has a favourable benefit:risk profile compared to fingolimod, natalizumab and alemtuzumab in patients with high disease activity.

B.1.4 Equality considerations

No equality issues have been identified for Cladribine Tablets.

B.2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify clinical trials relevant to the NICE decision problem. This systematic review assessed the efficacy, health-related quality of life (HRQoL), safety, and tolerability outcomes associated with key interventions in the treatment of RRMS. The systematic review was conducted for a global decision problem and therefore all licensed treatment for a RRMS population were considered to be relevant to the evidence base for Cladribine Tablets. This was to ensure a broad evidence base for the studies that may be able to contribute to the indirect treatment comparisons in all populations relevant to the NICE decision problem. The evidence base was segmented into the four patient populations in line with the final NICE scope and the European marketing authorisation for Cladribine Tablets (Table 6) (NICE 2017a; European Medicines Agency 2017a).

Table 6: Segmented patient populations for Cladribine Tablets

Subgroup		Description of patients included	Rationale
Active RRMS		RRMS patients who have experienced ≥1 relapse in the previous year	• ITT population in the pivotal RCTs for Cladribine Tablets
HDA-RRMS	RES-RRMS-RRMS	RRMS patients who have experienced ≥2 relapse in the previous year	• Population identified in the NICE scope as a relevant subgroup for the decision problem
	SOT-RRMS-RRMS	Patients previously treated with sub-optimal therapy	• Population identified in the NICE scope as a relevant subgroup for the decision problem

HDA-RRMS: High disease activity; ITT: Intention to treat; MCDA: Multiple criteria decision analysis; RCT: Randomised controlled trial; RES-RRMS: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT-RRMS: Sub-optimal therapy

The full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are summarised in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The systematic literature review identified two RCTs relevant to the decision problem; CLARITY and CLARITY-EXT. Both of these studies evaluated Cladribine Tablets as a monotherapy for the treatment of patients with RRMS and were included in the marketing authorisation application for Cladribine Tablets. Post-hoc analyses were conducted to support the marketing authorisation (HDA-RRMS) and HTA submission (RES-RRMS and SOT-RRMS). Two additional RCTs were also identified that evaluated Cladribine Tablets (ORACLE and ONWARD); however, due to either the patient population or the dosing regimen of Cladribine Tablets in the study, these RCTs did not meet the inclusion criteria of the systematic review. A fifth study (PREMIERE), an observational, prospective registry study evaluating long term safety outcomes in patients who were previously enrolled in one or more trials where the intervention included Cladribine Tablets 3.5 mg/kg, was also identified (Table 7).

Of the five studies identified, CLARITY and CLARITY-EXT are the pivotal trials and form the evidence base for the efficacy, safety and tolerability of 3.5 mg/kg Cladribine Tablets in the active RRMS, HDA-RRMS, RES-RRMS and SOT-RRMS populations relevant to the Decision Problem (Section B.1). These trials also support the posology of 3.5 mg/kg Cladribine Tablets i.e. 2 years of treatment with no treatment required for years 3 and 4. Specifically, CLARITY is used in the network meta-analysis (NMA) to demonstrate comparable efficacy and safety of 3.5 mg/kg Cladribine Tablets and relevant comparators (Section B.2.9) over the first two years of treatment. Results from CLARITY inform the cost-effective analysis of 3.5 mg/kg Cladribine Tablets presented in Section B.3.

Results from the CLARITY-EXT trial demonstrate the long-term efficacy and safety of 3.5 mg/kg Cladribine Tablets over a 4-year period (2 years of CLARITY and 2 years of CLARITY-EXT). Due to ethical reasons, patients who were randomised to the placebo arm in the CLARITY trial were allocated to a cumulative 3.5 mg/kg dose of Cladribine Tablets in the EXT trials; therefore there were no patients who exclusively received placebo across both CLARITY and CLARITY-EXT. The long-term efficacy

and safety results from this trial are the basis of the assumptions on the waning effect in the cost-effectiveness analysis of 3.5 mg/kg Cladribine Tablets (Section B.3). No comparative effectiveness analysis (i.e. ITC or NMA) of CLARITY-EXT was considered due to the lack of a common treatment arm with competitor trials and heterogeneity of the study designs associated with studies evaluating long term (greater than 2 years) data for MS treatments.

ONWARD is a trial that evaluated the efficacy and safety of Cladribine Tablets 3.5 mg/kg in a combination therapy with IFN-β and does not align with the intervention as stated in the marketing authorisation and Decision Problem. As such, efficacy results from ONWARD were not considered suitable for comparisons in this submission and will not be discussed.

Merck currently anticipates Cladribine Tablets to be indicated for the treatment of adult patients with either highly active relapsing MS (RMS) or the narrower indication, highly active RRMS. Therefore ORACLE MS and PREMIERE do not provide relevant efficacy data to support the 3.5 mg/kg dose of Cladribine Tablets in an RRMS population; however, they do provide vital safety data for its use in patients with RRMS. As such, the safety outcome from ORACLE MS and PREMIERE are incorporated into an integrated safety analysis in addition to CLARITY and CLARITY-EXT (Section B.2.10.3).

A summary of the clinical evidence for Cladribine Tablets is presented in Table 7.

Table 7: Clinical effectiveness evidence for efficacy and safety of Cladribine Tablets

Study	Registration studies		Additional RCTs (safety data)		Registry Study (safety data)
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**	**ORACLE MS (NCT00725985)**	**ONWARD (NCT00436826)**	**PREMIERE (NCT01013350)**
Study design	Phase III double-blind, placebo-controlled, 96-week RCT	Phase IIIb double-blind, 96-week RCT; safety extension trial	Phase III, double-blind, placebo-controlled, 96-week RCT	Phase IIb, placebo-controlled, multicentre, 96-week RCT	Prospective, observational registry study
Population	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study • Clinically stable and not had a relapse within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	• Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks	• Patients who experienced a single, first clinical event suggestive of MS (CIS) within 75 days prior to the initial screening visit, present for at least 24 hours • Patients must have had ≥2 clinically silent T2 lesions at screening, with a size of at least 3 mm, ≥1 of which was ovoid or periventricular or infratentorial • EDSS score between 0 to 5.0, inclusive	• Diagnosis of MS according to the McDonald criteria • Patients with active MS (RRMS or SPMS) who have experienced ≥1 relapse within 48 weeks of screening while receiving IFN-β treatment • A minimum of 48 weeks of continuous IFN-β treatment prior to screening and on a stable regimen of their current IFN-β therapy for a minimum of 3 months prior to screening	• Patient who had previously completed ≥1 RCT that included 3.5 mg/kg Cladribine Tablets as a treatment arm

Study	Registration studies		Additional RCTs (safety data)		Registry Study (safety data)
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**	**ORACLE MS (NCT00725985)**	**ONWARD (NCT00436826)**	**PREMIERE (NCT01013350)**
Intervention(s)	• Cladribine Tablets 3.5 mg/kg cumulative over 96 weeks (LL) • Cladribine Tablets 5.25 mg/kg cumulative over 96 weeks (HL)	• Patients were randomised upon entry to receive either further doses of 3.5 mg/kg Cladribine Tablets or placebo, resulting in five reporting groups: • LLPP - cumulative 3.5 mg/kg* • LLLL- cumulative 7.0 mg/kg • PPLL - cumulative 3.5 mg/kg • HLLL - cumulative 8.75 mg/kg • HLPP - cumulative 5.25 mg/kg	• Cladribine Tablets 3.5 mg/kg cumulative over 96 weeks* • Cladribine Tablets 5.25 mg/kg cumulative over 96 weeks	• Cladribine Tablets 3.5 mg/kg plus IFN-β	• No investigational product or placebo was administered during the study
Comparator(s)	Placebo	N/A	Placebo	Placebo plus IFN-β	N/A
Indicate if trial supports application for marketing authorisation	Yes	Yes	Yes (safety only)	No	Yes (safety only)
Indicate if trial is used in the economic model	Yes	No	No	No	No

Study	Registration studies		Additional RCTs (safety data)		Registry Study (safety data)
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**	**ORACLE MS (NCT00725985)**	**ONWARD (NCT00436826)**	**PREMIERE (NCT01013350)**
Rationale for use/non-use in the model	• This was the pivotal trial for Cladribine Tablets and included the licensed dose and target patient population. Safety and efficacy results were incorporated into the economic model and NMA	• This was a pivotal trial supporting the duration of efficacy and safety for a further 2 years (treatment duration of 4 years in total). Safety results were incorporated in the economic model and the efficacy results were used to support sustained duration of efficacy (i.e. waning effect over 4 years)	• This trial was focused on a CIS patient population, not relevant to the NICE decision problem and used primarily to demonstrate safety	• This trial evaluated Cladribine Tablets as an add-on therapy and, therefore, not relevant to the NICE decision problem.	• This study is a prospective observational study where patients were not administered further doses of Cladribine Tablets or placebo. This trial was used primarily used to demonstrate safety
Reported outcomes specified in the decision problem (bold text indicate outcomes incorporated into the economic model)	• Relapse rate • Severity of relapse • Disability (for example EDSS) • MRI lesions • Adverse effects of treatment • HRQoL.	• Relapse rate • Disability (for example EDSS) • Adverse effects of treatment	N/A	N/A	N/A

Study	Registration studies		Additional RCTs (safety data)		Registry Study (safety data)
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**	**ORACLE MS (NCT00725985)**	**ONWARD (NCT00436826)**	**PREMIERE (NCT01013350)**
All other reported outcomes – pre-planned	*Secondary endpoints* • Proportion of patients qualifying relapse-free • Mean number of new T1 Gd+, active T2, T1 hypointense and CU lesions *Tertiary endpoints* • Time to first qualifying relapse • Proportion of patients with no new T1 Gd+, active T2, T1 hypointense or CU lesions • Proportion of patients rescued with Rebif (IFN-β)	• Proportion of patients qualifying relapse-free • Time to first qualifying relapse • Time to second qualifying relapse • Time to treatment with rescue medication • Mean number and cumulative number of new T1 Gd+, active T2, T1 hypointense and CU lesions • Proportion of patients with no new T1 Gd+, active T2, T1 hypointense or CU lesions	N/A	N/A	N/A
Post-hoc analyses	• NEDA-3 • Time to 6-month EDSS progression • Patients with HDA-RRMS (anticipated licensed population) • Patients with RES-RRMS RRMS • Patients with SOT-RRMS	• NEDA-3 • Time to 6-month EDSS progression	N/A	N/A	N/A
References	• (Giovannoni 2010)	• (Cook 2016)	• (Leist 2014)	• (Merck 2017h)	• (Merck 2017i)

SOURCE: see table

* Licensed dose of Cladribine Tablets

CDMS: Clinically defined multiple sclerosis; CU: Combined unique; EDSS: Expanded disability status scale; HDA-RRMS: High disease activity RRMS; Gd+: Gadolinium-enhancing; HRQoL: Health-related quality of life; IFN: Interferon; MRI: Magnetic resonance imaging; NEDA; No evidence of disease activity; NMA: Network meta-analysis; RCT: Randomised controlled trial; RES-RRMS: Rapidly evolving severe RRMS; RRMS: Relapsing-remitting multiple sclerosis; SOT-RRMS: Sub-optimal therapy RRMS

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The RCTs identified as relevant to the decision problem in Section B.1 include CLARITY and CLARITY-EXT. These are the pivotal trials that supported the marketing authorisation for 3.5 mg/kg Cladribine Tablets in Europe and relevant to the NICE decision problem (Giovannoni 2010; Cook 2016).

The CLARITY trial has been included in the indirect treatment comparison and the economic model and forms the basis on the evidence base for Cladribine Tablets. The CLARITY-EXT trial was not used to populate the economic model but is included in sections B.2.2 to B.2.6. The results of this study support the posology of Cladribine Tablets (2 years of treatment and no further treatment required in years 3 and 4) and provide validation of the waning assumptions used in the model. The results from this study also form the basis of the switching analysis performed by Helen Bell-Gorrod and Nick Latimer to support the waning assumptions. This study was not included in the economic model due to a lack of a comparator arm. Due to the nature of extension studies and their inherent heterogeneity we were unable to include the CLARITY-EXT study in a comparative analysis such as a MAIC.

The methodologies of CLARITY and CLARITY-EXT are summarised in Table 8.

Table 8: Comparative summary of trial methodology

Trial	CLARITY	CLARITY-EXT
Trial design	• Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week	• Phase IIIb double-blind, parallel group, multicentre, 96-week
Eligibility criteria for participants	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study • Clinically stable and not had a relapse within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	• Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks
Settings and locations where the data were collected	• 155 investigative sites in 32 countries (28 patients in 6 sites across the UK)	• 133 investigative sites in 32 countries (11 patients in 6 sites across the UK)
Trial drugs - Interventions and comparators (dosing regimens are detailed in Section B.2.3.2)	Patients (N=1,326) were randomised (1:1:1) to receive: • LL: Cladribine Tablets 3.5 mg/kg cumulative over 96 weeks (n=433) • HL: Cladribine Tablets 5.25 mg/kg cumulative over 96 weeks (n=456) • PP: Placebo (n=437)	Patients from CLARITY (N=883) were randomised (2:1) to receive either further doses of Cladribine Tablets (LL) or placebo (PP)**; resulting in five treatment groups: • LLPP - cumulative 3.5 mg/kg* (n=98) • LLLL- cumulative 7.0 mg/kg (n=186) • PPLL - cumulative 3.5 mg/kg (n=244) • HLLL - cumulative 8.75 mg/kg (n=186) • HLPP - cumulative 5.25 mg/kg (n=92)
Trial drugs - permitted and disallowed concomitant medication	• Corticosteroids were permitted to treat acute relapses however, long-term use (>14 days) necessitated patient withdrawal • IFN-β1a (Rebif) was permitted as rescue medication following 24 weeks from the start of the trial – to qualify for Rebif rescue medication, patients had to meet the following criteria: o Patients who experience >1 qualifying relapse, and/or o Patients who have a sustained increase in their EDSS of ≥1 point (or ≥1.5 points if baseline EDSS was 0) over a period of 3 months or greater)	
Primary outcomes (including scoring methods and timings of assessments)	• Qualifying ARR – defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24	• Safety and tolerability

Trial	CLARITY	CLARITY-EXT
	hours, and preceded by ≥30 days of clinical stability or improvement	
Other outcomes used in the economic model/specified in the scope	• Disability progression • Mortality • Adverse effects of treatment • HRQoL • NEDA-3 (post-hoc) • 6-month CDP (post-hoc)	• Outcomes from CLARITY-EXT were not included in the economic model
Pre-planned subgroups	*Prior treatment* • Treatment-naïve • Treatment-experienced	*Prior treatment* • Treatment-naïve • Treatment-experienced *Treatment gap duration* • ≤4 weeks • >4 weeks to ≤43 weeks • >43 weeks
Post-hoc subgroups (defined in Section B.2.1)	• HDA-RRMS (licensed population) • RES-RRMS • SOT-RRMS	• HDA-RRMS (licensed population) • RES-RRMS

SOURCE: (Giovannoni 2010; Cook 2016)

* Licensed dose for Cladribine Tablets

** Results from CLARITY demonstrated that there were no considerable differences in the efficacy and safety of 3.5 mg/kg Cladribine Tablets and 5.25 mg/kg Cladribine Tablets. As such, 5.25 mg/kg Cladribine Tablets was omitted from the CLARITY-EXT trial

ARR: Annualised relapse rate; CDP: Confirmed disease progression; EDSS: Expanded disability status scale; H: High-dose Cladribine Tablets over 48 weeks; HDA-RRMS: High disease activity; HRQoL: Health-related quality of life; IFN-β1a: Interferon-β1a; L: Low-dose Cladribine Tablets over 48 weeks; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; P: Placebo; RES-RRMS: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT-RRMS: Sub-optimal therapy

B.2.3.1. Trial design

The methodologies of each study are described in Table 8. Briefly, CLARITY is the pivotal Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week trial that supports the MA for Cladribine Tablets (Giovannoni 2010). CLARITY-EXT was an Phase IIIb double-blind, parallel group, multicentre, 96-week extension trial of CLARITY that provides supportive evidence for sustained efficacy (i.e. 2 years of treatment and no further treatment required in years 3 and 4) (Cook 2016).

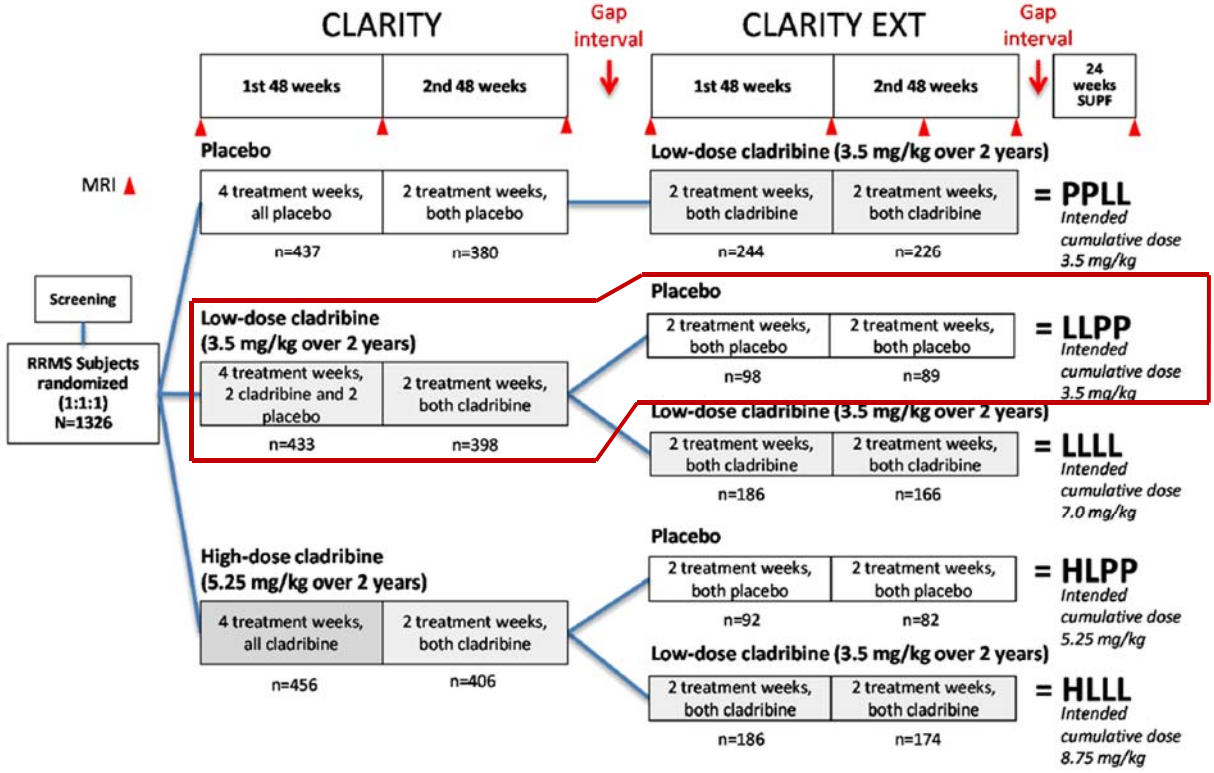
In CLARITY, a total of 1,326 patients were randomised 1:1:1 to receive 5.25 mg/kg dose Cladribine Tablets (HL), 3.5 mg/kg Cladribine Tablets (LL) or placebo (PP). Upon completion of CLARITY, patients were then eligible for entry into CLARITY-EXT. In total, 883 patients were screened and 806 patients participated in the CLARITY-EXT follow-up trial. Patients eligible for inclusion in the CLARITY-EXT trial were re-randomised (2:1) to receive either 3.5 mg/kg Cladribine Tablets (LL) or placebo (PP) (Cook 2016).

As a result, the overall distribution of patients across the two trials over 4 years was as follows:

- LLPP (licensed dose) - cumulative 3.5 mg/kg Cladribine Tablets (n=98)
- LLLL- cumulative 7.0 mg/kg Cladribine Tablets (n=186)
- PPLL - cumulative 3.5 mg/kg Cladribine Tablets (n=244)
- HLLL - cumulative 8.75 mg/kg Cladribine Tablets (n=186)
- HLPP - cumulative 5.25 mg/kg Cladribine Tablets (n=92)

Upon successful completion of the double-blind phase of CLARITY-EXT (up to 96 weeks), all patients were offered participation in the 24-week supplemental follow-up (SUPF) period. No treatment was given during the SUPF and patients were followed for clinical, laboratory, and MRI assessments (Cook 2016). A schematic of the trial design incorporating both CLARITY and CLARITY-EXT trials is illustrated in Figure 7.

Figure 7: Summary of CLARITY and CLARITY-EXT trial designs



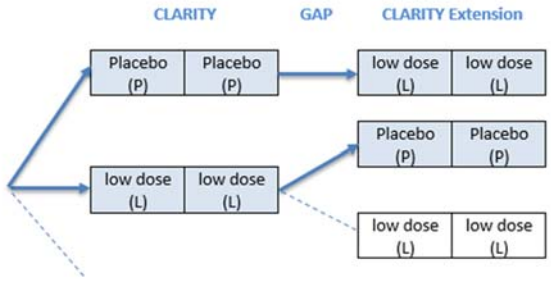
SOURCE: (Merck 2017f)

NOTE: Red box indicates the licensed dose

H: High-dose Cladribine Tablets over 48 weeks; L: Low-dose Cladribine Tablets over 48 weeks; P; Placebo; SUPF: Supplemental follow-up

It should be noted that across the 4 years of study treatment, there was no continuous placebo arm. Patients randomised to the placebo arm during the 2-year CLARITY trial and continued into CLARITY-EXT were switched to Cladribine Tablets 3.5 mg/kg (Figure 8). Based on regulatory advice, it would be unethical to withhold active treatment from patients with active RRMS over 4 years. Within oncology, treatment cross-over is a common occurrence but poses challenges when interpreting data for reimbursement. There is a well-established technique for estimating the treatment effect in these trials (DSU 16). Merck approached authors of the DUS16 guidance; Dr Nick Latimer (Health Economics and Decision Science; ScHARR, University of Sheffield) to determine the feasibility of conducting a similar approach to evaluate the treatment effect of Cladribine Tablets relative to placebo in the CLARITY-EXT trial. The findings of this analysis are reported in B.2.9.1.

Figure 8: Treatment switching analysis



SOURCE: (Merck 2017f)

L: Low-dose Cladribine Tablets over 48 weeks; P; Placebo

Due to the delay in the initiation of CLARITY-EXT, some patients who completed CLARITY were not immediately enrolled into CLARITY-EXT, resulting in a treatment gap period of varying lengths of time for each patient. During this between-trial period, patients were not monitored under controlled conditions, occurrences of relapses were self-reported and patients were able to receive alternative treatment for relapses. The median length of the gap period was 41 weeks (range: 0.1 weeks – 116 weeks) (Cook 2016). A total of 6 patients received treatment for a relapse during the gap period. To mitigate any potential bias or inconsistencies due to the variation in the gap period, and/or use of additional DMTs, the following procedures were performed (Cook 2016):

- Data regarding DMT use and relapses during the gap period were collected retrospectively and also prior to entry into CLARITY-EXT to establish baseline characteristics
- Patient baseline characteristics were reassessed upon entry into CLARITY-EXT to ensure measurements such as EDSS scores were captured as a starting point in the assessment of disease progression
- The time to first qualifying relapse was assessed across both the gap period (including data from the start of CLARITY to the end of CLARITY-EXT) and excluding the gap period (using CLARITY-EXT baseline as the starting point)
- The baseline MRI scan for CLARITY-EXT was taken at CLARITY-EXT study day 1 for patients who had a gap of longer than 4 weeks between CLARITY and CLARITY-EXT. For patients with a gap period of less than 4 weeks, the CLARITY 96-week scan was used as a baseline measurement of MRI lesions for CLARITY-EXT

A summary of the results from the analysis of patients in the treatment gap period are presented in Section B.2.7.2 and show that there was no consistent or meaningful relationship between the duration of the gap period and the majority of efficacy endpoints. In fact clinicians view the treatment gap as evidence of duration of efficacy beyond 4 years in some patients.

Furthermore, the baseline patient demographics in CLARITY were similar for those patients who did or did not enter CLARITY-EXT (Table 9).

Table 9: Summary baseline demographics of patients who did and did not enter CLARITY-EXT

	Patients entered and randomised into CLARITY-EXT			**Patients who never entered CLARITY-EXT**		
	Placebo (n=244)	**3.25 mg/kg (n=284)**	**5.25 mg/kg (n=278)**	**Placebo (n=171)**	**3.25 mg/kg (n=132)**	**5.25 mg/kg (n=156)**
Median age (years)	38.0	38.0	39.0	39.0	36.0	40.0
Sex female, n (%)	156 (63.9)	191 (67.3)	184 (66.2)	121 (70.8)	94 (71.2)	110 (70.5)
Disease duration (years), mean (SD)	4.82 (4.81)	4.36 (5.11)	4.86 (5.00)	5.68 (6.25)	5.09 (5.66)	5.43 (5.79)
Relapses in prior 12 months, n (%)						
0	0	0	0	0	0	2 (1.3)
1	179 (73.4)	203 (71.5)	193 (69.4)	114 (66.7)	87 (65.9)	110 (70.5)
2	57 (23.4)	65 (22.9)	73 (26.3)	45 (26.3)	37 (28.0)	38 (24.4)
≥3	8 (3.3)	16 (5.6)	12 (4.3)	12 (7.0)	8 (6.1)	6 (3.8)
EDSS at baseline, mean (SD)	2.81 (1.29)	2.79 (1.24)	2.92 (1.32)	3.15 (1.35)	2.93 (1.27)	3.10 (1.41)
Number of T1 Gd+ lesions at baseline, mean (SD)	0.9 (2.4)	1.1 (3.1)	1.0 (2.3)	0.7 (1.6)	0.9 (1.9)	0.9 (2.1)
Number of T2 lesions at baseline, mean (SD)	27.1 (17.8)	25.6 (17.6)	27.3 (15.6)	28.0 (18.2)	24.8 (13.6)	28.2 (17.5)

SOURCE: (Merck 2017a)

The full list of inclusion and exclusion criteria for CLARITY and CLARITY-EXT, and geographical locations for both trials are detailed in the Appendix D.

B.2.3.2. Trial drugs and concomitant medications

CLARITY evaluated Cladribine Tablets in two doses compared with placebo (Giovannoni 2010):

- High dose Cladribine Tablets (5.25 mg/kg cumulative)
- Low-dose Cladribine Tablets (3.5 mg/kg cumulative)

The CLARITY trial was divided into two 48-week treatment periods (year 1 and year 2) with four 28-day treatment cycles in year 1 (Week 1, Week 5, Week 9, Week 12) and two 28-day treatment cycles in year 2 (Week 48 and Week 52). Cladribine Tablets or placebo was administered orally as one or two 10 mg tablets for the first 4 or 5 days of each 28-day treatment cycle. Cladribine Tablets were given as 0.875 mg/kg/cycle. The number of tablets administered was standardised based on weight, using 10 kg weight ranges (i.e. 60 kg-69.9 kg, 70 kg-79.9 kg, etc.) (Table 10) (Giovannoni 2010).

Table 10: Dosing regimen for CLARITY

Treatment arms	Year 1				Year 2				Total cumulative dose over 96 weeks
	Cycle 1		Cycle 2		Cycle 1		Cycle 2		
	Week 1	Week 5	Week 9	Week 13	Week 48	Week 52	Week 56	Week 60	
Placebo (n=437)	P	P	P	P	P	P	-	-	-
LL (N=433)	C	C	P	P	C	C	-	-	3.5 mg/kg
HL (N=456)	C	C	C	C	C	C	-	-	5.25 mg/kg

SOURCE: (Giovannoni 2010)

C: Cladribine Tablets (active dose) given as 0.875 mg/kg/cycle; H: High-dose Cladribine Tablets over 48 weeks; L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo tablets

Following the four treatment periods within the first year of CLARITY, patients were assessed during follow-up visits at weeks 16, 24, 36, 44 and 48 to assess their safety status prior to commencement of the second year of treatment. Crucially, lymphocyte counts were monitored at week 44, to ensure that patients were not experiencing lymphopenia, a treatment-emergent adverse event (TEAE) due to the inherent mechanism of action of Cladribine Tablets. All patients had to have a total lymphocyte count of >500 mm^3 at-week 44 before receiving treatment at-week 48. Patients who had a total lymphocyte count of <500 mm^3 were not given the second cycle of treatment, but continued in the trial for regular assessments until-week 96/early termination (Giovannoni 2010; Cook 2016).

Results from CLARITY demonstrated that there were no considerable differences in the efficacy and safety of 3.5 mg/kg Cladribine Tablets and 5.25 mg/kg Cladribine Tablets. As such, 5.25 mg/kg Cladribine Tablets was omitted from the CLARITY-EXT trial (Giovannoni 2010).

The dosing regimen in CLARITY-EXT was similar to that in CLARITY (Table 10), where patients were treated at Weeks 1, 5, 48 and 52 with Cladribine Tablets as 0.875 mg/kg per 28-day treatment cycle. Unlike the CLARITY trial, no treatment was administered at Week 9 or Week 13, resulting in an equivalent LL or PP arm in the CLARITY-EXT trial (Cook 2016). This dosing regimen resulted in the formation of the following five treatment arms, based on overall cumulative dose of Cladribine Tablets over the course of both CLARITY and CLARITY-EXT (Cook 2016).

In addition to the trial drugs, the use of corticosteroids was permitted to treat acute relapses in both CLARITY and CLARITY-EXT. Patients requiring long-term use of corticosteroids (>14 days) were withdrawn from the trial (Giovannoni 2010; Cook 2016). Patients experiencing a relapse during the trial were given the option to use 'rescue therapy' after 24 weeks from the start of the trial and in patients who met the following criteria (Giovannoni 2010; Cook 2016):

- Experiencing more than one qualifying relapse, and/or
- Experiencing a sustained increase in their EDSS of ≥1 point (or ≥1.5 points if baseline EDSS was 0) over a period of 3 months or greater

The preferred rescue therapy specified in CLARITY and CLARITY-EXT was interferon-β1a (IFN-β1a), supplied by Merck. Other DMTs were also permitted if the patient and investigator decide that it was considered necessary for the patient's welfare. Patients who received rescue therapy were permanently discontinued from the trial medication but remained in the trial to provide all assessments according to the visit schedule (Giovannoni 2010; Cook 2016).

B.2.3.3. Trial outcomes

The pre-specified primary and secondary and outcomes for CLARITY and CLARITY-EXT are summarised in Table 11. The key outcomes from CLARITY used in the economic model include the primary outcome of ARR, disability progression, adverse events and HRQoL results. Additional secondary outcomes included in CLARITY were MRI measures (Giovannoni 2010).

The outcomes from CLARITY-EXT were not included in the economic model, however, exploratory clinical and MRI outcomes were considered in the analysis to support the claim that the majority of patients do not require further treatment following completion of the two indicated treatment courses of 3.5 mg/kg Cladribine Tablets (Cook 2016).

Table 11: Pre-planned trial outcomes for CLARITY and CLARITY-EXT

Outcomes	CLARITY	CLARITY-EXT
Primary outcome	• Qualifying ARR - defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement	• Safety and tolerability
Secondary/ exploratory outcomes	*Clinical efficacy:* • Proportion of relapse-free patients • Time to 3-month CDP • Time to use of rescue therapy *MRI efficacy:* • Mean number and proportion of patients with: o T1 Gd+ lesions o T2 lesions o CU lesions o T1 hypointense lesions • Volume of: o T2 lesions o T1 hypointense lesions *Safety and tolerability:* • Proportion of patients with AEs *Other outcomes:* • HRU • HRQoL • Effect of treatment on relapses • Effect of treatment on disability • Mortality • Time to use of rescue therapy	*Clinical efficacy:* • Qualifying ARR • Proportion of relapse-free patients • Time to first and second relapse • Time to 3-month CDP • Time to use of rescue therapy *MRI efficacy:* • Mean number, cumulative number and proportion of patients with: o T1 Gd+ lesions o T2 lesions o CU lesions o T1 hypointense lesions • Volume of: o T2 lesions o T1 hypointense lesions *Other outcomes:* • HRU • HRQoL • Characterisation of immune cell subsets • Immune competence • Gene expression profiles

SOURCE: (Giovannoni 2010; Cook 2016)

AE: Adverse events; ARR: Annualised relapse rate; CDP: Confirmed disease progression; CU: Combined unique; Gd+: Gadolinium-enhancing; HRQoL: Health-related quality of life; HRU: Healthcare resource use; KFS: Kurtzke Functional systems

This evaluation contains three sub-populations of the original CLARITY clinical trial; the licensed population (adult patients with highly active RRMS) and its own constituent subgroups, RES-RRMS and SOT-RRMS (as defined by NICE) (NICE 2017a).

A summary of the post-hoc analysis are presented in Table 12 (Giovannoni 2011; Cook 2016).

Table 12: Post-hoc analyses for CLARITY and CLARITY-EXT for all populations

Trial	Outcome	Definition
CLARITY	NEDA-3	• No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions
	Time to 6 month CDP	• CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0
	Proportion of patients with 6-month CDP	
CLARITY-EXT	NEDA-3	• No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions
	Time to 6 month CDP	• CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0
	Proportion of patients with 6-month CDP	
	Clinical and MRI efficacy outcomes as described for pre-planned CLARITY analyses	• See CLARITY in Table 11

SOURCE: (Giovannoni 2011; Cook 2016)

CDP: Confirmed disease progression; EDSS: Expanded disability status scale; Gd+: Gadolinium-enhancing; NEDA: No evidence of disease activity

B.2.3.4. Patient characteristics

The baseline characteristics of the patients were generally well-balanced in all treatment arms, although a numerically higher percentage of patients in the placebo arm were treatment experienced (30.2% vs. 25.4%, respectively) this was not statistically significant (Giovannoni 2011; Cook 2016). Approximately two thirds of each treatment arm was female (65.9% in placebo arm, 68.8% in the 3.5 mg/kg Cladribine Tablets arm) with a mean disease duration of approximately 5 years. The clinical presentation of RRMS symptoms was also similar between treatments arms (mean EDSS score, number of T1 Gd+ lesions and T2 lesions) (Giovannoni 2011; Cook 2016). The characteristics of patients at baseline for CLARITY are summarised in Table 13. In the CLARITY-EXT trial, the LLPP treatment group had similar patient characteristics as those from the CLARITY trial however only 18% of patients were treatment experienced and the mean disease duration was also lower; mean EDSS remained comparable.

Table 13: Baseline characteristics of patients in CLARITY and CLARITY-EXT (ITT analysis)

Characteristic	CLARITY		CLARITY-EXT
	Placebo (n=437)	Cladribine Tablets 3.5 mg/kg (n=433)	LLPP 3.5 mg/kg (n=98)
Mean (SD) age, years	38.7 (9.9)	37.9 (10.3)	38.1 (10.6)
Female, %	65.9	68.8	68.4
Previous DMT use, %	30.2	25.4	18.4
Mean disease duration, years	5.2	4.7	3.9
Mean (SD) EDSS	2.9 (1.3)	2.8 (1.2)	2.9
Mean (SD) T1 Gd+ lesions	0.8 (2.1)	1.0 (2.7)	0.3 (1.0)
Mean (SD) T2 lesions	27.4 (17.7)	25.3 (16.3)	39.0 (26.2)

SOURCE: (Giovannoni 2011; Cook 2016)

DMT: Disease-modifying treatment; EDSS: Expanded disability status score; Gd+: Gadolinium-enhancing; SD: Standard deviation

Table 14: Comparative characteristics of patient subgroups in CLARITY

CLARITY	Placebo subgroups			Cladribine Tablets 3.5 mg/kg subgroups		
	HDA-RRMS (n=149)	RES-RRMS (n=41)	SOT-RRMS (n=32)	HDA-RRMS (n=140)	RES-RRMS (n=50)	SOT-RRMS (n=19)
Mean (SD) age, years	37.1 (10.2)	33.3 (8.2)	38.0 (8.8)	36.3 (9.5)	33.4 (7.9)	34.7 (8.0)
Female, %	63.1	58.5	68.8	72.9	72.0	73.7
Previous DMT use, %	37.6	24.4	100.0	32.9	34.0	100.0
Mean disease duration, years	4.8	3.9	7.6	3.9	2.9	5.8
Mean (SD) EDSS	3.0 (1.4)	2.9 (1.4)	3.6 (1.6)	2.9 (1.3)	2.8 (1.4)	3.2 (1.5)
Mean (SD) T1 Gd+ lesions	1.0 (2.8)	3.5 (4.6)	1.2 (2.1)	1.3 (3.5)	3.6 (5.6)	0.5 (0.8)
Mean (SD) T2 lesions	29.9 (19.8)	36.8 (24.4)	35.7 (21.1)	25.2 (17.2)	31.6 (16.8)	26.6 (18.1)

SOURCE: (Giovannoni 2011; Cook 2016)

DMT: Disease-modifying treatment; EDSS: Expanded disability status score; Gd+: Gadolinium-enhancing; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SD: Standard deviation; SOT-RRMS: Sub-optimal therapy

Table 15: Comparative characteristics of patient subgroups in CLARITY-EXT

CLARITY-EXT	LLPP subgroups		
	HDA-RRMS (n=31)	RES-RRMS (n=13)	SOT-RRMS (n=4)
Mean (SD) age, years	36.2 (11.3)	29.9 (9.4)	No statistical analysis was available due to small sample size
Female, %	74.2	76.9	
Previous DMT use, %	29.0	30.8	
Mean disease duration, years	2.2 (3.0)	2.3 (2.6)	
Mean (SD) EDSS	2.9 (1.5)	2.4 (1.6)	
Mean (SD) T1 Gd+ lesions	0.6 (1.6)	1.3 (2.3)	
Mean (SD) T2 lesions	34.0 (22.0)	33.1 (17.1)	

SOURCE: (Giovannoni 2011; Cook 2016)

DMT: Disease-modifying treatment; EDSS: Expanded disability status score; Gd+: Gadolinium-enhancing; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SD: Standard deviation; SOT-RRMS: Sub-optimal therapy

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The primary objective in CLARITY was to evaluate the efficacy of Cladribine Tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in patients with active RRMS. To achieve this objective, the primary analysis was conducted in the intention-to-treat (ITT) patient population using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable in the model. Responses for patients with missing relapse, EDSS progression, or MRI lesion status were imputed on the basis of data for patients with a known status (i.e. either free or not free) at the end of 96 weeks. Imputation for secondary endpoints was performed according to the statistical analysis plan (SAP).

CLARITY-EXT was designed to evaluate the safety of extended treatment with Cladribine Tablets when administered according to a fixed annual dosing schedule to subjects who completed CLARITY. The primary safety analysis was conducted in all patients who received at least one dose of Cladribine Tablets and had at least one safety assessment during the course of the trial while efficacy analyses were performed using the ITT patient population. Missing data in the form of partial dates of patient history (including MS history, history of DMT use, relapse history, and relapses), concomitant medication use, adverse events (AEs) and AE severity, and unscheduled assessments were handled according to the SAP.

A summary of the statistical analyses for both CLARITY and CLARITY-EXT are presented in Table 16.

Table 16: Summary of statistical analyses

Trial	CLARITY	CLARITY-EXT
Hypothesis objective	To evaluate the efficacy of Cladribine Tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in patients with RRMS	To evaluate the safety of extended treatment with oral cladribine when administered according to a fixed annual dosing schedule to subjects who completed CLARITY
Statistical analysis	• The ARR endpoint was analysed using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable • An approximate Chi-square test based on Wald statistics was used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error	
Sample size, power calculation	A sample size of 1,290 patients (430 patients in each treatment arm) provided 90% power to detect a clinically meaningful 25% relative reduction in ARR at 96 weeks when comparing each Cladribine Tablets arm to the placebo arm*	A total of 1,326 subjects were randomized into CLARITY, of whom 867 completed CLARITY and enrolled in CLARITY-EXT. The number of subjects eligible to enter CLARITY-EXT was limited by the enrolment, retention, and rollover of subjects from the preceding CLARITY study. Therefore, no statistical estimation of the sample size was performed.
Data management, patient withdrawals	• The investigator was responsible for data management, ensuring eCRFs were completed appropriately to ICH GCP standards • Patients could withdraw from the trial at any time, but were asked to continue with all trial assessments and return for the week 96/early termination visit • Withdrawal was mandatory if the patient initiated treatment with another investigational drug, was non-compliant or violated protocol	

* Calculated using a 2-sided t-test assuming 1) the mean number of qualifying relapses during 96 weeks was 2.1 for the placebo treatment arm, 2) a relative 25% reduction in mean number of qualifying relapses and 3) a common standard deviation of 2.02 for the number of qualifying relapses, a 10% non-evaluable rate and a type I error rate for each Cladribine Tablets group versus the placebo group at 2.5%

ARR: Annualised relapse rate; eCRFs: Electronic case report forms; GCP: Good clinical practice; ICH: International Conference on harmonisation; RRMS: Relapsing-remitting multiple sclerosis

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 17: Quality assessment of the relevant clinical effectiveness evidence

Trial	CLARITY	CLARITY-EXT
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Appropriate methods were used to account for missing data*	Yes. Appropriate methods were used to account for missing data*

*Merck believe that the methods to account for missing data was more appropriate in the post-hoc analyses presented here compared with the CSR

B.2.6 Clinical effectiveness results of the relevant trials

The primary, secondary and tertiary analyses performed for CLARITY and CLARITY-EXT were conducted in the ITT patient population. Pre-specified and post-hoc subgroup analyses are presented in Section B.2.7. Note that only the Cladribine Tablets 3.5 mg/kg treatment groups from CLARITY and CLARITY-EXT will be discussed in this submission given that this is the anticipated licensed dose.

It should be noted that in the post-hoc analysis submitted to regulatory agencies, Merck amended its approach to the handling of missing data Hence there may be minor discrepancies in results presented here and those in the original Clinical Study Report (CSR) for CLARITY, which was prepared in 2010. All analyses reported in this submission are consistent in their approach to handling missing data with the statistics package submitted to EMA.

B.2.6.1. CLARITY

Overall, the results demonstrate that treatment with 3.5 mg/kg Cladribine Tablets was more effective than placebo in patients with RRMS across a broad spectrum of clinical and MRI efficacy outcomes (Merck 2017c). Cladribine Tablets were shown to statistically significantly reduce the qualifying ARR compared with placebo ($p<0.001$) and the risk of developing 6-month CDP was shown to be statistically significantly reduced compared with placebo ($p=0.0014$), as determined during the post-hoc analyses. Cladribine Tablets 3.5 mg/kg was also associated with an overall improvement in MRI outcomes such as the mean number of new T1 Gd+ and active T2 lesions. In a post-hoc analysis, the proportion of patients with NEDA-3 following treatment with 3.5 mg/kg Cladribine Tablets was shown to be significantly higher compared with placebo ($p<0.0001$) (Merck 2017c). A full description of the results from CLARITY is described below.

B.2.6.1.1. Endpoints associated with relapses

Qualifying ARR and time to first qualifying relapse in CLARITY

In the ITT population, treatment with 3.5 mg/kg Cladribine Tablets was associated with a statistically significant 58.22% relative reduction in qualifying ARR compared with placebo (0.14 vs. 0.34, respectively; $p<0.001$) (Table 18) (Merck 2017c).

Treatment with Cladribine Tablets was associated with a significant delay in the time to first qualifying relapse compared with placebo (HR: 0.45; 95% CI: 0.34, 0.58; $p<0.0001$) (Table 18). The Kaplan-Meier estimates show that while 61.1% (95% CI: 56.2, 65.6) of patients were relapse-free at the end of CLARITY following treatment with placebo, treatment with 3.5 mg/kg Cladribine Tablets resulted in 80.3% (95% CI: 76.1, 83.8) of patients who were relapse-free (Merck 2017c).

Table 18: Qualifying ARR at 96 weeks in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
Qualifying ARR at 96 weeks in CLARITY		
Qualifying ARR (95% CI)	0.14 (0.12, 0.17)	0.34 (0.30, 0.38)
Relative reduction in ARR, %	58.22	
Rate ratio (95% CI)	0.42 (0.33, 0.53)	
p-value	<0.001	
Time to first qualifying relapse in CLARITY		
K-M estimate of relapse-free patients, % (95% CI)	80.3 (76.1, 83.8)	61.1 (56.2, 65.6)
HR (95% CI) for Cladribine Tablets vs. placebo	0.45 (0.34, 0.58)	
p-value	<0.0001	

SOURCE: (Merck 2017c)

ARR: Annualised relapse rate; CI: Confidence interval; L: Low-dose Cladribine Tablets over 48 weeks; CI: Confidence interval; HR: Hazard ratio; L: Low-dose Cladribine Tablets over 48 weeks

Proportion of qualifying relapse-free patients

The proportion of patients who were qualifying relapse-free at 48 weeks was numerically higher in the 3.5 mg/kg Cladribine Tablets treatment group compared with placebo (81.5% and 68.6%, respectively) (Table 19). At the 96 week time point, the number of patients who were qualifying relapse-free remained higher in those from the 3.5 mg/kg Cladribine Tablets treatment group compared with placebo (75.5% vs. 54.2%) (Merck 2017c).

Table 19: Proportion of relapse-free patients at 96 weeks in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
Qualifying relapse-free at 48 weeks, n (%)		
Relapse	60 (13.9)	110 (25.2)
Relapse-free	353 (81.5)	300 (68.6)
Unknown*	20 (4.6)	27 (6.2)
Qualifying relapse-free at 96 weeks, n (%)		
Relapse	82 (18.9)	161 (36.8)
Relapse-free	327 (75.5)	237 (54.2)
Unknown*	24 (5.5)	39 (8.9)

SOURCE: (Merck 2017c)

* Patients who withdrew early before week 48/96 with no relapse are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CI: Confidence interval; L: Low-dose Cladribine Tablets over 48 weeks

B.2.6.1.2. Endpoints associated with disability

3-month confirmed disability progression

Treatment with 3.5 mg/kg Cladribine Tablets significantly prolonged the time to confirmed change in EDSS score over 96 weeks compared with placebo (p=0.0011) (Table 20). A reduction in the risk of disability progression at 96 weeks of 41% was observed in the 3.5 mg/kg Cladribine Tablets group versus placebo (HR: 0.59; 95% CI: 0.43, 0.81) (Merck 2017c).

Table 20: Time to 3-month confirmed disability progression in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
K-M estimate of progression-free patients, % (95% CI)	85.1 (81.3, 88.2)	76.3 (71.9, 80.2)
HR for Cladribine Tablets vs. placebo (95% CI)	0.59 (0.43, 0.81)	
p-value	0.0011	

SOURCE: (Merck 2017c)

CI: Confidence interval; HR: Hazard ratio; L: Low-dose Cladribine Tablets over 48 weeks

The absolute number of patients who were considered to be 3-month confirmed disability progression-free was considerably higher in patients who were treated with 3.5 mg/kg Cladribine Tablets at 48 weeks compared with placebo (Table 21). At 96 weeks (end of CLARITY), the same trend was observed where fewer patients treated with 3.5 mg/kg Cladribine Tablets had a 3-month confirmed disability progression compared with placebo (14.3% vs. 22.2%) (Merck 2017c).

Table 21: Proportion of patient with 3-month confirmed disease progression in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
3-month confirmed disability progression at 48 weeks, n (%)		
Progression	36 (8.3)	65 (14.9)
Progression -free	377 (87.1)	340 (77.8)
Unknown*	20 (4.6)	32 (7.3)
3-month confirmed disability progression at 96 weeks, n (%)		
Progression	62 (14.3)	97 (22.2)
Progression -free	344 (79.4)	292 (66.8)
Unknown*	27 (6.2)	48 (11.0)

SOURCE: (Merck 2017c)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

L: Low-dose Cladribine Tablets over 48 weeks

Post-hoc analysis of 6-month confirmed disability progression

In addition to a 3-month sustained disability progression analysis, the 6-month confirmed disability progression status of the patient population was also determined in a post-hoc analysis to demonstrate prolonged efficacy in the reduction of disability progression following 3.5 mg/kg Cladribine Tablets. The proportion of patients who remained free from a 6-month confirmed EDSS progression was significantly higher in patients treated with cladribine 3.5 mg/kg compared with placebo (90.6% vs. 83.3%; p=0.0014) (Table 22). Furthermore, the analysis demonstrated that patients treated with 3.5 mg/kg Cladribine Tablets were approximately 87% more likely to be free from a confirmed disability progression at 6 months (Merck 2017c).

The time to 6-month confirmed disability progression analysis is supplemented with absolute proportions of patients with 6-month confirmed disability progression. Over 48 weeks, the results show that 3.5 mg/kg Cladribine Tablets treatment resulted in fewer patients with a 6-month confirmed disability progression compared with placebo. This trend continued up to 96 weeks, to the end of CLARITY where only 9% of patients were reported to have a 6-month confirmed disability progression compared with 12.1% of patients from the placebo treatment group (Table 22) (Merck 2017c).

Table 22: 6-month confirmed disability progression in CLARITY (post-hoc analysis)

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
K-M estimate of progression-free patients, % (95% CI)	90.6 (87.4, 93.1)	83.3 (79.3, 86.6)
HR for Cladribine Tablets vs. placebo (95% CI)	0.53 (0.36, 0.78)	
p-value	0.0014	
6-month confirmed disability progression at 48 weeks, n (%)		
Progression	25 (5.8)	53(12.1)
Progression -free	386 (89.1)	348 (79.6)
Unknown*	22 (5.1)	36 (8.2)
6-month confirmed disability progression at 96 weeks, n (%)		
Progression	39 (9.0)	69 (15.8)
Progression -free	363 (83.8)	315(72.1)
Unknown*	31 (7.2)	53 (12.1)

SOURCE: (Merck 2017c)

CI: Confidence interval; HR: Hazard ratio; L: Low-dose Cladribine Tablets over 48 weeks;

* Patients who withdrew early before week 48/96 with no 6-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

B.2.6.1.3. Endpoints associated with MRI lesions

Results for endpoints associated with MRI lesions in CLARITY are presented in Appendix E.

In summary, treatment with 3.5 mg/kg Cladribine Tablets was shown to significantly reduce the overall number of T1 Gd+, active T2, combined unique (CU) and T1 hypointense lesions compared with placebo (p<0.0001 for all comparisons) (Merck 2017c). Furthermore, the proportion of patients shown to be free of MRI lesion activity was numerically higher following treatment with 3.5 mg/kg Cladribine Tablets compared with placebo (Merck 2017c).

These results demonstrate the efficacy of 3.5 mg/kg Cladribine Tablets and support the results associated with relapses and disability progression. Additional results on MRI lesion activity from CLARITY are discussed in Appendix E

B.2.6.1.4. Other endpoints

Additional pre-planned and post-hoc analyses were performed in the ITT population that were considered clinically important. However, those outcomes that do not drive the economic model for Cladribine Tablets and not considered to be relevant to the NICE Decision Problem are presented in Appendix E. These results include the following:

- MRI lesion activity - including T1 Gd+, T2, CU and T1 hypointense lesions)
- Severity of relapses – including relapses that led to hospitalisation, that did not lead to hospitalisation and treated with corticosteroids
- Confirmed worsening – EDSS ≥6

NEDA-3

NEDA-3 is a composite clinical outcome defined as no relapses, no 3-month confirmed EDSS progression, no new or enhancing T1 Gd+ lesions and no new or enlarging T2 lesions. The results show that a significantly greater proportion of patients treated with 3.5 mg/kg Cladribine Tablets had no evidence of disease activity over the entire duration of CLARITY (p<0.0001) (Table 23) (Merck 2017c).

Company evidence submission template for Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Table 23: Post-hoc analysis of patients with NEDA-3 status in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
K-M estimate of NEDA-3 status, % of patients (95% CI)	40.1 (34.5, 45.6)	12.6 (8.8, 17.0)
HR for Cladribine Tablets vs. placebo (95% CI)	2.21 (1.88, 2.61)	
p-value	<0.0001	

SOURCE: (Merck 2017c)

CI: Confidence interval; HR: Hazard ratio; K-M: Kaplan-Meier: L: Low-dose Cladribine Tablets treatment over 48 weeks; NEDA: No evidence of disease activity

Rescue medication use

Fewer patients treated with 3.5 mg/kg Cladribine Tablets required rescue therapy (IFN-β1a) during CLARITY compared with patients from the placebo treatment group, where 3.2% patients treated with 3.5 mg/kg Cladribine Tablets were rescued compared with 6.9% patients treated with placebo (Table 24). The majority of patients who received rescue medication were treated with Rebif, the preferred DMT as stated in the protocol (85.7% patients in the 3.5 mg/kg Cladribine Tablets arm and 86.7% patients in the placebo arm). Patients were also rescued with GA, interferon- β1b, natalizumab and mitoxantrone (Merck 2017c).

Table 24: Proportion of patients rescued at 96 weeks in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets (LL) (N=433)	Placebo (N=437)
Patients receiving rescue therapy, n (%)	14 (3.2)	30 (6.9)
Mean duration of rescue medication, days (SD)	199.23 (124.00)	200.36 (137.55)

SOURCE: (Merck 2017c)

L: Low-dose Cladribine Tablets over 48 weeks; SD: Standard deviation

HRQoL

The change from baseline in HRQoL of patients in CLARITY was captured by the disease-specific HRQoL measure, MSQoL-54. Secondary HRQoL measures included the use of the EQ-5D visual analogue scale (VAS) and index. In addition, the short-form health survey (SF-36) was also implemented in CLARITY, however, this assessment was not initiated at the start of the trial and therefore the majority of baseline measurements were not reported. Consequently, it was not possible to perform treatment effect analyses on SF-36 scores (Merck 2017b).

Specifically, the MSQoL-54 physical function domain was used as the primary outcome measure in CLARITY, as this was considered to be the most appropriate for assessing physical limitations. However, the MSQoL-54 physical function score demonstrated no statistically significant differences between the 3.5 mg/kg Cladribine Tablets and placebo groups, irrespective of the analysis method used (p=0.424 and p=0.473 based on non-imputed and imputed results) (Merck 2017b).

As secondary outcome measures, MSQoL-54 outcome scores outside of the physical domain were assessed (Merck 2017b). Patients in the 3.5 mg/kg Cladribine Tablets treatment group showed better outcomes in the health distress domain compared with placebo, although this difference was not statistically significant (p=0.056). The adjusted mean change in score from baseline to 96 weeks for 3.5 mg/kg Cladribine Tablets and placebo groups for the other secondary MSQoL measures did not show any statistically significant differences. The lack of statistical significance may have been due to high ceiling effects suggesting that patients tended to have a good level of HRQoL when entering the CLARITY trial, leaving little room for improvement. This may partly explain the difficulty in showing any clear differences in change in MSQoL-54 scores between patients treated with 3.5 mg/kg Cladribine Tablets and those treated with placebo. Along with the generally good level of patients' HRQoL over the course of the trial, the use of generic PRO instruments, as well as the limited sample size for the

MSQoL-54 questionnaire, may have contributed to the inconclusive results of the treatment effect analysis(Merck 2017b).

Assessment of patient reported outcomes in the EQ-5D VAS and index scores showed that 3.5 mg/kg Cladribine Tablets resulted in a slight numerical improvement in non-disease specific HRQoL. Further analyses demonstrated that this improvement was statistically significant for both the EQ-5D VAS and EQ-5D index scores (p=0.001 and p<0.001, respectively) (Merck 2017b).

B.2.6.2. CLARITY-EXT

The primary objective of CLARITY-EXT was to evaluate the safety and tolerability of 3.5 mg/kg Cladribine Tablets (Cook 2016). As such, the efficacy outcomes from CLARITY-EXT were exploratory. In addition, all efficacy analyses presented in this section were conducted in the active RRMS patient population (ITT analysis). Pre-specified and post-hoc subgroup analyses are presented in Section B.2.7.

Qualifying relapses were considered in the analyses for CLARITY-EXT, similar to CLARITY. An exception to the definition of qualifying relapse was made for the gap periods between CLARITY and CLARITY-EXT and between the end of CLARITY-EXT and the start of SUPF phase. As there was no prospective data collection during these periods, relapse data were captured retrospectively and self-reported by patients at the first visit of the following study or phase. Accordingly, all relapses reported during the gap intervals were included, whether or not their qualifying status was confirmed. Analyses that consider the entire period from CLARITY to CLARITY-EXT including the treatment gap period between the two trials, are reported in this section unless otherwise specified. Note that only the LLPP treatment group is discussed in this submission given that this is the licensed dose for Cladribine Tablets (Cook 2016).

Overall, the efficacy outcomes of CLARITY-EXT demonstrated that the licensed dosage and posology of Cladribine Tablets was more effective than placebo.

B.2.6.2.1. Endpoints associated with relapses

Qualifying ARR

The ARR for patients who received a cumulative dose of 3.5 mg/kg Cladribine Tablets over 4 years (including CLARITY) in the LLPP treatment group was 0.15 (97.5% CI: 0.09, 0.21) (Table 25). In addition, the ARR was numerically higher during CLARITY-EXT in the LLPP treatment group than that observed in the respective CLARITY treatment group however this difference was not considered statistically significant (p=0.4526) (Merck 2017e).

Based on the analyses of qualifying relapses in CLARITY-EXT, it was observed that 62.9% (95% CI: 42.9, 77.6) of patients from the LLPP reporting group were relapse-free (Merck 2017e).

During CLARITY-EXT, a high proportion of LLPP patients were considered to be qualifying relapse-free (86.7%) at 48 weeks. Over the course of the trial, the proportion of patients qualifying as relapse-free decreased slightly at 96 weeks and by the end of the trial, 70.4% of patients from the LLPP treatment arm were qualifying relapse-free (Merck 2017e).

Table 25: Qualifying ARR in CLARITY-EXT

Outcome	LLPP (N=98)
Relapses during CLARITY	
Number of qualifying relapses, mean (SD)	0.25 (0.59)
ARR (95% CI)	0.10 (0.06, 0.15)
Relapses during CLARITY-EXT	
Number of qualifying relapses, mean (SD)	0.35 (0.79)
ARR (95% CI)	0.15 (0.11, 0.21)
ARR during CLARITY vs. CLARITY-EXT	
Relative reduction	41.92
Median difference (97.5% CI)	0.00 (0.00, 0.00)
p-value	0.4526

SOURCE: (Merck 2017e)

Note: The CLARITY-EXT data in this table covers the 96-week double-blind phase and the 24-week SUPF phase (including the gap between periods)

ARR: Annualised relapse rate; CI: Confidence interval; L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo; SD: Standard deviation; SUPF: 24-week supplemental follow-up period

B.2.6.2.2. Endpoints associated with disability

3-month confirmed disability progression

In terms of time to 3-month confirmed disability progression, Kaplan-Meier estimates at last event indicated that 78.2% (95% CI: 67.2, 85.9) of patients were free from 3-month confirmed disability progression (Merck 2017e).

It was observed that the absolute proportion of patients from the LLPP treatment group considered to be free from 3-month confirmed disability progression at 48 weeks was 90.8% (Table 26). Throughout the duration of the trial, the proportion of patients with 3-month confirmed disability progression decreased slightly at 96 weeks and by end of the trial, 73.5% of patients from the LLPP treatment group were free from 3-month confirmed disability progression (Merck 2017e).

Table 26: Proportion of patients with 3-month confirmed disability progression at 96 weeks in CLARITY-EXT

Outcome	LLPP (n=98)
3-month confirmed disability progression at 48 weeks, n (%)	
Progression	5 (5.1)
Progression-free	89 (90.8)
Unknown*	4 (4.1)
3-month confirmed disability progression at 96 weeks, n (%)	
Progression	13 (13.3)
Progression-free	77 (78.6)
Unknown*	8 (8.2)
3-month confirmed disability progression at end of study, n (%)	
Progression	18 (18.4)
Progression-free	72 (73.5)
Unknown*	8 (8.2)

SOURCE: (Merck 2017e)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

** End of the study refers to the end of the 24-week SUPF period

L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo

Post-hoc analysis of 6-month confirmed disability progression

The Kaplan-Meier estimates determined for the time to 6-month confirmed disability progression showed that 85.2% (95% CI: 75.6, 91.2) of patients were free from 6-month confirmed disability progression (Merck 2017e).

Over the first 48 weeks of the CLARITY-EXT trial, similar to the results in CLARITY, the absolute proportion of patients from the LLPP treatment arm shown to be free from 6-month confirmed disability progression was 90.8%. At 96 weeks, there was a slight decrease in the proportion of patients without a 6-month confirmed disability progression and by the end of the study, 78.6% of patients were free from 6-month confirmed disability progression (Table 27) (Merck 2017e).

Table 27: Proportion of patients with 6-month confirmed disability progression at 96 weeks in CLARITY-EXT

Outcome	LLPP (n=98)
6-month confirmed disability progression at 48 weeks, n (%)	
Progression	5 (5.1)
Progression-free	89 (90.8)
Unknown*	4 (4.1)
6-month confirmed disability progression at 96 weeks, n (%)	
Progression	11 (11.2)
Progression-free	79 (80.6)
Unknown*	8 (8.2)
6-month confirmed disability progression at end of study, n (%)	
Progression	13 (13.3)
Progression-free	77 (78.6)
Unknown*	8 (8.2)

SOURCE: (Merck 2017e)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo

B.2.6.2.3. Endpoints associated with MRI lesions

For each lesion type assessed, the cumulative number of lesions across all scans was defined as the sum of the lesions of that type on all available scans from both scheduled and unscheduled visits during the study period (in the assessment of new T1 Gd+ lesions and new T1 hypointense lesions, baseline scans were excluded) (Merck 2017e).

The mean number of lesions per patient per scan during the study was defined as the cumulative number of lesions of that type divided by the number of available scans during the study period (Merck 2017e).

It should be noted that given the varying lengths of time and clinical events that occurred in the treatment gap periods for CLARITY-EXT patients following the end of the CLARITY trial, MRI results should be interpreted with caution. In particular, due to their transient nature, T1 Gd+ lesions that occurred during the gap period would only have been detected by CLARITY-EXT baseline MRI if their onset was a few weeks before entry into the CLARITY-EXT trial. Furthermore, the number and timing of MRI scans differed between CLARITY and CLARITY-EXT (scans were performed at weeks 24, 48, and 96 in CLARITY, and at weeks 24, 48, 72, and 96 during the double-blind phase of CLARITY-EXT). This

caution is particularly important for the analyses of cumulative numbers of MRI lesions and of proportions of lesion-free patients (Merck 2017e).

Overall, the reported MRI lesion activity in CLARITY-EXT support the results observed during CLARITY. Additional results on MRI lesion activity from CLARITY-EXT are discussed in Appendix E.

B.2.6.2.4. Other endpoints

NEDA-3

In the ITT population it was observed that 32.6% (95% CI: 23.20, 42.15) of patients from the LLPP treatment arm were free from disease activity, based on K-M estimates at 96 weeks (Merck 2017e).

Rescue medication use

Only seven of 806 subjects in the ITT analysis set received treatment with rescue medication during CLARITY-EXT, three of which were from the LLPP group (3.1%) (Merck 2017e).

HRQoL

Over the course of CLARITY and CLARITY-EXT, there was an overall improvement in HRQoL of patients in the LLPP treatment arm based on EQ-5D VAS and index scores, and MSQoL-54 mental and physical health composite scores (Merck 2017d).

B.2.7 Subgroup analysis

The RRMS patient population can be categorised into subgroups as determined by the patient experience with DMTs and by RRMS severity, the definitions of which are summarised in Table 28. The initial pre-planned analyses of treatment-naïve and treatment-experienced patient populations were incorporated into the initial CLARITY and CLARITY-EXT trials. Following the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice in December 2014, data from CLARITY was further analysed post-hoc to determine the benefits and risks of Cladribine Tablets in patient subgroups with high disease activity (HDA-RRMS), including those who have rapidly evolving severe (RES-RRMS) RRMS and those who have had sub-optimal therapy (SOT-RRMS) (European Medicines Agency 2017b).

The full dataset is summarised in Appendix E and a summary of the results are discussed in Section B.2.7.1 for the pre-planned subgroup analyses, Section B.2.7.2 for the treatment gap analyses and Section B.2.7.3 and Section B.2.7.4 for the post-hoc subgroup analyses.

Table 28: Definitions of RRMS subgroups

Analysis	Subgroup		Definition
Pre-planned	Treatment-naïve		Patients who have not had previous treatment
	Treatment-experienced		Patients who have received previous treatment
Post-hoc	RRMS with high disease activity (HDA-RRMS)*	RES-RRMS	Patients with ≥2 relapses in the prior year whether on treatment or not AND Patients with ≥1 T1Gd+ lesion
		SOT-RRMS	Patients with ≥1 relapse in the previous year while on treatment AND Patients with ≥1 T1 Gd+ lesion or ≥9 T2 lesions

* The highly active patient subgroup is the anticipated licensed indication according to the marketing approval application to the EMA and is applicable to patients with high disease activity

Gd+: Gadolinium-enhancing; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

B.2.7.1. Pre-planned subgroup analyses of CLARITY

The pre-planned subgroups of the CLARITY trial were an active RRMS patient population segmented by treatment history (treatment-naïve RRMS and treatment-experienced RRMS). Cladribine Tablets does not have MA for this patient population and therefore the results of these subgroups are not relevant to the NICE decision problem; therefore, these results have not been presented within this submission.

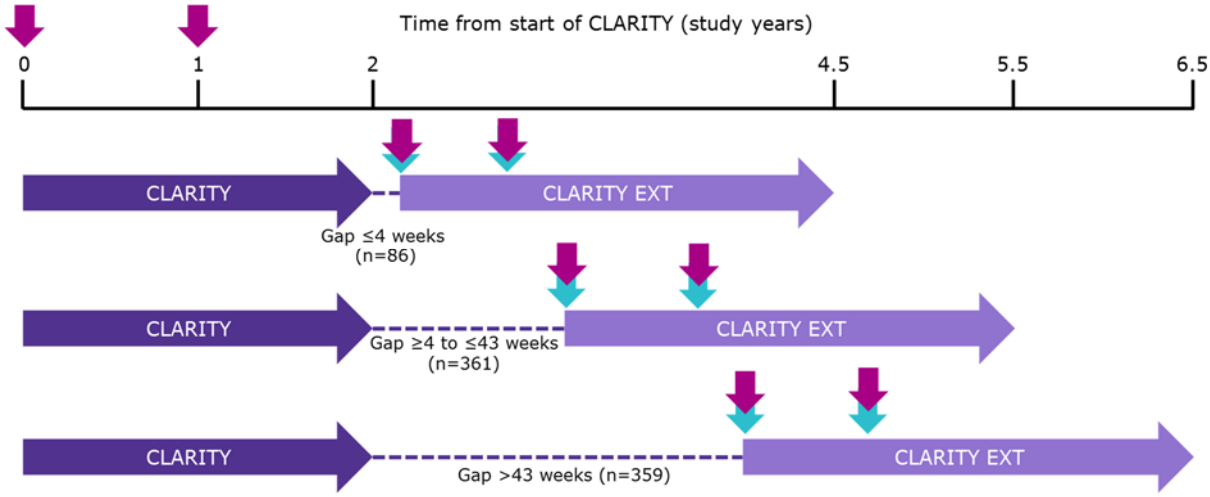
B.2.7.2. Treatment gap period

In parallel with the pre-planned analyses in CLARITY-EXT, additional analyses were performed to determine whether the duration of the treatment gap period between the end of CLARITY and the start of CLARITY-EXT had a significant effect on the outcomes of patients entered into the LLPP treatment arm. As such, patients were stratified by the duration of treatment gap period into the following subgroups:

- ≤4 weeks
- >4 weeks to ≤43 weeks
- >43 weeks

The median gap period (completion of CLARITY to the beginning of CLARITY Extension) was [redacted] however, this period ranged from [redacted] across all patients. The majority of patients were in the gap period for 43 weeks or less ([redacted] of patients) (Figure 9).

Figure 9: Timeline of patients who completed both CLARITY and CLARITY-EXT, including the gap period



Overall, the analysis suggests that for LLPP patients, there was no consistent or meaningful relationship between the duration of the gap period and the majority of efficacy endpoints.

Analysis of the qualifying ARR during CLARITY-EXT between subgroups defined by gap duration showed a minimal difference between LLPP patients (Merck 2017d). In addition, the mean number of qualifying relapses was similar between all three subgroups. These results suggest that gap duration was not an important predictor of both the number of qualifying relapses and the qualifying ARR during CLARITY-EXT. Furthermore, the results suggest that for LLPP patients, there was no relationship between the proportion of relapse-free patients and the duration of the gap period.

There was no clear relationship between the gap duration and change in EDSS score, with median changes in EDSS of zero for all gap duration categories, with the exception of the ≤4 weeks subgroup (median = 1.000) (Merck 2017d).

For MRI outcomes, the proportion of patients in the LLPP treatment group without active T2 lesions and the proportion of LLPP patients without CU lesions were similar for all three subgroups (Merck 2017e). In addition, the proportion of patients without new T1 Gd+ lesions was lower among patients with a gap duration >43 weeks [redacted] than among patients with a gap duration of >4 weeks and ≤43 weeks [redacted]

or patients with a gap duration of ≤4 weeks (87.5%) (Merck 2017e). The mean number of new T1 Gd+ lesions was higher among LLPP patients with a longer gap duration and the proportion of patients with a mean of ≥1 new T1 Gd+ lesion per scan were also higher among patients with gap duration >43 weeks compared with >4 and ≤43 weeks, and ≤4 weeks ([redacted] respectively) (Merck 2017e). Similar values were observed between the subgroups in the mean number of active T2 lesions per patient per scan, although a small difference between the subgroups was noted (Merck 2017e). The highest value was observed for patients with a gap period of between >4 weeks and ≤43 weeks ([redacted]), with a mean of 0.84 (1.16) observed for patients with a gap of ≤4 weeks and 1.10 ([redacted] for patients with a gap of >43 weeks between trials (Merck 2017e).

Overall, these analyses suggest that selection bias is unlikely to affect the conclusions of the CLARITY-EXT study.

B.2.7.3. Post-hoc subgroup analyses of CLARITY

The post-hoc analysis of the highly active RRMS subgroups identified that there were 140 patients with HDA-RRMS, 50 patients with RES-RRMS and 19 patients with SOT-RRMS in the cladribine 3.5 mg/kg Cladribine Tablets treatment arm (Table 29) (Merck 2017c).

Table 29: Patient distribution in subgroup populations of interest in CLARITY post-hoc subgroup analyses

Subgroup	Subgroup definition	3.5 mg/kg Cladribine Tablets	Placebo
ITT (active RRMS)	RRMS patients who have experienced ≥1 relapse in the previous year	N=433	N=437
HDA-RRMS	Patients with highly active disease as defined by clinical or imaging features	N=140	N=149
RES-RRMS	RRMS patients who have experienced ≥2 relapse in the previous year	[redacted]	[redacted]
SOT-RRMS	Patients previously treated with sub-optimal therapy	[redacted]	[redacted]

SOURCE: (Merck 2017c)

HDA-RRMS: High disease activity; ITT: Intention to treat; RES-RRMS: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT-RRMS: Sub-optimal therapy

B.2.7.3.1. Endpoints associated with relapses

PRIMARY OUTCOME: Qualifying ARR

Patients in the 3.5 mg/kg Cladribine Tablets treatment group with HDA-RRMS, RES-RRMS and SOT-RRMS all demonstrated a numerical reduction in qualifying ARR compared with placebo, consistent with the results for the ITT population. In addition, the reductions were shown to be statistically significant in patients with HDA-RRMS [redacted] (Merck 2017c).

Table 30: Qualifying ARR in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets (LL)	Placebo
HDA-RRMS, n	140	149
Qualifying ARR (95% CI)	0.16 (0.12, 0.22)	0.46 (0.38, 0.55)
Relative reduction in ARR, %	65.29	
Rate ratio (95% CI)	0.35 (0.24, 0.50)	
p-value	<0.0001	
RES-RRMS, n	[redacted]	[redacted]
Qualifying ARR (95% CI)	[redacted]	[redacted]
Relative reduction in ARR, %	[redacted]	
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	
SOT-RRMS, n	[redacted]	[redacted]
Qualifying ARR (95% CI)	[redacted]	[redacted]
Relative reduction in ARR, %	[redacted]	
Rate ratio (95% CI)	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017c)

ARR: Annualised relapse rate; HDA-RRMS: High disease activity; L: Low-dose Cladribine Tablets over 48 weeks; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

Time to first qualifying relapse

The HDA-RRMS subgroup analysis demonstrated that patients were at a significantly lower risk of experiencing a first qualifying relapse in the 3.5 mg/kg cladribine tablet groups compared with placebo (HR: 0.40; p<0.0001) (Table 31). In the RES-RRMS subgroup, the risk of experiencing a first qualifying relapse in the cladribine 3.5 mg/kg Cladribine Tablets treatment group were [redacted] with placebo [redacted]. However, [redacted] subgroup [redacted] (Merck 2017c)

Table 31: Time to first qualifying relapse in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets (LL)	Placebo
HDA-RRMS, n	140	149
K-M estimate of relapse-free patients, % (95% CI)	77.1 (68.8, 83.5)	53.3 (44.7, 61.2)
HR (95% CI) for Cladribine Tablets vs. placebo	0.40 (0.26, 0.61)	
p-value	<0.0001	
RES-RRMS, n	[redacted]	[redacted]
K-M estimate of relapse-free patients, % (95% CI)	[redacted]	[redacted]
HR (95% CI) for Cladribine Tablets vs. placebo	[redacted]	
p-value	[redacted]	
SOT-RRMS, n	[redacted]	[redacted]
K-M estimate of relapse-free patients, % (95% CI)	[redacted]	[redacted]
HR (95% CI) for Cladribine Tablets vs. placebo	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017c)

CI: Confidence interval; HDA-RRMS: High disease activity; HR: Hazard ratio; K-M: Kaplan-Meier; L: Low-dose Cladribine Tablets over 48 weeks; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

Proportion of patients qualifying relapse-free

Similar to the ITT analysis, patients treated with 3.5 mg/kg Cladribine Tablets in the HDA-RRMS subgroup analysis had a numerically higher proportion of patients qualifying as relapse-free at 96 weeks compared with placebo (72.1% vs. 46.3%) (Table 32). A numerically greater proportion of patients in the 3.5 mg/kg Cladribine Tablets group compared with placebo were considered relapse-free in both the RES-RRMS [redacted] and SOT-RRMS treatment groups [redacted] (Merck 2017c).

Table 32: Proportion of qualifying relapse-free patients at 96 weeks in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS: Qualifying relapse-free at 96 weeks, n (%)		
Relapse	30 (21.4)	66 (44.3)
Relapse-free	101 (72.1)	69 (46.3)
Unknown*	9 (6.4)	14 (9.4)
RES-RRMS: Qualifying relapse-free at 96 weeks, n (%)		
Relapse	[redacted]	[redacted]
Relapse-free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]
SOT-RRMS: Qualifying relapse-free at 96 weeks, n (%)		
Relapse	[redacted]	[redacted]
Relapse-free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

SOURCE: (Merck 2017c)

* Patients who withdrew early before week 48/96 with no relapse are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

B.2.7.3.2. Endpoints associated with disability

Time to 3-month confirmed disability progression

Results for the post-hoc subgroup analysis of time to 3-month confirmed disability progression in the HDA-RRMS subgroup were consistent with the results observed in the ITT population. Treatment with 3.5 mg/kg Cladribine Tablets in the HDA-RRMS subgroup was associated with a significant reduction in risk of 3-month confirmed disability progression of 72% compared with placebo (p=0.0001). However, a statistical difference was not observed between 3.5 mg/kg Cladribine Tablets and placebo in the RES-RRMS and SOT-RRMS subgroups (Table 33) (Merck 2017c).

Table 33: Time to 3-month CDP in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS		
K-M estimate of progression-free patients, % (95% CI)	91.0 (84.7, 94.8)	71.7 (63.4, 78.5)
HR for Cladribine Tablets vs. placebo (95% CI)	0.28 (0.15, 0.54)	
p-value	0.0001	
RES-RRMS		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
SOT-RRMS		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017c)

CDP: Confirmed disability progression; CI: Confidence interval; HDA-RRMS: High disease activity; HR: Hazard ratio; K-M: Kaplan-Meier; L: Low-dose Cladribine Tablets for 48 weeks; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

Proportion of patients with 3-month confirmed disability progression

In the HDA-RRMS subgroup, 82% of patients who received 3.5 mg/kg Cladribine Tablets were reported to be 3-month CDP-free compared with on 59.7% in the placebo treatment arm (Table 34). In addition, a higher percentage of patients in the SOT-RRMS subgroup treated with 3.5 mg/kg Cladribine Tablets were 3-month CDP-free compared with those treated with placebo (89.5% vs. 65.6%). However, there was no obvious difference in the proportion of 3-month CDP-free patients in the RES-RRMS subgroup between the 3.5 mg/kg Cladribine Tablets and placebo treatment arms ([redacted] (Merck 2017c).

Table 34: Proportion of patients with 3-month CDP in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS: 3-month CDP at 96 weeks, n (%)		
Progression	12 (8.6)	39 (26.2)
Progression -free	116 (82.9)	89 (59.7)
Unknown*	12 (8.6)	21 (14.1)
RES-RRMS: 3-month CDP at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression -free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]
SOT-RRMS: 3-month CDP at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression -free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

SOURCE: (Merck 2017c)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CDP: Confirmed disability progression; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

Time to 6-month confirmed disability progression

Results for the HDA-RRMS subgroup time to 6-month confirmed disability progression were similar to the ITT analysis. The risk of experiencing 6-month confirmed disability progression in the 3.5 mg/kg Cladribine Tablets group was significantly lower compared with placebo (HR: 0.18; p=0.0001). However, a statistical difference was not observed between 3.5 mg/kg Cladribine Tablets and placebo in the RES-RRMS and SOT-RRMS subgroups (Table 35) (Merck 2017c).

Table 35: Time to 6-month CDP in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS		
K-M estimate of progression-free patients, % (95% CI)	95.5 (90.2, 97.9)	77.7 (69.8, 83.8)
HR for Cladribine Tablets vs. placebo (95% CI)	0.18 (0.08, 0.44)	
p-value	0.0001	
RES-RRMS		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
SOT-RRMS		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017c)

CDP: Confirmed disability progression; CI: Confidence interval; HDA-RRMS: High disease activity; HR: Hazard ratio; K-M: Kaplan-Meier; L: Low-dose Cladribine Tablets for 48 weeks; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

Proportion of patients with 6-month confirmed disability progression

For all subgroups analysed, the absolute proportion of 6-month CDP-free patients was higher following treatment with 3.5 mg/kg Cladribine Tablets compared with placebo (Table 36) (Merck 2017c).

Table 36: Proportion of patients with 6-month CDP in CLARITY post-hoc subgroup analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS: 6-month CDP at 96 weeks, n (%)		
Progression	6 (4.3)	31 (20.8)
Progression -free	121 (86.4)	96 (64.4)
Unknown*	13 (9.3)	22 (14.8)
RES-RRMS: 6-month CPD at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression -free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]
SOT-RRMS: 6-month CDP at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression -free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

SOURCE: (Merck 2017c)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CDP: Confirmed disability progression; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SOT-RRMS: Sub-optimal therapy

B.2.7.3.3. Other endpoints

NEDA-3

The proportion of patients with NEDA-3 status was consistently higher following treatment with 3.5 mg/kg Cladribine Tablets compared with placebo in the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups. Furthermore, patients treated with 3.5 mg/kg Cladribine Tablets were significantly more likely to have no evidence of disease activity at 96 weeks compared with placebo in the HDA-RRMS ($p<0.0001$), RES-RRMS ([redacted]) and SOT-RRMS ([redacted]) subgroups (Table 37) (Merck 2017c).

Table 37: NEDA-3 status in CLARITY post-hoc subgroup analysis

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	43.7	6.9
HR for Cladribine Tablets vs. placebo (95% CI)	2.86 (2.14, 3.81)	
p-value	<0.0001	
RES-RRMS		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
SOT-RRMS		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017c)

CI: Confidence interval; HDA-RRMS: High disease activity; HR: Hazard ratio; K-M: Kaplan-Meier: L: Low-dose Cladribine Tablets treatment over 48 weeks; NEDA: No evidence of disease activity; RES-RRMS: Rapidly evolving severe: SOT-RRMS: Sub-optimal therapy

Rescue medication use

Numerically, the proportion of patients rescued at 96 weeks was lower in the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups of patients treated with 3.5 mg/kg Cladribine Tablets compared with placebo, similar to the results observed in the ITT population (Table 38) (Merck 2017c).

Table 38: Proportion of patients rescued in CLARITY post-hoc analyses

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
Patients receiving rescue therapy, n/N (%)		
HDA-RRMS	1/140 (0.7)	14/149 (9.4)
RES-RRMS	[redacted]	[redacted]
SOT-RRMS	[redacted]	[redacted]
Mean duration of rescue medication, days		
HDA-RRMS	522	202.43
RES-RRMS	[redacted]	[redacted]
SOT-RRMS	[redacted]	[redacted]

SOURCE: (Merck 2017c)

HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe: SOT-RRMS: Sub-optimal therapy

B.2.7.4. Post-hoc subgroup analyses of CLARITY-EXT

For the post-hoc analysis of subgroups in CLARITY-EXT, there were 31 patients with HDA-RRMS, 13 patients with RES-RRMS RRMS and 4 patients with SOT-RRMS in the LLPP reporting group, who were exposed to the licensed dosage of Cladribine Tablets (3.5 mg/kg). Due to the low numbers of the patients in the SOT-RRMS subgroup, post-hoc analyses were not performed for these patients. The

expanded results from this post-hoc analysis are presented in the appendix as these analyses were not used in the cost-effectiveness model.

B.2.7.4.1. Endpoints associated with relapses

PRIMARY OUTCOME: Qualifying ARR

In terms of qualifying ARR, patients with HDA-RRMS and RES-RRMS showed a similar result as the overall LLPP treatment arm ([redacted] (Table 39) (Merck 2017e).

Table 39: Qualifying ARR in CLARITY-EXT post-hoc subgroup analyses

Outcome	LLPP
HDA-RRMS: Qualifying ARR	
Mean (SD) number of qualifying relapses	0.32 (0.70)
Qualifying ARR (95% CI)	0.14 (0.08, 0.26)
HDA-RRMS: Qualifying relapse-free at week 96, n (%)	
Relapse	[redacted]
Relapse-free	[redacted]
Unknown*	[redacted]
RES-RRMS: Qualifying ARR	
Mean (SD) number of qualifying relapses	[redacted]
Qualifying ARR (95% CI)	[redacted]
RES-RRMS: Qualifying relapse-free at week 96, n (%)	
Relapse	[redacted]
Relapse-free	[redacted]
Unknown*	[redacted]

SOURCE: (Merck 2017e)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

ARR: Annualised relapse rate; CI: Confidence interval; HDA-RRMS: High disease activity; L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo; RES-RRMS: Rapidly evolving severe; SD: Standard deviation

The Kaplan-Meier estimate at the last event showed that 79.7% (95% CI: 60.3, 90.3) and [redacted] of patients were relapse-free in the HDA-RRMS and RES-RRMS subgroups, respectively. Compared with the ITT analysis, both HDA-RRMS and RES-RRMS subgroups had a numerically higher proportion of qualifying relapse-free patients (Merck 2017e).

The proportion of patients qualifying relapse-free in the HDA-RRMS subgroup was comparable to that observed for the ITT population (74.2% vs. 77.9%), however, this was lower for the RES-RRMS subgroup [redacted] (Merck 2017e).

B.2.7.4.2. Endpoints associated with disability

3-month confirmed disability progression

In terms of time to 3-month confirmed disability progression, the Kaplan-Meier estimate at last event for the proportion of patients shown to be free from a 3-month CDP was 86.4% in the HDA-RRMS subgroup and [redacted] in the RES-RRMS subgroup (Merck 2017e).

The absolute proportion of patients free from 3-month CDP was shown to be higher in the HDA-RRMS subgroup compared with RES-RRMS (80.6% vs. [redacted] (Table 40) (Merck 2017e).

Table 40: Proportion of patients with 3-month CDP in CLARITY-EXT post-hoc subgroup analyses

Outcome	LLPP
HDA-RRMS: 3-month confirmed disability progression at 96 weeks, n (%)	
Progression	4 (12.9)
Progression -free	25 (80.6)
Unknown*	2 (6.5)
RES-RRMS: 3-month confirmed disability progression at 96 weeks, n (%)	
Progression	[redacted]
Progression -free	[redacted]
Unknown*	[redacted]

SOURCE: (Merck 2017e)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CDP: Confirmed disability progression; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe

6-month confirmed disability progression

Similar to the 3-month confirmed disability progression results, the Kaplan-Meier estimate at last event, calculated that the proportion of patients shown to be free from a 6-month CDP was 86.4% for the HDA-RRMS subgroup and [redacted] for the RES-RRMS subgroup (Merck 2017e).

The absolute proportion of patients free from 6-month CDP in the HDA-RRMS subgroup was 80.6% and [redacted] in the RES-RRMS subgroup (Table 41) (Merck 2017e).

Table 41: Proportion of patients with 3-month CDP in CLARITY-EXT post-hoc subgroup analyses

Outcome	LLPP
HDA-RRMS: 6-month confirmed disability progression at 96 weeks, n (%)	
Progression	4 (12.9)
Progression -free	25 (80.6)
Unknown*	2 (6.5)
RES-RRMS: 6-month confirmed disability progression at 96 weeks, n (%)	
Progression	[redacted]
Progression -free	[redacted]
Unknown*	[redacted]

SOURCE: (Merck 2017e)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CDP: Confirmed disability progression; HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe

B.2.7.4.3. Other endpoints

NEDA-3

In the post-hoc subgroup analysis of CLARITY-EXT, the proportion of patients with NEDA-3 (based on 3-month CDP data) was shown to be 34.9% for the HDA-RRMS subgroup and [redacted] for the RES-RRMS subgroup (Table 42) (Merck 2017e).

Table 42: NEDA-3 status in CLARITY-EXT post-hoc subgroup analyses

Subgroup	K-M estimate of NEDA-3 status at last event, % of patients (95% CI)
HDA-RRMS	34.9, (18.3, 52.0)
RES-RRMS	[redacted]

SOURCE: (Merck 2017e)

HDA-RRMS: High disease activity; NEDA: No evidence of disease activity; RES-RRMS: Rapidly evolving severe

Rescue medication use

Throughout CLARITY-EXT nine patients reported using rescue medication in the LLPP reporting group, one of which was from the HDA-RRMS subgroup and one was from the RES-RRMS subgroup (Merck 2017e).

B.2.8 Meta-analysis

A meta-analysis was not possible as only one study included Cladribine Tablets at the anticipated licensed dose (3.5 mg/kg as monotherapy) and target patient population (HDA-RRMS). A meta-analysis requires two or more studies that contain the intervention of interest.

B.2.9 Comparative effectiveness

B.2.9.1. Summary of results

The sub-populations of patients who are relevant to this decision problem are RES-RRMS and SOT-RRMS. A classic NMA was undertaken (see Appendix D) to establish the comparative effectiveness of Cladribine Tablets versus its relevant comparator treatments. However, in the sub-populations of patients who are relevant to this decision problem – RES-RRMS and SOT-RRMS – additional analyses were required to fully inform the inputs for the cost-effectiveness analysis. This was specifically the case for comparisons with alemtuzumab where, as noted in previous NICE appraisals (TA441), it is challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network. Therefore, Merck have conducted a meta-regression analysis to allow for comparisons of Cladribine Tablets versus relevant comparators in RES-RRMS and SOT-RRMS patients. This analysis is presented in detail in the economic section (Section B.3).

For completeness, the NMA findings for the full HDA-RRMS population are summarised briefly below (Table 43), with full methods and results available in Appendix D.

Table 43: Summary of efficacy results between Cladribine Tablets and comparators in HDA-RRMS population

Cladribine Tablets 3.5mg/kg versus	ARR	CDP3M 24M	CDP6M 24M	CDP6M At any time point	RF24M
Placebo	↑	↑	↑	↑	↑
Alemtuzumab, 12mg, qd	↔	-	↑	↑	-
DMF, 240mg, bid	↑	↑	-	-	↑
Fingolimod, 0.5mg, qd	↔	↑	-	-	↓
GA, 20mg, qd	↑	↑	-	-	↑
INF-β-1a (Avonex)	↑	-	-	-	-
INF-β-1a (Rebif 44µg)	-	-	↑	↑	-
Natalizumab, 300mg, q4w	↓	-	-	-	-
Teriflunomide, 14mg, od	↑	-	-	-	-
Teriflunomide, 7mg, od	↑	-	-	-	-

Notes-↑ Indicates better efficacy for Cladribine Tablets 3.5mg/kg; ↓ indicates lower efficacy for Cladribine Tablets 3.5mg/kg; "↔" indicates equivalent efficacy of Cladribine Tablets 3.5mg/kg and comparator; Cells highlighted in green represent statistically significant results in favour of Cladribine Tablets 3.5mg/kg; "-"indicates that analyses were not feasible for these comparisons considering limited evidence

ARR: Annualised Relapse Rate; bid: twice a day; CDP: Confirmed Disease Progression; DMF: dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; M: Months; µg: microgram; mg: milligram; od: once daily; qd: per day; q1w: once weekly; q4w: every 4 weeks; RF: Relapse Free

NMA analyses for the HDA-RRMS population, Cladribine Tablets were associated with a statistically significantly better efficacy profile than placebo in terms of all outcomes including ARR, and disability progression (CDP3M and CDP6M). Cladribine Tablets were also associated with a statistically significant reduction in ARR when compared with teriflunomide and did not differ significantly from the other DMTs evaluated. Although, the analyses in the subgroups (RES-RRMS and SOT-RRMS) were limited in terms of comparisons to other DMTs, the results supported the positive efficacy of Cladribine Tablets; however, these results were not statistically significant.

When tolerability and safety were considered the NMA results indicated that Cladribine Tablets did not differ significantly from placebo for all-cause treatment discontinuations, discontinuations because of AEs, the incidence of AEs or grade 3 or 4 AEs. Cladribine Tablets were not significantly worse than any comparator DMT for any of these outcomes.

Results of sensitivity analyses generally found that the findings for ARR, CDP3M and CDP6M at 24 months were robust. There was no change in the direction of relative treatment differences between Cladribine Tablets and comparators, although in some instances the significance of findings changed. Sensitivity analyses also indicated that there was an effect on the findings for Cladribine Tablets versus teriflunomide 14mg and alemtuzumab for proportions of patients relapse free at 24 months, such that between-intervention significance was lost in some analyses. No other results were affected.

The results of the meta-regression analysis shows significant overlap in the credible intervals for the hazard ratios of confirmed disability progression at six months, with no therapy statistically dominating in terms of efficacy. At the point estimate level, Cladribine Tablets was predicted to be more efficacious than fingolimod (log hazard ratio relative to placebo of [redacted] for Cladribine Tablets versus [redacted] for fingolimod) and alemtuzumab [redacted] versus [redacted]), but marginally less efficacious than natalizumab [redacted]) and daclizumab [redacted]) for the RES-RRMS population. The corresponding normalised hazard ratios were [redacted] for treatment effect of Cladribine Tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, in the RES-RRMS and [redacted] for natalizumab versus placebo.

The log-hazard ratios in Table 69 were un-centered and transformed to produce an estimate of DMT effect consistent with the baseline risk in SOT-RRMS. The corresponding normalised hazard ratios in this population were [redacted] for Cladribine Tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, and [redacted] for fingolimod versus placebo. Overall, the meta-regression predicted that all DMT's are less effective in the SOT-RRMS population than in RES-RRMS..

Overall, the results of the meta-regression suggest that Cladribine Tablets are of equivalent efficacy to these therapies on the endpoint of confirmed disability progression at 6 months.

B.2.9.2. Uncertainties in the indirect and mixed treatment comparisons

The limitation of an NMA in the sub-groups relevant to the NICE decision problem (specifically SOT-RRMS) is well known and understood. This limitation largely stems from the paucity of data available for subgroups across the HTA relevant outcomes for all DMTs.

As noted above, it proved particularly challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations via a classic NMA due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network. Attempts were made to improve these connections, e.g. through a series of post-hoc analysis that incorporated unpublished data from the phase III PRISMS trial (details available in Appendix D). However this offered an incomplete solution (the absence of a link with alemtuzumab in SOT-RRMS patients was not solved). Given the importance of the comparison with alemtuzumab in the UK, Merck conducted a series of meta-regression analyses with the goal of estimating the efficacy of drug therapies the RES-RRMS and SOT-RRMS, by relating efficacy to baseline risk, and centering baseline risk to the expected value in each group. The aim of the meta-regression analysis was to provide a more robust comparison between Cladribine Tablets and alemtuzumab, particularly in the SOT-RRMS population.

B.2.10 Adverse reactions

Adverse events (AEs) were reported in the pivotal CLARITY and CLARITY-EXT trials where the study-specific safety analyses are presented in Section B.2.10.1 and Section B.2.10.2, respectively (Merck 2017b; Merck 2017d). In addition, an integrated safety analysis was performed on combined data from CLARITY, CLARITY-EXT, ORACLE MS and the PREMIERE registry (Section B.2.10.3) (Merck 2017f).

B.2.10.1. Overview of AEs in CLARITY

The safety analysis was performed on all patients who received at least one dose of study medication with follow-up safety data in CLARITY (Merck 2017b). Of the 1,319 patients included in the safety population, 430 were randomised to 3.5 mg/kg Cladribine Tablets, and 435 were randomised to the placebo group, with the remaining patients randomised to 5.25 mg/kg Cladribine Tablets (Merck 2017b).

In general, treatment discontinuations due to AEs were relatively few, although a greater proportion of patients withdrew prematurely from treatment due to AEs in the Cladribine Tablets groups compared with the placebo group (3.5% [n=15] and 2.1% [n=9], respectively) suggesting that orally administered 3.5 mg/kg Cladribine Tablets were relatively well-tolerated by patients with RRMS during this 96-week double-blind trial (Merck 2017b). A summary of all AEs that lead to treatment discontinuation reported in CLARITY are summarised in Table 44.

Table 44: Summary of AEs leading to treatment discontinuation in CLARITY

AE	Cladribine Tablets 3.5 mg/kg (LL) (n=430)		Placebo (n=435)	
	Patients	Events	Patients	Events
Any AE leading to discontinuation, n (%)	15 (3.5)	15 (0.6)	9 (2.1)	14 (0.7)
Reasons for discontinuation				
Blood and lymphatic system disorders	2 (0.5)	2 (0.1)	0	0
Lymphopenia	2 (0.5)	2 (0.1)	0	0
Investigations	2 (0.5)	2 (0.1)	0	0
Lymphocyte count decreased	1 (0.2)	1 (0.2)	0	0
Lymphocyte count abnormal	1 (0.2)	1 (0.2)	0	0

AE	Cladribine Tablets 3.5 mg/kg (LL) (n=430)		Placebo (n=435)	
	Patients	Events	Patients	Events
Infections and infestations	0	0	2 (0.5)	2 (0.1)
Appendicitis	0	0	1 (0.2)	1 (0.1)
Varicella	0	0	1 (0.2)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	0	0	3 (0.7)	3 (0.2)
Pregnancy	0	0	3 (0.7)	3 (0.2)
Hepatobiliary disorders	1 (0.2)	1 (0.0)	1 (0.2)	1 (0.1)
Hepatitis toxic	1 (0.2)	1 (0.0)	0	0
Liver disorder	0	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (0.7)	3 (0.1)	0	0
Fibroadenoma of breast	1 (0.2)	1 (0.0)	0	0
Ovarian cancer	1 (0.2)	1 (0.0)	0	0
Uterine leiomyoma	1 (0.2)	1 (0.0)	0	0
Skin and SC tissue disorders	3 (0.7)	3 (0.1)	0	0
Dermatitis	1 (0.2)	1 (0.0)	0	0
Dermatitis allergic	1 (0.2)	1 (0.0)	0	0
Rash erythematous	1 (0.2)	1 (0.0)	0	0
Psychiatric disorders	0	0	2 (0.5)	2 (0.1)
Completed suicide	0	0	1 (0.2)	1 (0.1)
Intentional self-injury	0	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	0	0	2 (0.5)	2 (0.1)
Cough	0	0	1 (0.2)	1 (0.1)
Pulmonary oedema	0	0	1 (0.2)	1 (0.1)
Cardiac disorder	1 (0.2)	1 (0.0)	1 (0.2)	1 (0.1)
Cardiac hypertrophy	0	0	1 (0.2)	1 (0.1)
Myocardial infarction	1 (0.2)	1 (0.0)	0	0
Gastrointestinal disorders	2 (0.5)	2 (0.1)	0	0
Colitis ulcerative	1 (0.2)	1 (0.0)	0	0
Nausea	1 (0.2)	1 (0.0)	0	0
Metabolism and nutrition disorders	0	0	1 (0.2)	1 (0.1)
Anorexia	0	0	1 (0.2)	1 (0.1)
Nervous system disorders	0	0	1 (0.2)	1 (0.1)
Haemorrhagic stroke	0	0	1 (0.2)	1 (0.1)
Renal and urinary disorders	0	0	1 (0.2)	1 (0.2)
Nephrosclerosis	0	0	1 (0.2)	1 (0.2)
Reproductive system and breast disorders	1 (0.2)	1 (0.0)	0	0
Breast mass	1 (0.2)	1 (0.0)	0	0

SOURCE: (Merck 2017b)

B.2.10.1.1. TEAEs

During the 96-week trial phase, the 3.5 mg/kg Cladribine Tablets and placebo groups had a similar proportion of patients reporting treatment-emergent AEs (TEAEs; 80.7% and 73.3%, respectively) (Merck 2017b). The most common TEAEs reported by patients (>5% of patients) were from the following system organ classes (Merck 2017b):

- Infections and infestations - 3.5 mg/kg Cladribine Tablets (47.7%); placebo (42.5%)
- Gastrointestinal disorders - 3.5 mg/kg Cladribine Tablets (31.6%); placebo (29.7%)
- Nervous system disorders - 3.5 mg/kg Cladribine Tablets (32.6%); placebo (29.0%)
- Blood and lymphatic system disorders - 3.5 mg/kg Cladribine Tablets (26.5%); placebo (5.7%)

The most frequently reported TEAEs in the treatment groups were headache, nasopharyngitis, upper respiratory tract infection and nausea. Headache occurred more frequently in the 3.5 mg/kg Cladribine Tablets group (24.2%) than in the placebo group (17.2%). The frequency of nasopharyngitis was comparable between 3.5 mg/kg Cladribine Tablets and placebo groups (14.4% vs. 12.9%, respectively). However, the frequency of upper respiratory tract infections in the 3.5 mg/kg Cladribine Tablets group (12.6%) was greater than that observed in the placebo-treated group (9.7%). The frequency of nausea was similar between the 3.5 mg/kg Cladribine Tablets and placebo groups (10% and 9%, respectively). A summary of the most common TEAEs reported in 5% or more of patients is shown in Table 45. The other AEs occurred with relatively low frequency across all treatment groups (<5%). Other AEs of interest that occurred in >1% of the treatment groups were as follows for the 3.5 mg/kg Cladribine Tablets and placebo groups, respectively (Merck 2017b):

- Depression: 4.2% versus 3.0%
- Vertigo: 3.3% versus 2.5%
- Hypertension: 3.7% versus 2.3%
- Pyrexia: 3.3% versus 1.8 %
- Alopecia: 3.5% versus 1.1%
- Rash: 2.3% versus 1.1%

Table 45: Summary of TEAEs reported in ≥5% of patients in CLARITY

AE	Cladribine Tablets 3.5 mg/kg (LL) (n=430)		Placebo (n=435)	
	Patients	Events	Patients	Events
Headache	104 (24.2)	264 (10.5)	75 (17.2)	189 (9.7)
Lymphopenia	93 (21.6)	123 (4.9)	8 (1.8)	11 (0.6)
Nasopharyngitis	62 (14.4)	107 (4.3)	56 (12.9)	95 (4.9)
Upper respiratory tract infection	54 (12.6)	118 (4.7)	42 (9.7)	80 (4.1)
Nausea	43 (10.0)	74 (2.9)	39 (9.0)	49 (2.5)
Back pain	34 (7.9)	39 (1.6)	28 (6.4)	42 (2.1)
Urinary tract infection	23 (5.3)	39 (1.6)	39 (9.0)	51 (2.6)
Influenza-like illness	34 (7.9)	48 (1.9)	31 (7.1)	40 (2.0)
Diarrhoea	30 (7.0)	45 (1.8)	29 (6.7)	37 (1.9)
Influenza	28 (6.5)	34 (1.4)	27 (6.2)	43 (2.2)
Fatigue	20 (4.7)	27 (1.1)	26 (6.0)	29 (1.5)
Arthralgia	27 (6.30)	44 (1.8)	21 (4.8)	23 (1.2)
Pharyngolaryngeal pain	19 (4.4)	32 (1.3)	25 (5.7)	29 (1.5)
Leukopenia	24 (5.6)	26 (1.0)	3 (0.7)	6 (0.3)

SOURCE: (Merck 2017b)

AE: Adverse event; L: Low-dose Cladribine Tablets over 48 weeks

B.2.10.1.2. Serious TEAEs

The proportion of patients experiencing serious TEAEs was low and without apparent significant differences in the nature or frequency of serious TEAEs between the 3.5 mg/kg Cladribine Tablets and the placebo groups (Merck 2017b). During the 96-week trial period, 105 patients experienced serious TEAEs. Serious TEAEs were experienced by 36 patients (8.4%) in the 3.5 mg/kg Cladribine Tablets group, and 28 patients (6.4%) in the placebo group, with the remaining serious TEAEs were in the 5.25 mg/kg Cladribine Tablets group. The system organ classes with the largest proportion of serious TEAEs were as follows (Merck 2017b):

- Infections and infestations: 3.5 mg/kg Cladribine Tablets (2.3%); placebo (1.6%)
- Hepatobiliary disorders: 3.5 mg/kg Cladribine Tablets (0.7%); placebo (0.7%)
- Gastrointestinal disorders: 3.5 mg/kg Cladribine Tablets (0.9%); placebo (0.5%)

A total of six deaths were reported during CLARITY: two patients in the placebo treatment group, two patients in the 3.5 mg/kg Cladribine Tablets treatment group, and two patients in the 5.25 mg/kg Cladribine Tablets treatment group. All deaths during CLARITY were considered unrelated to the study drug (Merck 2017b).

B.2.10.1.3. TEAEs of special interest

Lymphopenia was an expected event based on the mechanism of action of cladribine, occurring more frequently in the 3.5 mg/kg Cladribine Tablets treatment group (21.6%) compared with the placebo group (1.8%) (Table 46) (Merck 2017b). In the "investigations" system organ class, decreasing lymphocyte and white blood cell count was reported only in the 3.5 mg/kg Cladribine Tablets group, however, the incidence was infrequent and classed as non-serious. Lymphopenia resulted in treatment discontinuation in four patients randomised to the 3.5 mg/kg Cladribine Tablets group (Merck 2017b). At the end of the 96-week CLARITY study, a total of eight (0.9%) patients in the 3.5 mg/kg Cladribine Tablets group had Grade ≥3 lymphopenia at their final evaluation. Further follow-up of these patients showed that all recovered to a lymphocyte count of Grade 0 or Grade 1. There were no serious or opportunistic infections reported in these patients (Merck 2017b).

Table 46: TEAEs and discontinuations relating to lymphopenia in CLARITY

System organ class preferred term	Cladribine Tablets 3.5 mg/kg (LL) (n=430)	Placebo (n=435)
Discontinuations due to lymphopenia, n (%)	2 (0.5)	0
Discontinuations due to decreased or abnormal lymphocyte count, n (%)	2 (0.5)	0
Number of patients reporting lymphopenia as a TEAE, n (%)	93 (21.6)	8 (1.8)
Number of lymphopenia related TEAE events (%)	123 (4.9)	11 (0.6)
Number of patients reporting lymphopenia as a serious TEAE	1 (0.3)	0
Number of deaths due to lymphopenia	0	0

SOURCE: (Merck 2017b)

L: Low-dose Cladribine Tablets over 48 weeks; TEAE: Treatment-emergent adverse event

The system organ class with the greatest frequency of adverse events was infection and infestations. The incidence of infections and infestations was 47.7% in the Cladribine Tablets 3.5 mg/kg group and 42.5% in the placebo group. Most of these infections involved the upper respiratory tract. Reports of herpes infection were common in the Cladribine Tablets group, with eight patients experiencing herpes zoster infections. The majority of these infections were mild to moderate in severity, and all cases resolved without sequela, except for a single case of herpes oticus (Ramsay-Hunt), which was associated with persistent, intermittent right-sided ear pain, but which was reported to have stabilized by the end of the trial (Merck 2017b).

Three subjects treated with Cladribine Tablets in CLARITY experienced isolated malignancies involving different organ systems – malignant melanoma, and ovarian and metastatic pancreatic carcinomas (the latter resulted in death) (Merck 2017b). Further detail on malignancies is provided in Section B.2.10.3.3.

B.2.10.2. Overview of AEs in CLARITY-EXT

Among the LLPP patients in the safety analysis of CLARITY-EXT (N=98), 75.5% reported one or more AEs (Merck 2017d). The AEs were considered treatment-related for 42.9% of patients. The rate of discontinuation from treatment due to AEs for LLPP patients was low (3.1%) and the rate of discontinuation of the CLARITY-EXT trial due to TEAEs was also low (2.0%), suggesting that Cladribine Tablets treatment in year 1 and year 2 (CLARITY) followed by no active treatment in year 3 and year 4 (CLARITY-EXT) was relatively well-tolerated by patients with RRMS. The reasons for discontinuation were pregnancy, Basedow's disease (toxic diffuse goitre), and hepatitis B infection (n=1 for each). Study discontinuation due to AEs was reported for two LLPP patients, both of which were due to death and judged to be probably unrelated to Cladribine Tablets treatment (Merck 2017d).

B.2.10.2.1. TEAEs

In the LLPP treatment group, the most frequently reported TEAEs were headache (20.4%), nasopharyngitis (19.4%), influenza (11.2%), back pain (9.2%), lymphopenia (9.2%), pain in extremity (8.2%), nausea (8.2%), upper tract infection (8.2%), and diarrhoea (7.1%) (Merck 2017d). All TEAEs reported in the LLPP treatment group of CLARITY-EXT are summarised in Table 47.

The frequency of these TEAEs was not markedly increased in the CLARITY-EXT trial compared with the CLARITY trial for LLPP patients who had received treatment with 3.5 mg/kg Cladribine Tablets in CLARITY and no active treatment in CLARITY-EXT (Merck 2017d). For example, for patients treated with 3.5 mg/kg of Cladribine Tablets in the CLARITY trial, the frequency of headache was similar as for patients in the LLPP group of CLARITY-EXT (24.2% compared with 20.4%). These results suggest that treatment for 2 years with 3.5 mg/kg Cladribine Tablets followed by 2 years of no active treatment is not associated with a considerable increase in TEAEs for patients with RRMS (Merck 2017d).

Table 47: Summary of TEAEs reported in ≥5% of patients in CLARITY-EXT

System organ class preferred term	LLPP (N=98) n (%)
Patients with any TEAEs	**74 (75.5)**
Blood and lymphatic system disorders	**17 (17.3)**
Leukopenia	1 (1.0)
Lymphopenia	9 (9.2)
Neutropenia	2 (2.0)
Ear and labyrinth disorders	**7 (7.1)**
Vertigo	5 (5.1)
Gastrointestinal disorders	**27 (27.6)**
Diarrhoea	7 (7.1)
Nausea	8 (8.2)
Toothache	4 (4.1)
Vomiting	1 (1.0)
General disorders and administration site conditions	**20 (20.4)**
Fatigue	5 (5.1)
Influenza like illness	5 (5.1)
Infections and infestations	**48 (49.0)**
Bronchitis	6 (6.1)
Influenza	11 (11.2)
Nasopharyngitis	19 (19.4)
Upper respiratory tract infection	**8 (8.2)**
Urinary tract infection	6 (6.1)
Musculoskeletal and connective tissue disorders	**27 (27.6)**
Arthralgia	5 (5.1)
Back pain	9 (9.2)
Pain in extremity	8 (8.2)
Nervous system disorders	**21 (21.4)**
Headache	20 (20.4)
Psychiatric disorders	**14 (14.3)**
Anxiety	5 (5.1)
Depression	6 (6.1)
Vascular disorders	**5 (5.1)**
Hypertension	4 (4.1)

SOURCE: (Merck 2017d)

L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo; TEAE: Treatment-emergent adverse event

B.2.10.2.2. Serious TEAEs

A low number of patients in the LLPP reporting group reported serious TEAEs in the CLARITY-EXT trial (N=16; 16.3%) (Table 48). For LLPP patients, the system organ classes with reports of serious TEAEs were as follows (Merck 2017d):

- Neoplasms benign, malignant and unspecified (including cysts and polyps) (3.1%)
- Blood and lymphatic system disorders (2.0%)

- Eye disorders (2.0%)
- Infections and infestations (2.0%)
- Gastrointestinal disorders (1.0%)
- Hepatobiliary disorders (1.0%)
- Musculoskeletal and connective tissue disorders (1.0%)

The most frequently reported individual serious TEAEs in the LLPP treatment arm were iridocyclitis (2.0%), cholelitiasis, cholecystitis, intervertebral disc protrusion, and malignant melanoma (1.0%, each) (Merck 2017d).

Table 48: Summary of serious TEAEs in CLARITY-EXT

System organ class preferred term	LLPP (N=98) n (%)
Patients with any serious TEAEs	16 (16.3)
Blood and lymphatic system disorders	2 (2.0)
Cardiac disorders	1 (1.0)
Endocrine disorders	1 (1.0)
Eye disorders	2 (2.0)
Gastrointestinal disorders	1 (1.0)
General disorders and administration site conditions	2 (2.0)
Hepatobiliary Disorders	1 (1.0)
Infections and infestations	2 (2.0)
Investigations	1 (1.0)
Musculoskeletal and connective tissue disorders	1 (1.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (3.1)
Nervous system disorders	1 (1.0)
Psychiatric disorders	1 (1.0)
Respiratory, thoracic and mediastinal disorders	1 (1.0)

SOURCE: (Merck 2017d)

L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo; TEAE: Treatment-emergent adverse event

B.2.10.2.3. TEAEs of special interest

TEAEs of special interest include lymphopenia, malignant or unspecified tumours, herpes viral infections, viral infectious disorders, and opportunistic infections (Table 49) (Merck 2017d). As expected, and with the exception of viral infectious disorders, the incidence of these TEAEs of special interest was low for patients in the LLPP treatment arm who did not receive treatment with Cladribine Tablets during the CLARITY-EXT trial. Viral infectious disorders were the most frequently reported TEAE of special interest in this category and were reported for 20 patients (20.4%). All cases were of mild to moderate severity, and included influenza (18.2%), respiratory tract viral infections (9.1%), herpes viral infections (6.1%), and viral upper respiratory tract infections (4.5%) (Merck 2017d).

Lymphopenia was observed in 10.2% of LLPP patients, which was expectedly lower than observed in the CLARITY trial (21.6%) due to the length of time with no Cladribine Tablets treatment in the CLARITY-EXT trial. Grade 3/4 lymphocyte count decrease was observed in 5.1% of patients, which was similar to the proportion observed in the CLARITY trial (4.4%) (Merck 2017d). No patient treated with Cladribine Tablets experienced a Grade 4 lymphopenia.

Table 49: TEAEs relating to lymphopenia in CLARITY-EXT

Lymphopenia outcome	LLPP (N=98) n (%)
Any TEAE of lymphopenia	10 (10.2)
Any Grade 3 or 4 lymphocyte count decrease	5 (5.1)

SOURCE: (Merck 2017d)

L: Low-dose Cladribine Tablets over 48 weeks; P: Placebo; TEAE: Treatment-emergent adverse event

B.2.10.3. Overview of AEs in integrated safety analysis

During the overall clinical development of Cladribine Tablets, a greater number of patients were recruited for Cladribine Tablets 3.5 mg/kg treatment groups compared with placebo. This resulted in larger exposure in terms of patient-years of treatment and follow-up for Cladribine Tablets-treated patients compared with placebo (Table 50) (Merck 2017f).

Table 50: Summary of treatment exposure in the integrated safety analysis

Outcome	Cladribine Tablets 3.5 mg/kg	Placebo
Number of patients exposed to Cladribine Tablets, n	923	641
Total patient-years	3432.65	2025.97
Mean time on study, weeks (SD)	194 (111)	164 (106)
Median time on study, weeks (SD)	156	133

SOURCE: (Merck 2017f)

Includes data from CLARITY, CLARITY-EXT, ORACLE, and PREMIERE

SD: Standard deviation

The number of AEs per 100 patient-years (PYs) based on the integrated safety analysis was marginally higher in the cohort exposed to Cladribine Tablets 3.5 mg/kg compared with the placebo cohort (103.29 and 94.26, respectively) (Table 51) (Merck 2017f). Similarly, the number of severe and serious TEAEs per 100 patient-years was similar between oral monotherapy (3.7 and 3, respectively) and placebo (4.0 and 3.6, respectively). Treatment discontinuations per 100 patient-years were generally low in both oral monotherapy and placebo cohorts (2.07 and 1.05, respectively). No relevant difference was observed in deaths per 100 PYs (PYs) between cohorts (≤0.26 for both cohorts) (Merck 2017f). No statistical analyses were performed between the placebo and Cladribine Tablets groups.

Table 51: Summary of AEs in the integrated safety analysis

Outcome	Placebo (n=641)			Cladribine Tablets 3.5 mg/kg (LL) (n=923)		
	n	T, years	AE per 100 PY	n	T, years	AE per 100 PY
Any TEAE	515	546.3	94.26	773	748.4	103.29
At least 1 related TEAEs	291	1162.8	25.03	542	1605.5	33.76
At least 1 severe TEAE	57	1912.5	2.98	115	3111.2	3.70
At least 1 serious TEAE	67	1876.3	3.57	124	3096.8	4.00
At least 1 serious TEAE leading to death	5	2024.7	0.25	9	3431.0	0.26
At least 1 TEAE leading to treatment discontinuation	21	1993.7	1.05	67	3229.0	2.07

SOURCE: (Merck 2017f)

AE: Adverse event; PY: Patient-years; T: Total patient-years on study; TEAE: Treatment-emergent adverse event

B.2.10.3.1. TEAEs

The most common TEAE was headache, which was reported in similar incidence per 100 PYs in the Cladribine Tablets 3.5 mg/kg and placebo cohorts (8.71 and 8.82, respectively) (Merck 2017f). TEAEs observed more frequently per 100 PYs in the Cladribine Tablets 3.5 mg/kg cohort compared with the placebo cohort (with a difference of ≥0.50 events per 100 PYs) are presented in Table 52. Based on these criteria, lymphopenia was the most commonly reported TEAE in the 3.5 mg/kg Cladribine Tablets cohort compared with placebo (7.9 and 1.06, respectively) (Merck 2017f). This was expected as lymphopenia is linked to the mechanism of action of Cladribine Tablets. The slightly higher rate of leukopenia associated with Cladribine Tablets compared with placebo can be explained by the higher incidence of lymphopenia in the Cladribine Tablets-treated patients.

Assessment of the rates of anxiety and back pain in the placebo and Cladribine Tablets cohort during the first 2 years of treatment indicates only small numeric difference in incidence (Merck 2017f). For Cladribine Tablets and placebo cohorts, the incidence per 100 PYs for anxiety was 1.96 and 1.52, respectively and for back pain was 5.64 and 4.79, respectively) (Merck 2017f). No clear dose response or temporal relationship between Cladribine Tablets and back pain or anxiety was observed (Merck 2017f). Moreover, the occurrence of anxiety and back pain cannot be explained by the known pharmacologic action of Cladribine Tablets. Both events are therefore considered not to be adverse reactions of treatment with Cladribine Tablets.

A higher incidence of bronchitis was observed in the 3.5 mg/kg Cladribine Tablets treatment group compared with placebo (1.70 and 1.12 incidences per 100 patient years, respectively) (Merck 2017f). However, the incidence of bronchitis in the 5.25 mg/kg Cladribine Tablets cohort (1.40 incidences per 100 PYs) indicates no dose response relationship (Merck 2017f).

Table 52: Summary of TEAEs reported in the integrated safety analysis with ≥0.5 events per 100 PYs difference

TEAE	Events per 100 PYs	
	Placebo	Cladribine Tablets 3.5 mg/kg
Lymphopenia	1.06	7.94
Back pain	2.43	3.27
Bronchitis	1.12	1.70
Leukopenia	0.40	1.31
Anxiety	0.60	1.12
Herpes zoster	0.20	0.83
Decreased lymphocyte count	0.10	0.78

SOURCE: (Merck 2017f)

PYs: Patient-years; TEAE: Treatment-emergent adverse event

B.2.10.3.2. Serious TEAEs

The majority of TEAEs in the 3.5 mg/kg Cladribine Tablets cohort were mild or moderate in severity. Apart from lymphopenia, there was no discernible difference in the incidence of serious TEAEs between the 3.5 mg/kg Cladribine Tablets and placebo cohorts (Table 53) (Merck 2017f).

Table 53: Summary of serious TEAEs reported in the integrated safety analysis occurring in >0.1 events per 100 PYs

Serious TEAE	Events per 100 PYs	
	Placebo	Cladribine Tablets 3.5 mg/kg
Blood creatine phosphokinase	0.20	0.21
Pneumonia	0.15	0.18
Uterine leiomyoma	0.10	0.15
Lymphopenia	0.00	0.12
Urinary tract infection	0.05	0.12

SOURCE: (Merck 2017f)

PYs: Patient-years; TEAE: Treatment-emergent adverse event

B.2.10.3.3. TEAEs of special interest

Lymphopenia

Lymphopenia events during the Cladribine Tablets clinical trials were reported as AEs and/or as laboratory abnormalities of various grades (Merck 2017f). Assessment of lymphopenia through pooling of laboratory data from different studies has proven to be complex due to the treatment gaps of variable length between studies (during which, lymphocyte counts were not routinely measured), patient drop-outs, concomitant treatment with IFN-β, and varying study designs. Therefore, the main assessment of lymphopenia was based on the combination of laboratory data from the Phase II/III trials of CLARITY, CLARITY-EXT, ORACLE MS and ONWARD, rather than pooling (Merck 2017f).

Overall, the incidence rate of lymphopenia AEs and those lymphopenia AEs that led to treatment discontinuation was higher in patients exposed to Cladribine Tablets compared with placebo (Merck 2017f). Re-exposure in years 3 and 4 was associated with an increase in the incidence rates of lymphopenia AEs and lymphopenia AEs that led to treatment discontinuation. The incidence rate of severe lymphopenia AEs and those lymphopenia AEs that led to treatment discontinuation in the 3.5 mg/kg treatment group was lower than that in the 5.25 mg/kg dose treatment group (0.72 vs. 1.07 and 0.90 vs. 1.63 per 100 PY) respectively, indicating that lymphopenia was a dose-dependent response to Cladribine Tablets (Merck 2017f).

Lymphopenia, as determined by laboratory values of lymphocyte counts, was also consistently dose-dependent across the clinical program for Cladribine Tablets (Merck 2017f). The 5.25 mg/kg cladribine dose groups consistently showed higher incidence of Grade ≥3 lymphopenia than the 3.5 mg/kg dose groups: in CLARITY, Grade ≥3 lymphopenia occurred in 110 (25.6%) and 204 (44.9%), of subjects in 3.5 mg/kg and 5.25 mg/kg dose groups, respectively. Patients with lymphopenia were able to recover and no serious opportunistic infections were reported in patients treated with Cladribine Tablets during CLARITY. At the end of the 96-week CLARITY study, eight (0.9%) patients treated with 3.5 mg/kg Cladribine Tablets and 21 (2.4%) patients treated with 5.25 mg/kg Cladribine Tablets had Grade ≥3 lymphopenia at their final assessment. All patients who were treated with 3.5 mg/kg Cladribine Tablets during CLARITY recovered to a lymphocyte count of Grade 0 or Grade 1. Patients treated for more than 4 years (CLARITY and CLARITY-EXT; cumulative dose of 7 mg/kg) provided lymphocyte counts of Grade 0 at baseline of year 1 and Grade 0 or Grade 1 at each of the subsequent yearly treatment courses where approximately 86% of patients recovered to Grade 0 or Grade 1 by the end of each treatment year (Merck 2017f).

Given the expectant result of lymphopenia in patients treated with Cladribine Tablets, a risk mitigation plan was developed to reduce the onset of severe, sustained lymphopenia. Strict haematological criteria were adopted where patients are required to have the following (Merck 2017j):

- Normal lymphocyte counts before initiating Cladribine Tablets in year 1
- Lymphocyte counts of at least 800 cells/mm³ before initiating Cladribine Tablets in year 2

- If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the patient should not receive Cladribine Tablets anymore.

To assess the effectiveness of the lymphopenia risk mitigation plan, an analysis was conducted in patients who were exposed to 2 years of Cladribine Tablets during CLARITY and CLARITY-EXT (reporting groups consisted of LLPP, PPLL, and LLLL) (Merck 2017f). The assessment indicated that the risk mitigation plan reduced the incidence of Grade 3 lymphopenia in patients at the end of the treatment years 1 and 2 (Table 54). The incidence of Grade 3 lymphopenia in patients who had lymphopenia Grade 1 at start of year 1 and Grade 0 to Grade 1 at the start of year 2; Grade ≥2 at start of year 2 (0.5% and 0.8% of patients at the end of year 1 and year 2, respectively) was lower compared with patients who had lymphopenia Grade 1 at start of year 1 and Grade ≥2 at start of year 2 (3.6% and 12.2% of patients at the end of year 1 and year 2, respectively) (Merck 2017f).

Table 54: Assessment of lymphopenia risk mitigation plan

Incidence of Grade 3 lymphopenia at the end of treatment year, %	Patients with Grade 1 at start of year 1; Grade ≥2 at start of year 2	Patients with Grade 0 at start of year 1; Grade 0 to Grade 1 at start of year 2
Year 1	3.6	0.5
Year 2	12.2	0.8

SOURCE: (Merck 2017f)

Infections

The integrated analysis on infections was conducted using pre-defined Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

The incidence rate of the most common infections, including severe infections, were similar between placebo and 3.5 mg/kg cladribine tablet cohorts, with the exception of herpes zoster infections (Table 55) (Merck 2017f). The overall incidence of any infection was 24.92 and 27.05 events per 100 PYs and the incidence for any herpes zoster infection was 0.83 and 0.20 events per 100 PYs in the 3.5 mg/kg Cladribine Tablets and placebo cohorts, respectively. The incidence of herpes zoster in the 3.5 mg/kg cladribine tablet cohort was higher during periods of Grade 3 or Grade 4 lymphopenia compared with periods where patients who were not experiencing Grade 3 or Grade 4 lymphopenia (2.16 and 0.75 events per 100 PYs, respectively) (Merck 2017f).

Discontinuation of treatment due to a herpes zoster infection only occurred in one patient treated with Cladribine Tablets 3.5 mg/kg (Merck 2017f). Two patients in the 3.5 mg/kg Cladribine Tablets cohort reported a serious herpes zoster infection; both of which were reported as resolved (Merck 2017f).

Regarding opportunistic infections, there was no evidence for an increased risk in patients treated with 3.5 mg/kg Cladribine Tablets compared with placebo (1.08 and 1.17 events per 100 PYs, respectively) (Merck 2017f). In addition, the presence of lymphopenia did not affect the rate of opportunistic infections in the 3.5 mg/kg Cladribine Tablets cohort: 1.72 events per 100 PYs in patients who experienced lymphopenia compared with 1.03 events per 100 PYs in patients who did not experience lymphopenia (Merck 2017f).

Table 55: Incidence of infections in the integrated safety analysis

Infection	Incidence, events per 100 PYs	
	Placebo (n=641)	Cladribine Tablets 3.5 mg/kg (n=923)
Any infection	27.05	24.93
Any severe infection	0.86	0.84
Any herpes zoster infection	0.20	0.83
Any severe herpes zoster infection	0.05	0.09
Oral herpes	0.55	0.59
Herpes simplex	0.05	0.15
Genital herpes	0.00	0.03
Any opportunistic infection	1.17	1.08

SOURCE: (Merck 2017f)

PYs: Person years

Herpes zoster and opportunistic infections are considered an important potential identified risk of Cladribine Tablets and as such, the following risk mitigation measures are proposed (Merck 2017j):

- Screening for latent infections, in particular tuberculosis and hepatitis B and C, must be performed prior to initiation of therapy in year 1 and year 2
- Initiation of Cladribine Tablets should be delayed until the infection has been adequately treated.

Given that Cladribine Tablets may cause lymphopenia as a result of its mechanism of action, the possibility of serious infections such as progressive multifocal leukoencephalopathy (PML) may be of concern. In clinical trials of Cladribine Tablets in MS, no cases of PML have been reported during a total observation period of more than 8,500 PYs (Merck 2017f).

Malignancies

For the analysis of malignancies, data from the clinical trials as well as the Global Drug Safety database (cut-off date 5th November 2015) were used (Merck 2017f). Since the original marketing authorisation application of Cladribine Tablets in 2009, the availability of data pertaining to patient exposure to Cladribine Tablets has increased substantially, to 8,650 PYs (4.2-fold increase) in patients exposed to cladribine and to 2,361 PYs for placebo (2.9-fold increase). As such, some patients have now been followed for more than 8 years via the PREMIERE registry and extension studies (Merck 2017f).

A single analysis group was developed for the malignancy cases from all cladribine studies in MS used in the integrated analysis of safety (Merck 2017f). This includes data from the early Scripps studies, all dose levels, patients treated with concomitant IFN-β and patients treated with other DMTs in the PREMIERE registry. The broad cladribine analysis group was established to ensure a conservative approach to analyses. If a patient received placebo and then crossed over to a cladribine treatment arm, all subsequent data was considered for the cladribine analysis group. Conversely, if a patient was treated with Cladribine Tablets followed by placebo, the patient would always remain a part of the cladribine analysis group (Merck 2017f).

The various study designs and conservative approach have resulted in considerable number of long-term follow-up patients who have been exposed to cladribine compared with placebo (Merck 2017f). Such an imbalance in observational follow-up should be taken into account when interpreting conclusions based on safety observations.

The malignancy incidence rate comparison between the cladribine and placebo groups was performed using both the difference in incidence risk (RD; risk difference) and the incidence rate ratio (RR) (Merck 2017f). In the extreme case that a zero malignancy rate is reported, as in the case for the placebo cohorts in CLARITY and ORACLE MS, it can be difficult to correctly assess the cladribine malignancy

data in relation to placebo. As such, neither a RD nor RR can be calculated. Compared with Phase III trials of other DMTs, this finding of a zero malignancy rate is considered unique (Merck 2017f).

The RDs and RRs have been calculated for cladribine versus placebo are summarised in Table 56. The risk difference of malignant tumours between patients treated with cladribine compared with placebo in the placebo-controlled double-blind and exposed cohort both include zero and therefore, based on these analyses, there was no conclusive evidence for an increased malignancy risk with cladribine (Merck 2017f). In addition, the current pattern of malignancies observed in the Cladribine Tablets clinical trial programme in MS (all exposed subjects) does not show an obvious difference compared with the available data on malignancies in the general population, or in MS patients (Merck 2017f).

Table 56: Comparison of incidence of malignancies between exposure to cladribine and placebo

Cohort	Incidence, n/PYs	Incidence rate per 100 PYs (95% CI[1])	Risk difference per 100 PYs (95% CI[2])
Placebo-controlled double-blind cohort*			
All cladribine patients	8/2397	0.33375 (0.1669, 0.6674)	0.2457 (-0.1803, 0.5849)
Placebo	1/1135	0.08810 (0.0124, 0.6254)	
All exposed cohort**			
All cladribine patients	32/8579	0.37299 (0.2638, 0.5274)	0.2033 (-0.0785, 0.3947)
Placebo	4/2357	0.16970 (0.0637, 0.4522)	

SOURCE: (Merck 2017f)

* Cohort includes CLARITY, CLARITY-EXT, ORACLE MS, PREMIERE, MS-001, Scripps-A, Scripps-B, Scripps-C, and MS-Scripps

** Includes all patients exposed to cladribine, oral, SC injection and IV

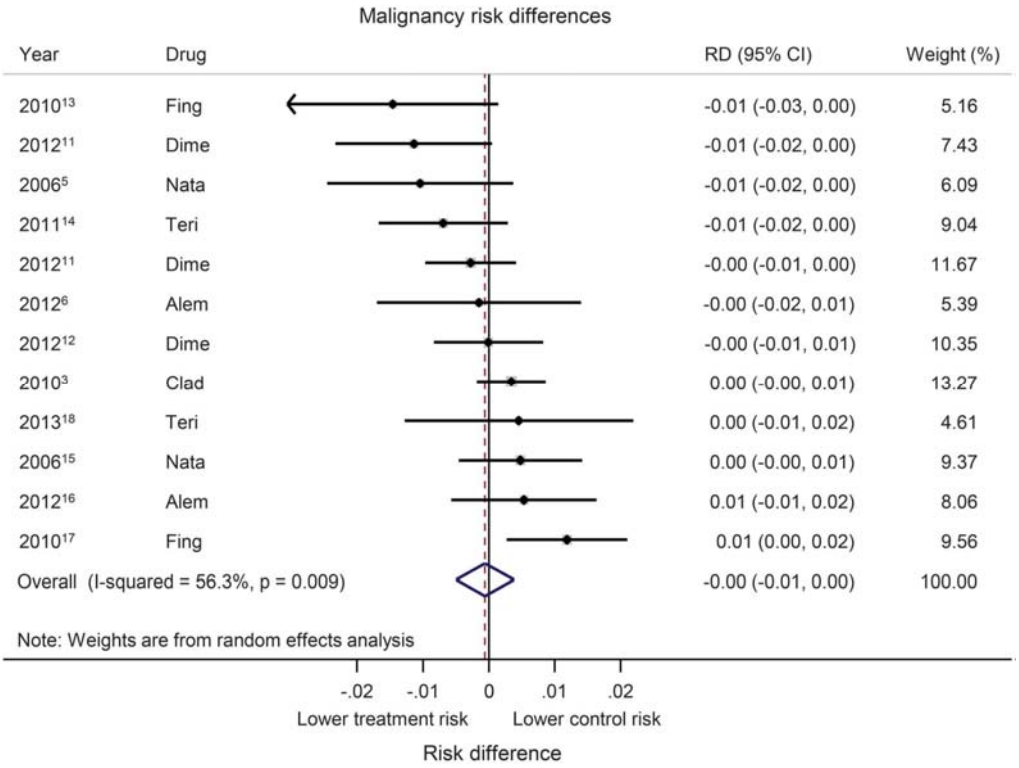
[1] CI is computed with exact Clopper-Pearson formula

[2] CI is computed using the Mittinen and Nurminen method

CI: Confidence interval; PY: Patient-years

The conclusion of the RD analyses described above is supported by an independent meta-analysis of 11 trials (including CLARITY) of licensed DMTs for the treatment of RRMS, which also found that the rate of cancer was significantly lower in the placebo treatment arm of CLARITY compared with all other placebo groups (0% and 1.19%, respectively; p=0.0159) (Pakpoor 2015). The meta-analysis which investigated treatments including Cladribine Tablets, dimethyl fumarate, fingolimod, teriflunomide, natalizumab, alemtuzumab, and glatiramer acetate also found no significant difference in the rate of cancer in CLARITY compared with trials of other DMTs (Figure 10) (Pakpoor 2015).

Figure 10: Malignancy risk differences



SOURCE: (Pakpoor 2015)

Forest plot of malignancy risk differences (RDs) using Mantel-Haenszel pooling. Alem: Alemtuzumab; CI: Confidence interval; Clad: Cladribine Tablets; Dime: Dimethyl fumarate; Fing: Fingolimod; Nata: Natalizumab; Teri: Teriflunomide

Based on the integrated safety analysis, while there were numerical differences in the number of reported malignancies between Cladribine Tablets and comparator groups, the safety data did not provide conclusive evidence that the malignancy risk is increased with Cladribine Tablets. Furthermore, there was no dose-dependent relationship and no evidence of time pattern of the onset of malignancies in relation to the start of treatment with Cladribine Tablets.

B.2.11 Ongoing studies

A time and motion study is currently underway by Merck to quantify the burden of HDA-RRMS for the NHS. Cladribine Tablets can help to address these capacity challenges, because of its own reduced administration and monitoring requirements - linked to the oral, short course posology. When launched, Cladribine Tablets will be the lowest-cost high-efficacy DMT treatment alternative for HDA-RRMS patients with the capacity to deliver an effective treatment for patients that is cost-saving for the NHS. Initial results will become available during the course of this appraisal and will be provided to NICE.

An international Discrete Choice Experiment (DCE) is currently ongoing to elicit patient and clinician preferences on product attributes for the treatment of MS. Merck commissioned this DCE, to establish if there was legitimate patient/clinician requirement, or preferences for different treatments. The UK arm of this study specifically related to patient preferences for treatment characteristics of Multiple Sclerosis (MS) products and sought to provide a timely assessment of the value of the characteristics of a new medicine (Cladribine Tablets) in the eyes of these patients. This study was independently executed by the Institute for Medical Technology Assessment (iMTA) and systematically investigates UK patient preferences for the characteristics of all available Disease Modifying Treatments (DMT's) for MS.

The results of the UK arm of this study are available in time of submission. It reported on the preferences of [redacted] RRMS patients from the UK. It has concluded that Cladribine tablets, when added to the current current competitive landscape of licensed treatment options[redacted] treatment options (overall) and [redacted] [redacted] treatment option. The top line results are presented in

Table and the full UK report is available from Merck on request.

Table [redacted]

B.2.12 Innovation

Cladribine Tablets is an efficacious DMT with a unique posology that can provide multiple benefits for the patient, clinician and healthcare providers.

The key innovations for patients relate to the drug's posology:

- Short course, oral treatment: Cladribine Tablets requires two short courses of oral treatment over 2 years, which could be self-administered at home, providing efficacy over a total of 4 years with no additional treatment required in years 3 and 4. This allows patients to be treated with minimal disturbance to their lives, with fewer medications to take and fewer hospital appointments compared with other DMTs.
- Monitoring burden: The contrast in monitoring requirements between Cladribine Tablets and other DMTs is significant and the impact on patients' daily life is likely to be considerable. Alemtuzumab, another annual treatment (for 2 years) for example, requires monthly blood monitoring, in contrast to the six that will be recommended for Cladribine Tablets during the first 2 years of treatment
- Fewer restrictions on family planning: MS typically affects young adults between the age of 20 and 40 years and twice as many women than men. Patients receiving DMTs are recommended to stop treatment when they become pregnant, thereby increasing the risk of a relapse. The unique posology of Cladribine Tablets allows patients to be treated in Year 1 and Year 2 with no further treatment in Year 3 and Year 4 means that family planning can be considered from 6 months following the last dose of Cladribine Tablets in Year 2.
- Patient preference: The short course, oral nature of cladribine treatment was considered by the ABN as a potential motivator to some patients, preferred over the frequent monitoring burden and adverse effects associated with infusions, a comment that was reflected in the responses from the MS Society and MS Trust in the NICE scope consultations.
- In a Discrete Choice Experiment in the UK. MS patients considered that the attributes of Cladribine Tablets would provide [redacted] treatment options (overall) [redacted] treatment option in a future treatment landscape.

The key benefits for the healthcare system are financial, associated with the considerably lower administration and monitoring burden compared with other DMTs:

- Administration: Over the 4 years of Cladribine Tablets treatment, 20 days of oral dosing is required compared with 8 days of infusion for alemtuzumab, monthly infusions of natalizumab (approximately 48 over 4 years) and over 1,400 oral tablets where patients take one tablet per day.
- Monitoring: During their 2 years of treatment, patients receiving Cladribine Tablets will only require a total of six blood tests over 2 years (patients with severe lymphopenia may require more tests) and monitoring for PML, which is a common opportunistic infection that can be fatal in patients with weakened immune systems (although no case of PML has been reported to date with Cladribine Tablets). However, a baseline MRI should be considered performed before initiating Cladribine Tablets (usually within 3 months) (Merck 2017j). In comparison, patients receiving natalizumab, fingolimod or alemtuzumab require multiple blood tests and additional analyses such as urinalysis, ophthalmological analyses, MRI and cardiovascular monitoring. The lower monitoring burden of patients treated with Cladribine Tablets compared with other DMTs results in lower monitoring costs over 4 years and increases the potential cost savings to NHS England.

Merck is currently conducting the feasibility and pilot stage of a time and motion study which will quantify the burden on the NHS of the monitoring associated with DMTs. This will enable a real world examination of the current pressures which a treatment such as cladribine may help to alleviate (see Section B.2.11). Preliminary results may become available during the course of this appraisal and will be shared with NICE. This study will consolidate the conclusion from our own budget impact analyses that Cladribine Tablets is the lowest cost high efficacy treatment for adults with HDA-RRMS, providing value to both payers and patients because of its short course, oral posology.

Merck believes there are additional system benefits from the innovative dosing regimen of Cladribine Tablets including improved treatment choice, equity of access no matter the geographical location and the opportunity to offer a different clinician-patient/carer experience through a self-management and increased patient accountability approach, leading to improved outcomes and QoL.

At no extra cost to NHS England, Merck will provide an innovative patient support program (PSP) for patients and healthcare professionals that fully integrates the support of a single service provider to enrol and manage patients who receive Cladribine Tablets. This PSP aims to further reduce the administrative and monitoring burden of hospitals and concomitantly accumulate and maintain a registry of patients on Cladribine Tablets to track performance and health-related outcomes.

The innovative aspects of the Cladribine Tablets highlighted in this section provide a considerable step-change in the current treatment pathway to potentially improve the overall management of active RRMS and the lifestyle of affected patients.

B.2.13 Interpretation of clinical effectiveness and safety evidence

There are a wide range of DMTs currently available in the UK providing patients and prescribing neurologists with alternative treatment options for RRMS. In spite of this, there remains an unmet need for effective and well-tolerated treatments for patients with highly active disease.

In Section B.2.3., Merck has summarised the relevant evidence from the clinical development programme for Cladribine Tablets. CLARITY and CLARITY EXT provide the evidence base for the efficacy of Cladribine Tablets and, alongside other studies in an integrated safety analysis, characterise the safety of Cladribine Tablets. The studies provide the evidence for the efficacy of 3.5 mg/kg Cladribine Tablets, delivered in a short-course regimen (2 treatment weeks in year 1 and then again in year 2, and no further Cladribine Tablets treatment in years 3 and 4), which has the capacity to address the unmet needs of patients and the healthcare system for treatments with reduced administration and monitoring burden.

The CLARITY trial demonstrates that treatment with 3.5 mg/kg Cladribine Tablets was more effective than placebo in patients with RRMS across a broad spectrum of clinical and MRI efficacy outcomes (Merck 2017c). Cladribine Tablets were shown to statistically significantly reduce the qualifying ARR compared with placebo ($p<0.001$) and post-hoc analyses showed that the risk of developing 6-month CDP was statistically significantly reduced compared with placebo ($p=0.0014$).

The safety profile is particularly well-characterised through an integrated safety analysis which provides more than 3,000 patient years (PYs) of exposure data. In this analysis, the number of AEs per 100 PYs was marginally higher in patients exposed to Cladribine Tablets compared with placebo (103.29 and 94.26, respectively). Similarly, the number of severe and serious TEAEs per 100 PYs was similar (Cladribine Tablets: 3.7 and 3, respectively versus placebo: 4.0 and 3.6, respectively). Treatment discontinuations per 100 PYs were generally low in both Cladribine Tablets and placebo cohorts (2.07 and 1.05, respectively). There were no relevant differences in deaths per 100 PYs between cohorts (≤0.26 for both cohorts).

Of specific relevance to this decision problem are the results of post-hoc subgroup analyses in patients with HDA-RRMS (including its constituent subgroups, RES and SOT), all demonstrating a numerical reduction in qualifying ARR compared with placebo, consistent with the results for the ITT population. The reductions were statistically significant in patients with HDA-RRMS and RES-RRMS ($p<0.0001$) but not for SOT-RRMS ($p=0.0857$), potentially linked to the small patient numbers in this subgroup. The risk of experiencing 6-month confirmed disability progression (CDP) in the 3.5 mg/kg Cladribine Tablets HDA-RRMS group was significantly lower compared with placebo (HR: 0.18; $p=0.0001$), numerically reduced in RES, albeit not significantly (0.46; $p=0.1599$), and was not estimable in SOT due to zero events in the treated arm.

Robust indirect comparisons conducted for this appraisal confirm that Cladribine Tablets has comparable efficacy to alemtuzumab, natalizumab and fingolimod on key outcomes of relevance, with widely overlapping credible intervals. They are utilised in the economic modelling to build pairwise and incremental analyses for the comparators of interest in this appraisal. This conclusion is supported by a MCDA, conducted by Merck following advice from the EMA, which concluded that Cladribine Tablets has a favourable benefit:risk profile compared to fingolimod, natalizumab and alemtuzumab in patients with high disease activity.

In summary, the considerable clinical data available for Cladribine Tablets describes a positive benefit:risk profile, confirming its place alongside other DMTs for patients with HDA-RRMS.

B.2.13.1.1. Key clinical issues

- Across the 4 years of study treatment, there was no continuous placebo arm. To address this, Merck conducted a treatment switching analysis in collaboration with ScHARR, the results of which are presented in section B.2.9.1.
- Due to the delay in the initiation of CLARITY EXT, some patients who completed CLARITY were not immediately enrolled into CLARITY EXT, resulting in a gap period of varying lengths of time to entry into CLARITY EXT for each patient. However, there was no consistent or meaningful relationship between the duration of the gap period and the majority of efficacy endpoints, suggesting that selection bias is not a concern.
- It was particularly challenging to compare alemtuzumab to other in-scope therapies in the RES and SOT populations due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network. To address this, Merck conducted a meta-regression analysis, utilising unpublished data from the PRISMS trial, to extrapolate the effect size estimates from the active RRMS population to the RES and SOT groups, by relating efficacy to baseline risk, and centring baseline risk to the expected value in each group

B.3. Cost-effectiveness

B.3.1 Published cost-effectiveness studies

Published cost-effectiveness studies in RRMS were identified via a systematic literature review of biomedical literature databases in accordance with the NICE methods guide (NICE 2013). Searches were conducted in January 2017 and the review covered:

- Published peer-reviewed economic evaluations
- Economic models submitted to the NICE STA process
- Unpublished data held by the company

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix G. The completed Philipp's and Drummond's checklists are available in an Excel file in the appendix.

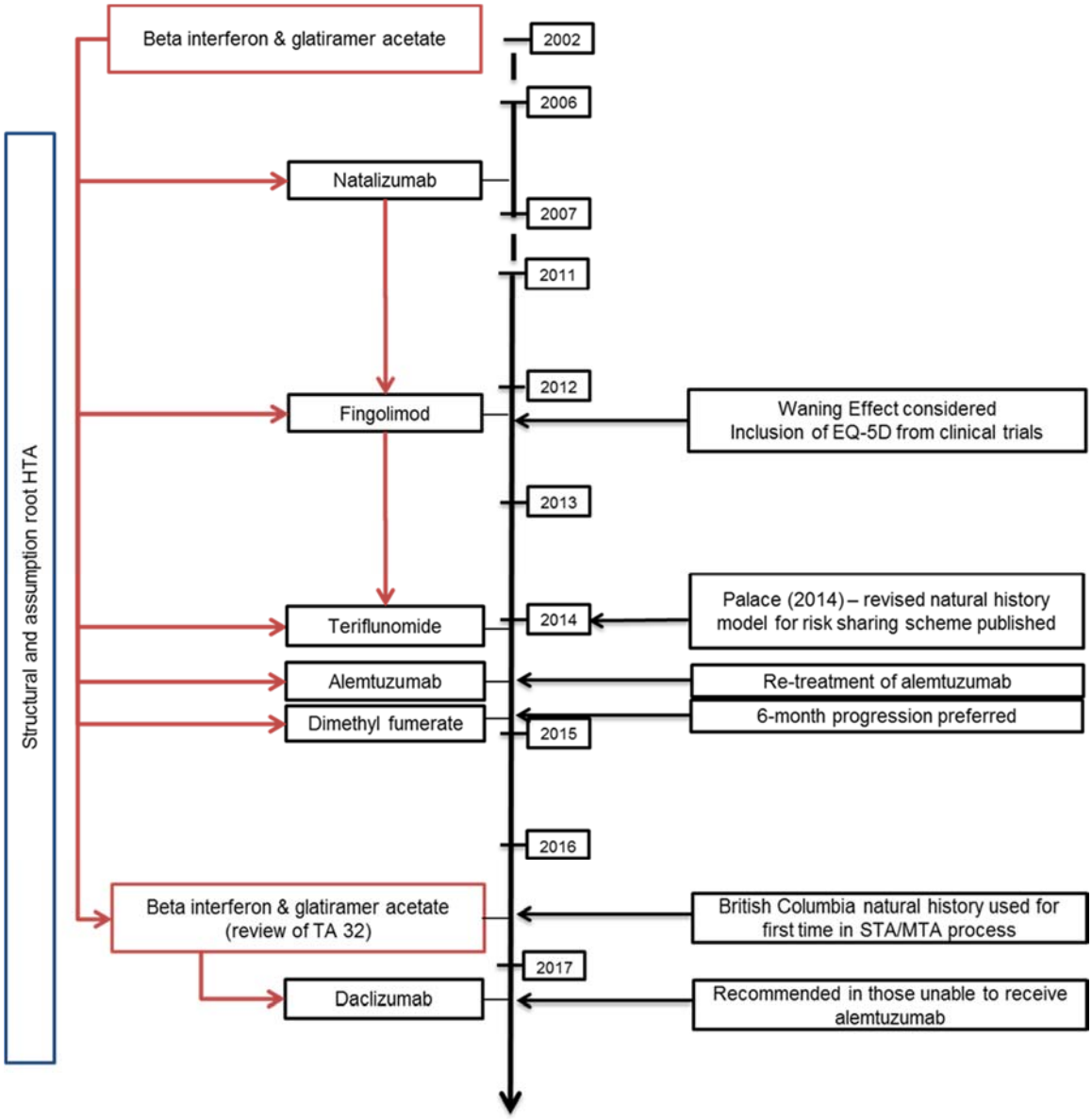
In summary, the searches identified 8 published cost-effectiveness studies reporting from a UK perspective, and 11 economic models that had been submitted to the NICE TA process. None of the studies identified reported the cost-effectiveness of Cladribine Tablets.

The 11 economic models submitted to NICE include 6 submitted to the STA process and 5 submitted to an ongoing MTA:

- Natalizumab (Tysabri): TA127 [STA]
- Fingolimod (Gilenya): TA254 [STA]
- Teriflunomide (Aubagio): TA303 [STA]
- Alemtuzumab (Lemtrada): TA312 [STA]
- Dimethyl Fumarate (Tecfidera): TA320 [STA]
- Daclizumab (Zinbryta): TA441 [STA]
- Beta-interferon and glatiramer acetate (review of TA32): ID809 (ongoing) [MTA]

An overview of the chronology of NICE technology appraisals in RRMS is provided in Figure 11.

Figure 11: Chronology of NICE appraisals for DMT in RRMS



All models submitted to NICE since 2005 have used the same 21-health state structure based on the assessment group model developed for TA32; a multiple technology appraisal of beta-interferon and glatiramer acetate in RRMS. This model includes the use of a cohort-based Markov state transition structure based on the discrete stages of the Expanded Disability Status Scale (EDSS), with separate EDSS states for the relapse-remitting and secondary progressive forms of MS.

The preferred data inputs and modelling assumptions have changed with each successive appraisal. A summary of the key issues highlighted from previous appraisals is shown below:

- “Waning” of drug efficacy beyond the follow up of clinical trials
- Use of EQ-5D data from clinical trials versus published observational studies
- Re-initiation of therapy with alemtuzumab
- 6 versus 3 month confirmed disability progression
- Modelling of the natural history of RRMS, and its associated subgroups
- Consideration of non-medical costs

In TA254, the Committee was concerned about the assumption in the manufacturer's model that the treatment effect observed in the 1-2 year clinical trials was maintained at the same level during the on-treatment periods. It was noted that the model was sensitive to variation in this assumption. The Committee adopted a cautious approach by reducing the efficacy of the drug by 50% after 5-years. In TA303, it was assumed that treatment effect reduced to 75% at year 2 and 50% at year 5. Similar assumptions were applied in TA312, TA320 and TA441. In ID809, the effect of beta-interferon and glatiramer acetate was assumed to reduce by 50% after year 10 of treatment.

In TA127, concerns were raised over the use of a published survey of people with MS to estimate health state utilities due to the potential for selection bias and the generalizability of data from a broader MS population to subgroups. The same survey was used in the manufacturer's base case analyses presented in TA254, TA303, TA312, and TA320. In TA254, the Committee concluded that it was more reasonable to use EQ-5D data collected in the manufacturer's trials, and to use literature estimates for utilities not available in the trials (e.g. for EDSS 6.0 or greater). In all subsequent single technology appraisals (TA303, TA312, TA320 and TA441), the manufacturer's base case analyses used utilities derived from clinical trials and supplemented by literature estimates.

In TA312, the Committee discussed the potential for re-initiation of alemtuzumab, the first therapy in MS with a posology that recommends treatment in years 1 and 2 followed by observation for disease progression. Clinical specialists consulted for TA312 had highlighted that re-initiation with alemtuzumab after the initial two courses was likely in UK practice, and that this trend was likely time-dependent with rates declining for each successive cycle. The costs of re-initiation were considered in the analysis used to inform the final appraisal determination for TA312. Since TA312, only one appraisal has been conducted where alemtuzumab was a comparator within the appraisal scope; TA441. In TA441, the cost of re-initiation with alemtuzumab was considered for years 3-5 with rates modelled based on literature estimates.

In TA320, the Committee concluded that confirmed disability progression at 6 months provided a more robust indication of treatment effect than progression confirmed at 3 months as the latter endpoint may be influenced by relapses. This is in line with guidance issued by the European Medicines Agency that states that an accurate and reliable definition of confirmed progression should include two sequential examinations at least 6 months apart. In TA441, disease progression was modelled based on the 6 month endpoint where data were available. All previous appraisals had used the 3 month endpoint in the model base case analysis.

In TA254, the Committee noted the concerns of clinical specialists that the manufacturer's model did not allow for improvement in EDSS and used data from the London Ontario registry which contained EDSS measures collected in the 1970s and 1980s. It was argued that the model may not reflect the natural history of MS in current UK practice given the use of historical data and because all improvements in EDSS were censored in the original analysis. The implications of using London Ontario data for the natural history model were highlighted in TA312, where the Committee raised concerns that the manufacturer model yielded an implausibly low QALY (~4 QALYs) relative to life years (18 years) for a population with MS treated with DMT. The review group stated that this was probably linked to the use of the London Ontario data and its associated faster rate of progression.

In TA320 and TA441, the inherent limitations of London Ontario were partially addressed by the use of transition probability matrices derived from the placebo arms of clinical trials in place of the London Ontario data for lower EDSS states. These matrices allowed for improvements in EDSS at the rates observed in the clinical studies. For higher EDSS states, London Ontario data were used in the absence of a suitable alternative. In ID809 and TA441, London Ontario data were replaced completely by matrices derived from the British Columbia (BC) registry and published by Palace et al (Palace 2014). In both appraisals, it was concluded that the BC dataset provided a more appropriate set of transitions for the natural history of RRMS than London Ontario, and was hence the preferred source of natural history data.

In TA441, the manufacturer modelled the natural history of disease in people with high disease activity and rapidly evolving disease using data from a less active population in the BC registry. This assumed that progression rates were the same across groups, which clinical experts considered to lack plausibility given that patients with high disease activity or rapidly evolving disease usually progress to higher EDSS states faster than people with less active disease. Alternative data sources were submitted by the manufacturer including placebo matrices from the highly active disease group of DEFINE and CONFIRM and the rapidly evolving severe group of AFFIRM.

In TA303, the Committee was concerned that non-health costs including investment and social community care contributed to a high proportion of costs in the model. It was also unclear to what extent these costs can be considered under the NHS and personal social services perspective in the NICE reference case. Similar concerns were raised in TA312, TA320 and TA441. In TA312 and TA320, the evidence review group and Committee recommended that non-health costs be excluded from the analyses unless it was proven that these costs fall under the personal social services budget. The relevance of non-health care costs was assessed further in TA441, where the evidence review group concluded that some non-health costs would be paid for by the NHS and personal social services. Based on data from Kobelt et al, the review group estimated that 47% of investment costs and 80% of community costs would be borne by the NHS and personal social services.

Finally, it is important to note assumptions and inputs where there is consistency and acceptance amongst past appraisals. These assumptions include:

- Analysis of individual drugs instead of a sequence of therapies: None of the models submitted to NICE have considered the cost-effectiveness of a sequence of therapies in its base case. The benefits of conducting cost-effectiveness analyses of a sequence of therapies were acknowledged in a number of appraisals. However, the NICE Committees for TA303 and TA320 concluded that that the analysis of individual drugs (without a sequence) was the appropriate basis for decision making given uncertainties in the treatment pathway and the modelling of drug sequences, difficulties in cross-model validation and recognizing that consideration of treatment sequences goes beyond the scope of a single technology appraisal
- Consideration of the impact of disability progression on the health utility of caregivers: All of the models submitted to NICE since TA127 have considered the impact of progression on the health of caregivers. This has been accepted by Committees in all recent appraisals
- Benefits of an oral drug may not be fully captured in the QALY estimates: The NICE Committees in TA303 and TA320 acknowledged that the modelled analyses did not capture the potential health benefits of taking an oral drug instead of an injectable or infusion therapy because of the need to assume the same utilities across different formulations. It was therefore recognized that oral drugs provide quality of life benefits other than those captured in the QALY calculations

A summary of the results of the published economic studies is provided in Table 57.

Of the 8 published UK studies identified in the electronic database searches, only two reported the cost-effectiveness of DMT in RES-RRMS or SOT-RRMS.

Maruszczak et al (2015) reported the cost-effectiveness of fingolimod versus dimethyl fumarate in patients with SOT-RRMS. Montgomery et al reported the cost-effectiveness of fingolimod versus natalizumab in patients with RES-RRMS. Neither study reported the cost-effectiveness for all treatments listed in the scope of the appraisal. Hence they are not discussed in detail here. Further review of these studies is provided in Appendix G.

Table 57: Summary list of published cost-effectiveness studies in RES-RRMS or SOT-RRMS

Study	Year	Summary of model	Patient population (average age in years)	Time Horizon	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained)
Maruszczak 2015	2014	Objective: This study sought to model the cost-effectiveness of fingolimod compared to dimethyl fumarate (DMF), for HA RRMS from the perspective of the National Health Service (NHS) in England. A cohort Markov model based on EDSS scores, similar to previous model designs, was constructed. The model considered costs from an NHS and PSS perspective.	Highly active RRMS as per the SmPC for Fingolimod. NR (clinical characteristics based on pooled baseline characteristics for HA RRMS patients from TRANSFORMS, FREEDOMS, and FREEDOMS II studies).	Lifetime (50 years)	Fingolimod: £357 976 Dimethyl Fumarate: £347 618	Fingolimod: 4.70 Dimethyl Fumarate: 3.94	£14 076
Montgomery 2017	2015	To analyse the cost-effectiveness of natalizumab and fingolimod in the RES-RRMS population, from the perspective of the National Health Service (NHS) in the UK. A DES model was developed to track individual RES-RRMS patients, based on EDSS scores. Individual patient characteristics were taken from the RES-RRMS sub-groups of the pivotal trials for fingolimod. The model simulates the events experienced based on patient-specific attributes, and calculates the associated costs and utilities for each individual patient in the cohort.	RES-RRMS-RRMS defined by the presence of 2 or more disabling relapses in one year, with evidence of increasing lesions on magnetic resonance imaging (MRI) scans (1 or more gadolinium-enhancing lesions or a significant increase in T2 lesion load as compared to a previous recent MRI). NR (pivotal phase III trials of fingolimod; TRANSFORMS, FREEDOMS and FREEDOMS II)	Lifetime	Fingolimod: £334 897.93 Natalizumab: £337 501.15	Fingolimod: 6.18 Natalizumab: 6.35	£15,313.06 (SW quadrant)*

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

B.3.2 Economic analysis

A de novo economic analysis was performed to assess the incremental cost-effectiveness of Cladribine Tablets versus relevant alternative treatments within its expected marketing authorisation for HDA-RRMS.

A de novo analysis was required because of the absence of published cost-effectiveness studies for Cladribine Tablets.

In line with published studies and previous NICE appraisals, the de-novo cost-effectiveness analysis was performed using a decision analytical model based on the discrete stages of the EDSS. The model structure used for this appraisal considers the preferences outlined in the Committee deliberations for TA127, TA254, TA303, TA312, TA320, and TA441.

The de novo model allows for:

- Inclusion of the long-term waning in drug efficacy for all therapies including Cladribine Tablets
- Improvements and progression in EDSS as modelled using the preferred natural history data set from British Columbia
- A faster rate of progression in those with SOT-RRMS or RES-RRMS when compared to less active disease
- Use of the European Medicines Agency preferred endpoint of 6 month confirmed disability progression
- Use of health state utility values from the CLARITY study
- Re-initiation of alemtuzumab and Cladribine Tablets

Further detail on each aspect is provided in later sections of the submission.

B.3.2.1. Patient population

As outlined in the Decision Problem (section B.1.1), the expected marketing authorisation for Cladribine Tablets is for the treatment of adults (aged >18 years) with HDA-RRMS as defined by the following clinical and/or imaging features:

- 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMTs, or
- 2 or more relapses in the previous year, whether on DMT or not

This authorisation will permit the use of Cladribine Tablets in people with RES-RRMS and people with SOT-RRMS, as defined in the scope:

- RES-RRMS: People with 2 or more relapses in prior year whether on treatment or not, and at least 1 T1Gd+ lesion
- SOT-RRMS: People with 1 or more relapse in the prior year while on DMT , and at least 1 T1Gd+ lesion or 9 T2 lesions

In line with the final scope for this appraisal, the economic analysis focuses on the use of Cladribine Tablets in people with RES-RRMS and SOT-RRMS.

The RES-RRMS and SOT-RRMS populations are further divided into those who are able to receive alemtuzumab and those who are unable to receive alemtuzumab, in line with the daclizumab NICE recommendation. Overall, there are four populations of interest:

- RES-RRMSa: RES-RRMS and able to receive to alemtuzumab
- RES-RRMSb: RES-RRMS but unable to receive to alemtuzumab
- SOT-RRMSa: SOT-RRMS and able to receive to alemtuzumab
- SOT-RRMSb: SOT-RRMS but unable to receive to alemtuzumab

No analyses are presented for people with active RRMS, including those listed in the final scope as treatment-naïve or previously treated, as these populations are not covered within the expected marketing authorisation for Cladribine Tablets.

The cost-effectiveness analysis was modelled on the characteristics of the RES-RRMS and SOT-RRMS groups of the CLARITY study. The same characteristics are assumed to apply to those who are able to receive alemtuzumab and those who are not, in the absence of defined markers for an inability to receive alemtuzumab.

A summary of the characteristics of the ITT, RES-RRMS, and SOT-RRMS population of CLARITY is shown in Table 58.

Table 58: Patient characteristics in the economic analysis

Characteristic	ITT (for reference only, population not considered)	SOT-RRMS	RES-RRMS
Age at treatment (years): mean	38.7	[redacted]	[redacted]
Standard error	0.474	[redacted]	[redacted]
Female to male ratio:	1.933	[redacted]	[redacted]
Relapse in prior 12 months 0 1 2 >3	 0 (0.0%) 306 (70.0%) 110 (25.2%) 21 (4.8%)	[redacted]	[redacted]
Weight distribution			
40-50kg	6.8%	[redacted]	[redacted]
50-60kg	21.8%	[redacted]	[redacted]
60-70kg	27.4%	[redacted]	[redacted]
70-80kg	23.1%	[redacted]	[redacted]
80-90kg	11.3%	[redacted]	[redacted]
90-100kg	5.3%	[redacted]	[redacted]
100-110kg	2.9%	[redacted]	[redacted]
>110 kg	1.5%	[redacted]	[redacted]
Baseline EDSS status			
EDSS 0	2.9%	[redacted]	[redacted]
EDSS 1.0	3.0%	[redacted]	[redacted]
EDSS 2.0	31.4%	[redacted]	[redacted]
EDSS 3.0	24.3%	[redacted]	[redacted]
EDSS 4.0	23.7%	[redacted]	[redacted]
EDSS 5.0	9.8%	[redacted]	[redacted]
EDSS 6.0	5.1%	[redacted]	[redacted]

Source: Data on file

The ITT population in CLARITY is considered generalizable to the population with MS in clinical practice in England, given that the profile of the active RRMS group in CLARITY (e.g. intention to treat) is similar to that of patients enrolled to the UK multiple sclerosis risk sharing scheme (age 39.4 years, relapses in the past 2 years (median=3), disease duration 8.8 years) reported in Palace et al. No data are available on the characteristics of people with RES-RRMS and SOT-RRMS in England.

As expected, the RES-RRMS and SOT-RRMS groups had a higher number of relapses in the year prior to enrolment compared to the ITT active RRMS population in CLARITY. The RES-RRMS group, in

particular, had a lower mean baseline age ([redacted] 38.7 all patients), a lower female to male ratio ([redacted] versus 1.933 all patients) and a higher number of relapses in the prior year ([redacted] versus 1.348 all patients) than the ITT population and patients with SOT-RRMS. This is consistent with the profile of people with RES-RRMS in the AFFIRM clinical trial (age (years): 33.7 versus 35.6 all patients; number of relapse in the prior year: 2.45 versus 1.53 all patients), the only study identified in the clinical review that published baseline characteristics specific to RES-RRMS.

B.3.2.2. Model structure

A cohort-based multi-state Markov state transition model was developed to simulate the costs and effectiveness of treatment in people with RES- and SOT-RRMS. An annual cycle length was adopted with outcomes evaluated over a time horizon of 50-years. The length of the cycle period is based on approaches accepted in previous appraisals (Tappenden 2001; Tappenden 2009; Peninsula Technology Assessment Group (PenTAG) 2007; Palace 2015; Gani 2008; Chilcott 2003).

The model was programmed in Microsoft Excel 2010 and used visual basic for applications for probabilistic and deterministic sensitivity analyses. In line with the NICE reference case, cost-effectiveness was assessed in terms of the cost per Quality Adjusted-Life Years (QALY) gained. Both costs and health outcomes were discounted at a rate of 3.5% per annum.

As outlined in Table 59, the model for Cladribine Tablets uses a simplified version of the model structures used in previous NICE submissions. In all other respects, the model was developed consistent with precedents set in previous NICE appraisals in RRMS.

Table 59 Features of the economic analysis

Factor	Previous appraisals							Current appraisal	
	Natalizumab (Tysabri): TA127	**Fingolimod (Gilenya): TA254**	**Teriflunomide (Aubagio): TA303**	**Alemtuzumab (Lemtrada): TA312**	**Dimethyl Fumarate (Tecfidera): TA320**	**Daclizumab (Zinbryta): TA441**	**Beta-interferon and glatiramer acetate (review of TA32): ID809 [MTA]**	**Chosen Value**	**Justification**
State structure	21 states based on 10 EDSS states for RRMS, 10 EDSS states for SPMS, and 1 death state	Same as TA127	Same as TA127	Same as TA127	Same as TA127	Same as TA127	Same as TA127	11 states based on 10 EDSS states representing RR and SP forms of MS, and 1 death state	Simplification of 21 state model that combines RR and SP forms of MS together. Further justification provided in the following section.
Time horizon	20 years	50 years	50 years	50 years	30 years	50 years	50 years	50 years	In line with approaches accepted in TA254, TA303, TA312, TA441 and ID809
Treatment waning effect? Manufacturer assumptions Review group assumptions	Not applied	Treatment efficacy was assumed to be reduced by 50% or 75% after the first 2 years	Assume constant treatment effects.	Assumed no waning, but re-treatment; rates of re-treatment commercial in confidence Scenario analyses: assuming long-term waning of treatment effect by 25% or 50% after year 5 for all treatments	75% after 2 years and to 50% after 5 years	25% after 2 years and by 50% after 5 years for all therapies	50% after year 10 for interferon beta and glatiramer acetate	Cladribine Tablets: Treatment effect at100% of levels predicted by meta-analysis for years 0-4 based on evidence from treatment switching analysis of CLARITY and CLARITY extension study. NICE Committee preferred assumptions of 75% of effect in year 4-5, and 50% of effect for year 5 thereafter. Comparators: Treatment effect at 100% of levels predicted in meta-analysis in years 0-2, 75% in years 2-5 and 50% after 5 years for all comparators	In line with Committee preferences in TA320 and TA441
	Not applied	ERG: applied 50%, 75% or 100% after 2 years and 5 years	ERG applied 75% treatment effect after 2 years and 50% treatment effect after 5 years	ERG: applied 75% for year 10 and beyond, or 75% from year 6 to year 9 and 50% from year 10 and beyond	-	-	-		

Factor	Previous appraisals							Current appraisal	
	Natalizumab (Tysabri): TA127	**Fingolimod (Gilenya): TA254**	**Teriflunomide (Aubagio): TA303**	**Alemtuzumab (Lemtrada): TA312**	**Dimethyl Fumarate (Tecfidera): TA320**	**Daclizumab (Zinbryta): TA441**	**Beta-interferon and glatiramer acetate (review of TA32): ID809 [MTA]**	**Chosen Value**	**Justification**
Source of utilities	UK MS survey as published in Orme et al	UK MS survey amended to include EQ-5D from clinical trial blended with MS survey data after review group critique	Same as TA254 using EQ-5D from TEMSO and TOWER clinical studies	Same as TA303	EQ-5D from clinical trials (DEFINE and CONFIRM) blended with MS survey data	EQ-5D from clinical trial blended with MS survey data	Blend of data from literature sources	EQ-5D in CLARITY study supplemented by literature data (Hawton et al)	Following preference for trial data supplemented for literature estimates Literature estimates from best source identified in de novo literature review
Source of costs	(Tyas 2007) (Joint Formulary Committee 2015) (Curtis 2015)	(Tyas 2007) (Joint Formulary Committee 2015) (Curtis 2015)	(Tyas 2007) (Joint Formulary Committee 2015) (Curtis 2015)	(Tyas 2007) (Joint Formulary Committee 2015) (Curtis 2015)	(Tyas 2007) (Joint Formulary Committee 2015) (Curtis 2015)	Manufacturer burden of illness study which was excluded at 2nd meeting ERG included 47% of the investment costs, and 80% of the community and social care costs based on (Kobelt 2000)and compared the cost-effectiveness results using each source (Joint Formulary Committee 2015) (Curtis 2015)	(Kobelt 2000)	(Hawton 2016b) (Joint Formulary Committee 2015) (Curtis 2015)	Preferred data source identified in de novo literature review; consistent with source of data used for health state utilities (Joint Formulary Committee 2015) (Curtis 2015)

B.3.2.2.1. Overview of model structure

The model comprises two mathematical models:

1. a natural history reference model, developed using data on the disability and relapse status of people receiving best supportive care (BSC), and
2. a treatment-adjusted model, which combines the natural history reference model with data on the comparative efficacy and safety of DMT versus placebo

The reference and treatment-adjusted models use the same core 11-health state structure as illustrated in Figure 12. This structure comprises 10 health states representing disability status according to the EDSS, and a single state for death from all causes. Categorisation of the EDSS is based on the approach used by Palace et al (Table 60).

The health state structure used in this appraisal is a simplified version of the 21-health state structure used in previous RRMS appraisals, and which included 10 EDSS states for RRMS, 10 EDSS states for SPMS, and a single state for death. The simplified 11-health state structure excludes the 10 EDSS states for SPMS, and instead models disability progression in patients who develop SPMS together with those who remain RR. This is justified on the basis that health-related quality of life is more closely related to EDSS state than to clinical form of MS, because it is difficult to clearly identify the transition from the RRMS into the SPMS subtype it is difficult to reliably model the conversion from one form to another, and the addition of SPMS-specific health states requires the use of SPMS-specific transition rates from the London Ontario registry as the only source of SPMS-specific natural history data. As summarized in the economic review, there are concerns regarding the limitations of the London Ontario registry.

The pooling of the RRMS and SPMS states is consistent with the approach taken by Palace et al when modelling the natural history of RRMS for the UK risk sharing scheme (Palace 2014). This included the use of all EDSS scores collected in people with RRMS including those recorded after a person had developed SPMS. Differences in transition rates between the RRMS and SPMS stages are accounted for in the averaged transition rates reported by Palace et al, and when subsequently applied in the economic model for Cladribine Tablets. When developing the Markov model, Palace et al did not consider MS course (i.e. RRMS versus SPMS) as a covariate in the analysis, because SPMS is “simply a later stage of the relapsing remitting form of the disease and the transition has considerable overlap”.

Table 60: Kurtzke Expanded Disability Status Scale (EDSS)

Score	Description	EDSS state in model
0	Normal neurological exam	0
1.0	No disability, minimal signs in one FS	1
1.5	No disability, minimal signs in more than one FS	
2.0	Minimal disability in one FS	2
2.5	Mild disability in one FS or minimal disability in two FS	
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking	3
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking	
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m	4
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m	
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m	5
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m	
6.0	Requires a walking aid - cane, crutch, etc. - to walk about 100m with or without resting	6
6.5	Requires two walking aids - pair of canes, crutches, etc. - to walk about 20m without resting	
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day	7
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair	
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms	8
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions	
9.0	Confined to bed. Can still communicate and eat	9
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow	
10.0	Death due to multiple sclerosis	Death

SOURCE: (Kurtzke 1983)

B.3.2.2.2. Detailed summary of modelled clinical pathway

At model entry, the cohort was proportionally assigned to the 10 EDSS states according to the baseline EDSS distribution in the CLARITY study population (Table 58). Over yearly cycle periods, the cohort was at risk of:

- experiencing disability progression (move to a higher EDSS state)
- improving in disability status (move to a lower EDSS state),
- remaining at their current level of disability (remain in their current EDSS state),
- death

The cohort was also at risk of experiencing one or more acute relapse events during each cycle. These events were modelled separately to EDSS-related disability progression and were calculated by applying an annualised relapse rate to the number of patients alive in the model. This is in line with approaches adopted in previous appraisals.

The costs are calculated from the time spent in each EDSS state and with relapses, combined with the costs assigned to each state. This includes costs covered under the National Health Service (NHS) and Personal Social Services (PSS) perspective, such as drug acquisition, administration, and monitoring, the support and treatment given for relapse events, direct EDSS-related medical and non-medical care costs, and costs for managing drug-related adverse events. A societal perspective that includes the substantial wider societal costs of MS was also included as sensitivity analysis in the submission.

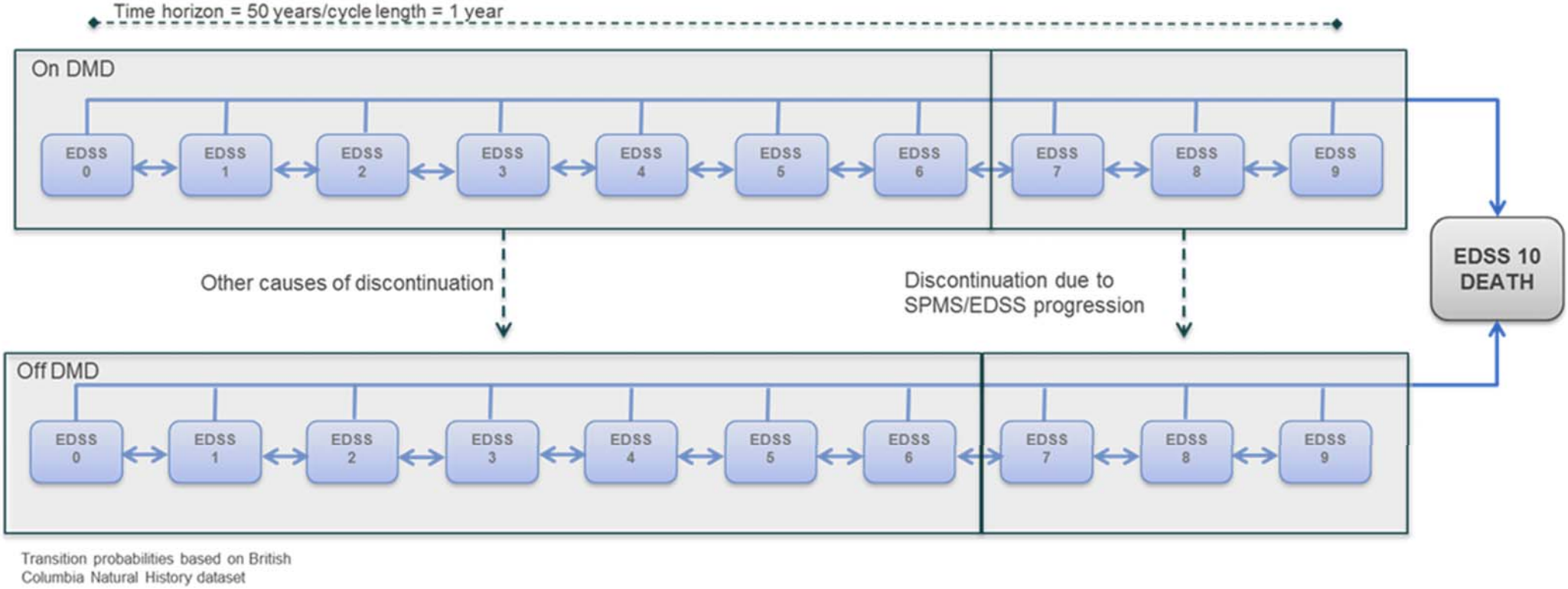
In line with previous models, the majority of costs are modelled based on the mid-cycle occupancy for each state, which is estimated from the average number of patients in each state at the start and end of each cycle (e.g. equivalent to half-cycle correction). The exceptions are the acquisition and administration costs for Cladribine Tablets and alemtuzumab, which are given at model entry and at the start of year 1 (excluding re-initiation beyond the fixed course). These costs are applied to state occupancy at the start of each “treated” cycle. This follows Committee preferred approaches in TA312, and TA441.

The health effects of treatment were modelled in terms of QALYs; a combined measure of the quality and duration of life. The quality of life aspect was modelled using health state utilities (HSU) derived from various sources including the literature and EQ-5D questionnaires collected in CLARITY. This is in line with Committee preferences in TA254, TA303, TA312, TA320, and TA441.

The model considered the impact of disability status, relapses, and drug-related adverse events on the health related quality of life of the person with MS. In line with previous NICE appraisals, an additional QALY loss associated with the impact of disability status on the quality of life of caregivers was also included.

The QALYs accrued from the EDSS progression and infusion and injection site reactions were modelled on the mid-cycle occupancy of each state (e.g. equivalent to half-cycle correction). The QALYs associated with relapse and all other adverse events were modelled as QALY losses based on the number of events experienced.

Figure 12: health state structure of the 11-state model including periods on and off DMT



B.3.2.2.3. Treatment-adjusted model

The treatment-adjusted model combines the reference model detailed in the previous section with the comparative efficacy and safety of DMT versus placebo. As with the natural history model, the treated cohort was at risk of progressing, improving, or staying in the same EDSS state, or entering the death state.

Treatment with a DMT was assumed to alter the natural course of disease by:

- decreasing the probability of progressing in EDSS state over time, versus BSC
- decreasing the annualised rate of relapse versus BSC
- altering the incidence of drug-related adverse events

There was no assumed effect of DMT on the probability of improving in EDSS and the probability of death, which were fixed to the values used in the natural history model. The probability of remaining in the same EDSS state was increased to reflect that fewer patients progressed on DMT. This follows approaches accepted in all previous appraisals in RRMS.

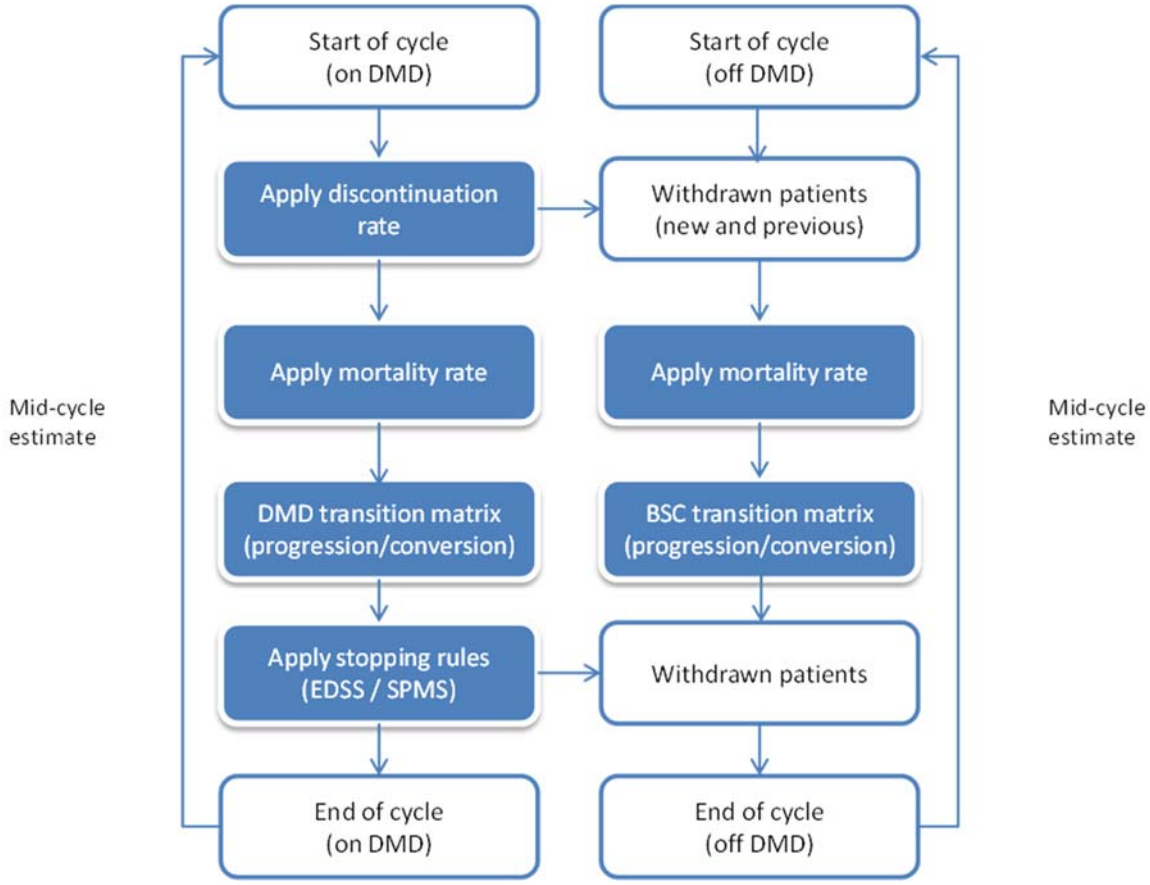
The efficacy and safety inputs to the model were derived from meta-analyses of clinical data identified from the systematic literature review. Further detail is provided in section B.3.6.1.

As in previous appraisals, patients were assumed to benefit from treatment while “on DMT”. These effects were assumed to gradually wane over time. In each model cycle, patients “on DMT” were at risk of discontinuing treatment for reasons such as loss of efficacy and tolerability. Further detail on the discontinuation rules is provided in section B.3.2.3.2

Patients who discontinued treatment were assumed to retain the cumulative benefits of DMT up to the point of discontinuation. Upon discontinuation, patients immediately switched to BSC, with progression and relapse rates based on the natural history model. No further treatment was given in line with models accepted in previous NICE appraisals.

A schematic of the calculation process for the treatment-adjusted model is shown in Figure 13.

Figure 13: Calculation process for DMT-treated patients



BSC: Best supportive care; DMT: Disease modifying drugs; EDSS: Kurtzke Expanded Disability Status Scale; SPMS: Secondary progRES-RRMSsive multiple sclerosis

The costs and outcomes of drug-related adverse events were considered in the model, and included serious but rare "one-off" events (Progressive Multifocal leukoencephalopathy (PML)), macular oedema, hypersensitivity, autoimmune thyroid-related events, immune thrombocytopenic purpura (alemtuzumab only), and "ongoing" events related to infusion and injection site reactions.

Relevant adverse events were identified from a review of the summary of product characteristics for each drug in scope, from previous economic models (Tappenden 2001; Tappenden 2009; Peninsula Technology Assessment Group (PenTAG) 2007; Palace 2015; Gani 2008; Chilcott 2003), and following consultation with clinical experts.

B.3.2.2.4. Clinical justification for health state structure

The state structure of the 11-health state model is based on the natural history transition matrix reported by Palace et al and used in the UK risk sharing scheme and recent NICE multiple technology appraisal of interferon beta and glatiramer acetate (Warwick Evidence 2016).

The model uses the EDSS system for defining disability status and estimates the full impact of disease from pre-diagnosis at EDSS 0 (normal neurological examination) to EDSS 9.5 (confined to bed) and death. The EDSS is an appropriate tool for assessing disability as increasing EDSS has been shown to correlate with increasing levels of socio-economic burden (e.g. productivity), and decreasing levels of HSU in people with MS (Kappos 2010; Ahlgren 2012; Gani 2008; Gold 2010). EDSS is also the recommended tool for measuring disability progression by the European Medicines Agency (EMA) and is the preferred measure of disability progression in MS clinical trials, making it an appropriate measure for the comparison (e.g. meta-analysis) of drug effects on disability status.

The model also captures the independent effects of relapses on the costs and health related quality of life of people with MS. The inclusion of relapse events separately to EDSS progression is justified on

the basis that relapses have been associated with an increase in visits to health care professionals, absenteeism from work, the need for additional support to undertake routine tasks, as well as impact on the health related quality of life of people with MS (Duddy 2014). These effects have been shown to occur independently of EDSS state (Orme 2007; Ruutiainen 2016). Reduction in relapse events is also a key goal of DMT, and the primary endpoint of most clinical trials in RRMS highlighting its importance as measures of clinical effect in MS.

Patients who discontinue DMT or experience progression after alemtuzumab or Cladribine Tablets were assumed to receive BSC. In practice some patients are likely to receive further DMT treatment upon discontinuation or evidence of progression. This has been noted in previous appraisals, where Committees have highlighted the value of assessing the cost-effectiveness of treatments when given in a sequence of therapies. However, in TA303 and TA320, the NICE Committees concluded that the analysis of individual drugs (without a sequence) should be the basis for decision-making because of:

- Lack of an established common treatment pathway
- Uncertainties related to the modelling of sequencing
- Difficulty with cross-model validation
- Treatment sequencing goes beyond the scope of a single technology appraisal

Hence, following NICE precedent, the economic analysis for Cladribine Tablets does not consider the cost-effectiveness of treatment when given within a sequence of therapies.

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention and comparators

The economic analysis presented in this submission focuses on the use of Cladribine Tablets in people with RES-RRMS and SOT-RRMS.

The final scope for this appraisal lists the following comparators:

RES-RRMS:

- Natalizumab
- Alemtuzumab
- Daclizumab (subject to ongoing appraisal)

SOT-RRMS:

- Fingolimod
- Alemtuzumab
- Daclizumab (subject to ongoing appraisal)

The final appraisal determination (FAD) for daclizumab (TA441) was published shortly after finalisation of the Cladribine Tablets scope. The FAD for TA441 states that daclizumab is recommended as a treatment for RES-RRMS and SOT-RRMS in people who are contraindicated or otherwise unable to receive alemtuzumab.

To comply with the original scope for this appraisal, the RES-RRMS and SOT-RRMS populations were divided into two further sub-groups representing those who are able to receive alemtuzumab and those who are contraindicated or otherwise unable to receive alemtuzumab. This is to reflect that daclizumab is not a recommended comparator to Cladribine Tablets in people who are able to receive alemtuzumab.

After excluding daclizumab, the relevant comparators to Cladribine Tablets in people able to receive alemtuzumab are fingolimod and alemtuzumab for SOT-RRMS and natalizumab and alemtuzumab for RES-RRMS. For people who are contraindicated or otherwise unable to receive alemtuzumab, the recommended options are daclizumab and fingolimod for SOT-RRMS and daclizumab and natalizumab

for RES-RRMS. By definition, alemtuzumab is not a relevant choice for those who are contraindicated or otherwise unable to receive alemtuzumab.

A summary of the comparators by population is shown in Table 61.

Table 61: Summary of populations and comparators considered within scope

Population	Definition	Comparators within scope
Comparators listed in the final scope, within the expected marketing authorisation for Cladribine Tablets		
RES-RRMS	People with 2 or more relapses in prior year whether on treatment or not, and at least 1 T1Gd+ lesion	Natalizumab Alemtuzumab Daclizumab
SOT-RRMS	People with 1 or more relapse in the prior year while on DMT , and at least 1 T1Gd+ lesion or 9 T2 lesions	Fingolimod Alemtuzumab Daclizumab
Economic analyses conducted in line with final scope and daclizumab FAD		
RES-RRMSa	RES-RRMS and able to receive to alemtuzumab	Natalizumab Alemtuzumab
RES-RRMSb	RES-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Natalizumab Daclizumab
SOT-RRMSa	SOT-RRMS and able to receive to alemtuzumab	Fingolimod Alemtuzumab
SOT-RRMSb	SOT-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Fingolimod Daclizumab

Fingolimod and daclizumab are available to the NHS at a discounted list price as agreed in their patient access schemes (TA254 and TA441). The discounts agreed in the patient access schemes are commercial in confidence.

B.3.2.3.2. Discontinuation rules

The rules for discontinuing DMT in the economic analysis were based the NHS England Clinical Commissioning Policy for DMT in RRMS (NICE 2014) (NHS England/D04/P/b, and the Association of British Neurologists guidelines for prescribing DMT in RRMS (revised in 2015).

The NHS commissioning policy states that fingolimod (SOT-RRMS) and natalizumab (RES-RRMS) should be stopped if one or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 3-month period of therapy
- Unacceptable adverse effects of the drug
- The patient is pregnant, breast feeding or attempting conception
- Development of confirmed secondary progressive disease causing inability to walk for more than 6 months
- The current policy does not report stopping criteria that relate specifically to daclizumab or alemtuzumab.

The 2015 revised ABN guidelines for prescribing DMT in RRMS state that clinicians should consider stopping treatment in the following scenarios:

- Significant side effects
- Development of non-relapsing SPMS
- Pregnancy

The ABN guidelines do not provide stopping rules that are specific to an individual DMT. Overall, the ABN guideline and NHS commission policy advocate similar criteria for stopping DMT.

The modelling of discontinuation due to the onset of SPMS causing an inability to walk was captured through the transition of patients between EDSS states, and the application of a "discontinuation rule" for patients who transition beyond a set EDSS level in the model. On the advice of Dr. Jacqueline Palace, a UK clinical expert familiar with the BC natural history data set, it was assumed that any patient transitioning to EDSS state 7.0 or greater would be considered SPMS and hence discontinued from therapy. The model includes the flexibility to vary the "cut-off" for EDSS discontinuation, which were explored as part of the comprehensive sensitivity analysis.

The modelling of discontinuations due to reasons unrelated to clinical diagnosis (e.g. tolerability) was captured through a separate annual discontinuation probability applied in each cycle. In the base case, the probability of discontinuation was assumed constant over time following TA441. The Excel model allows for probabilities to vary over the periods of 0-2, 2-10 and 10+ years to account for differences in the longer term risk of drug tolerability and compliance. Sensitivity analyses were performed to test the sensitivity of results to variation in discontinuation probabilities over time.

Alemtuzumab and Cladribine Tablets are fixed course treatments that each have a posology that recommends 2 treatment courses administered over a 2 year period, with an interval of 12 months between first and second courses. For alemtuzumab, the summary of product characteristics states that "therapy is recommended as 2 treatment courses with safety follow-up of patients from initiation of treatment and until 48 months after the last infusion". For Cladribine Tablets, the draft summary of product characteristics states that "Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied". For alemtuzumab and Cladribine Tablets, the usual concept of treatment "discontinuation" does not apply as most patients are expected to receive two short courses of treatment and to then undergo observation for disease progression. The probability of discontinuation for Cladribine Tablets and alemtuzumab was therefore applied to the first cycle only to capture discontinuations between the first and second courses.

Patients who complete the two courses were assumed to remain "on DMT" without actively receiving drug, and hence were no longer considered at risk of discontinuation. The efficacy of Cladribine Tablets and alemtuzumab was assumed to wane over time in recognition that the full effect may not persist for a lifetime. This is in line with Committee preferred approaches for modelling the efficacy of alemtuzumab in TA312 and TA441. For consistency with continuously administered drugs, it was also conservatively assumed that the effects of Cladribine Tablets and alemtuzumab would stop after a patient transitioned beyond EDSS state 7.0 (i.e. developed SPMS).

B.3.3 Clinical parameters and variables

B.3.3.1. Natural history reference model

The following section contains a summary of the data sources used to model acute relapse events, EDSS disability progression, and mortality in the natural history reference model.

B.3.3.1.1. Natural history model - acute relapse events

During each cycle of the simulated time horizon, the total number of acute relapse events experienced by the cohort was calculated by multiplying the number of patients alive by the annualised relapse rate derived from published sources.

The relapse rate was modelled as a function of time as opposed to EDSS state. This differs to approaches used in previous appraisals, where relapse rates were modelled as a function of EDSS state using data from UK MS surveys conducted at least 10 years prior.

By relating relapse rate to EDSS state, previous models had incorporated an additional indirect effect of DMT on relapse rate through its effect on progression rate, which leads to double-counting of the benefits of DMT when applying independent effects to both EDSS progression and relapse rate. This approach also relies upon historical data that may not accurately reflect relapse rates in contemporary practice given the trend towards lower annualized rates in the placebo arms of contemporary clinical

trials (Steinvorth 2013). For these reasons, the annualised relapse rate in the model was assumed to be independent of EDSS.

The annualised relapse rate was calculated as follows:

- Estimate the annualised relapse rate during the first year of the simulation
- Estimate the change in annualised relapse rate over time

The annualised relapse rate in the first year was modelled on the rates from the placebo arm of CLARITY. This was to ensure consistency between relapse rate and the baseline characteristics of the modelled population, which was also based on the CLARITY study population.

A summary of the annualised relapse rate for RES-RRMS and SOT-RRMS is shown in Table 62, alongside the rate from the ITT population of CLARITY (not used in model provided as reference).

Table 62: Annualised relapse rate in placebo arm of CLARITY trial

Population	Mean rate	Lower 95% confidence interval	Upper 95 confidence interval
Active RRMS	0.34	0.30	0.38
SOT-RRMS (a and b)	[redacted]	[redacted]	[redacted]
RES-RRMS (a and b)	[redacted]	[redacted]	[redacted]

Source: (Merck 2017c)

The annualised relapse rate in the second and subsequent years were modelled by combining the rate in the first year with the annual change in relapse rate per additional year of disease, via the following equation:

$$ARR(t) = \begin{cases} ARR(1) & if\ t = 1 \\ ARR(t-1) \times RR & otherwise \end{cases}$$

Where t is time period, ARR is annualised relapse rate, and RR is the change in relapse rate per additional year with MS.

The change in relapse rate was obtained from the published literature as clinical trials are not designed to provide assessments of the trend in relapse rate over time.

For consistency with the modelling of EDSS progression, data on the change in relapse rate over time were sought from the British Columbia Multiple Sclerosis (BCMS) registry. A single study by Tremlett et al was identified (Tremlett 2010), which reported the longitudinal relationship between annualised relapse rate and the characteristics of sex, age at onset, current age and disease duration using patient-level data from BCMS registry (Tremlett 2010).

The annualised relapse rate in the BCMS decreased by an average of 17% every 5 years based on a median follow-up of 20.6 years, 51,120 person-years of exposure and 11,722 post-onset relapses (Tremlett 2010). Age of onset of MS was strongly associated with the rate of decline, with estimates ranging from 30.5%, to 6.9% in onset ages of 40+ years to less than 20 years old respectively. The mean age of onset for the average patient in CLARITY was 30-40 years based on a mean baseline age of 38.7 years and disease duration of 5.18 years. The rate reduction corresponding to this group was used in the base case (22.9% [95% confidence interval 19.4-26.2%] for every 5 years).

The 5-year decline in annualised relapse rate was converted to a yearly decrement using the following formula:

$$RR = e^{(\frac{1}{t} \times \ln(RR_t))}$$

Where RR is the rate reduction and t is the time period over which the reduction occurs (e.g. 5-years). For the base case, the proportional reduction was estimated at 5.07% per year[1].

A plot showing the annualised relapse rate over time for the BSC population in the RES-RRMS and SOT-RRMS populations is shown in **Error! Reference source not found.**.

[1] Or 94.9% of ARR for each cycle in the model

In the probabilistic analysis, the mean annualised relapse rate was sampled using a log-normal distribution, and the proportional reduction in annualised relapse rate was sampled using a beta distribution.

B.3.3.1.2. Natural history model - duration of relapse event

The health effects of relapses were measured as QALY losses, and were calculated from the mean duration of each relapse event multiplied by the loss in utility associated with each relapse.

The mean duration of each relapse event was obtained from data collected in the CLARITY study (Table 63). Relapse data were summarised according to the requirement for hospitalisation and were pooled across treatment groups in CLARITY. The pooled data were applied to relapses experienced on all treatments in the analysis.

Table 63: Duration of relapse event recorded in the ITT population of the CLARITY clinical study by treatment group and hospitalisation status

Event	Placebo, N=437	Cladribine, N=433	Total
Duration of relapses requiring hospitalisation	Mean = 39.14 SD = 7.59	Mean = 29.64 SD = 4.85	Mean = 34.41 SD = 6.38 SE = 0.22
Duration of relapses not requiring hospitalisation	Mean = 42.94 SD=7.27	Mean = 34.31 SD = 4.89	Mean = 38.64 SD = 6.20 SE = 0.21

Source: (Merck 2017c)

B.3.3.1.3. Natural history model - EDSS progression

The transition of people between each EDSS state was modelled using a Markov state transition matrix. The dimension of the transition matrix was 10x10 for the 11-health state structure. The 11th health state in the model corresponds to the death state, which was modelled separately to EDSS transitions.

Transition matrices for the natural history of RRMS were identified from previous NICE appraisals (NICE Technology appraisal guidance 2012; NICE Technology appraisal guidance 2014a; NICE Technology appraisal guidance 2014b; NICE Technology appraisal guidance 2014c), and publications associated with the UK risk sharing scheme (Palace 2014; Palace 2015).

The publications by the UK risk sharing scheme (RSS) included a review and critical appraisal of MS natural history data sets, conducted by the scientific advisory group to the scheme (Department of Health. 2002). The review included a detailed independent examination of patient registries through literature reviews, expert opinion, discussion with the clinical leads for the scheme, and through

collaboration with the Sylvia Lawry Centre for Multiple Sclerosis Research (Palace 2014). The RSS review considered the availability of EDSS score measurements, the use of data smoothing or manipulation, the size of the database, and the similarities of the database to the UK health system in determining the best data to use as the natural history comparator in future economic evaluations.

A brief summary of the sources is provided in Table 64.

Table 64: Summary of available data sources for modelling the natural history of RRMS

Source	Population	Notes
British Columbia	• Population who meet the ABN criteria for disease modifying drugs • Naïve patients eligible for first-line therapy	• Long-term study (~10 years) • Cohort characteristics matched to the UK risk sharing scheme population • Matrices allows for improvements in EDSS as observed in clinical studies and other natural history studies
London Ontario	• Data available in patients with active RRMS	• Long-term study (up to 20 years); • Subject to intrinsic flaws, because of post-hoc data censoring. • Matrix does not allow for improvements in EDSS as observed in clinical studies and other natural history studies
Gani et al, 2007	• Placebo population of the AFFIRM clinical study • Separate analyses performed on people with active RRMS, and RES-RRMS	• Short-term RCT (up to 2-years) • Matrix allows for improvements in EDSS as observed in clinical studies and other natural history studies. • Data specific to patients with active RRMS or RES-RRMS

SOURCE: (Ebers 2001; Palace 2014; Gani 2008; Gani 2007)

ABN: Association for British Neurologists; SOT-RRMS: Highly active relapsing-remitting multiple sclerosis; HTA: Health technology assessment; RCT: Randomized controlled trial; RES-RRMS: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; UK: United Kingdom

The scientific advisory group to RSS concluded that the BCMS was the best data set available for modelling the natural history of RRMS, scoring highly in terms of the methodology used to capture EDSS score (EDSS prospectively captured) and registry completeness (covering an estimated 80% of the BCMS population). The BCMS was therefore the preferred data source for the model for Cladribine Tablets.

The transition matrices for the BCMS registry were published in Palace et al (Palace 2014). The objective of this analysis was to generate a natural history Markov state transition matrix for untreated patients who could be used as a historical control in the UK risk sharing scheme. The analyses were therefore performed on a cohort of people with MS that met the eligibility criteria for DMT treatment in the UK as outlined below:

- EDSS ≤6.5
- Age ≥18 years old
- Definite diagnosis of MS, as per Poser criteria
- Two previous relapses in the last two calendar years

The registry data were cleansed prior to analysis to ensure that the output reflected EDSS progression independent of relapses in an untreated cohort. This included:

- Excluding EDSS scores collected at the time of relapses or when disability was affected by confounding factors (i.e. hip fractures)
- Excluding EDSS scores collected after 1995, the last full year that DMT were not used widely in the database population

Analyses were performed on integer EDSS scores with fractional values rounded down (e.g. EDSS 1.5 was scored as EDSS 1.0).

Transition probability matrices were derived using both discrete and continuous-time multi-state methods, and with and without baseline covariates. The discrete time model was judged to provide a poor fit to the data underestimating EDSS in earlier years and overestimating in later years. This model was not considered further and instead analyses were performed using the continuous time model.

Baseline covariates including sex, age at MS onset, and disease duration were considered in the statistical analysis. A model containing onset age as a binary covariate was deemed the most suitable model for the RSS analysis. This led to matrices conditional on median age of onset of 1) less than 28 years and 2) over 28 years, shown in Table 65 and Table 66.

The matrix based on a median age of onset of over 28 years was used in the base case given the mean baseline age (38.7 years) and disease duration (5.18 years) of the modelled population. Sensitivity analyses were performed using the matrix for median onset less than 28 years.

Table 65: Annual transition probabilities (multiple sclerosis age of onset <28 years)

From \To	0	1–1.5	2–2.5	3–3.5	4–4.5	5–5.5	6–6.5	7–7.5	8–8.5	9–9.5	N
0	0.68704	0.21102	0.07195	0.02236	0.00434	0.00136	0.00176	0.00012	0.00003	0.00000	326
1–1.5	0.06122	0.67867	0.16643	0.06462	0.01698	0.00474	0.00667	0.00052	0.00014	0.00001	317
2–2.5	0.01692	0.12656	0.59550	0.17291	0.04537	0.01842	0.02190	0.00182	0.00054	0.00005	317
3–3.5	0.00620	0.05215	0.11647	0.54386	0.09452	0.05730	0.11480	0.01070	0.00366	0.00035	317
4–4.5	0.00176	0.02251	0.06671	0.12107	0.48737	0.10090	0.16644	0.02621	0.00690	0.00067	317
5–5.5	0.00055	0.00562	0.02915	0.05936	0.09153	0.47268	0.28098	0.03961	0.01910	0.00143	317
6–6.5	0.00012	0.00141	0.00447	0.02516	0.03208	0.04241	0.72834	0.11509	0.04566	0.00525	317
7–7.5	0.00001	0.00016	0.00052	0.00260	0.00730	0.00419	0.12197	0.68145	0.16286	0.01895	317
8–8.5	0.00000	0.00001	0.00004	0.00030	0.00057	0.00053	0.01884	0.05747	0.86099	0.06124	317
9–9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00004	0.00178	0.00596	0.17090	0.82125	317

Source: (Palace 2014)

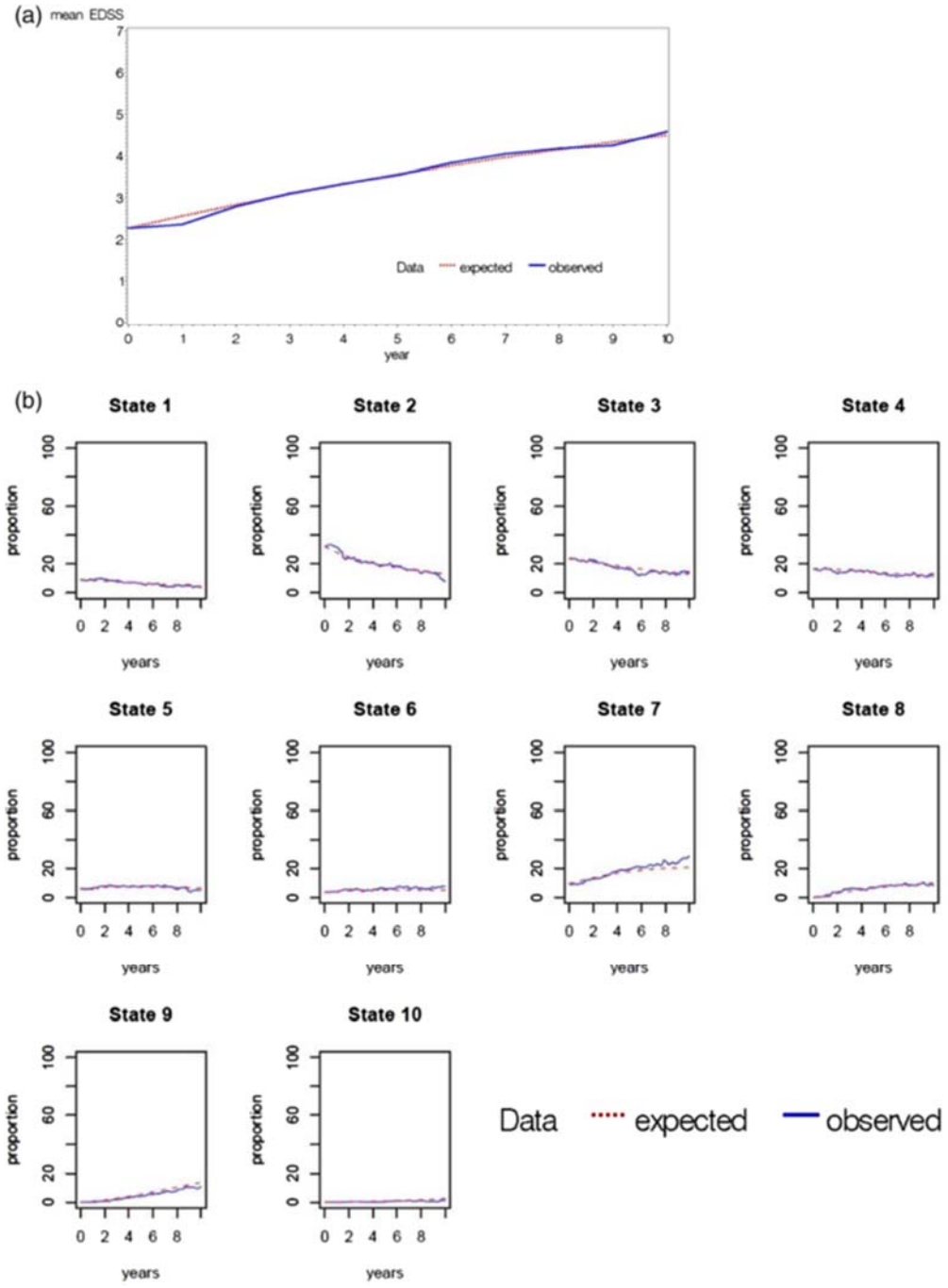
Table 66: Annual transition probabilities (MS age of onset ≥28 years)

From \To	0	1–1.5	2–2.5	3–3.5	4–4.5	5–5.5	6–6.5	7–7.5	8–8.5	9–9.5	N
0	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000	326
1–1.5	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001	317
2–2.5	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004	317
3–3.5	0.00594	0.04960	0.12006	0.54422	0.09109	0.05845	0.11649	0.01030	0.00355	0.00030	317
4–4.5	0.00165	0.2214	0.06660	0.11519	0.48935	0.10388	0.16811	0.02580	0.00671	0.00056	317
5–5.5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.27310	0.03880	0.01883	0.00102	317
6–6.5	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74069	0.10897	0.04377	0.00423	317
7–7.5	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559	317
8–8.5	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01881	0.05574	0.90340	0.02066	317
9–9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832	317

Source: (Palace 2014)

Figure 14 shows a comparison of the predicted mean EDSS from the transition matrix versus the observed mean EDSS in the BCMS registry population reproduced from Palace et al (Palace 2014). These plots show that the fitted matrices provide an excellent prediction of transitions to and from EDSS states, and of mean EDSS over time.

Figure 14: Mean EDSS projected over ten years comparing the observed mean EDSS versus the expected mean EDSS using the continuous time model



In the probabilistic analysis, the matrices were sampled using the Dirichlet distribution (Briggs 2006) based on the sample size for each EDSS transition. These data were not reported in Palace et al(Palace 2014), and therefore had to be estimated by redistributing the total number of transitions reported in the study (6357) across the 10 EDSS states in the two matrices (e.g. 50% of sample assigned to the matrix for below age of onset and 50% to above age of onset). The sample sizes were rounded down such that an integer number were applied to each state. The sample was evenly distributed across EDSS states 1 to 9, with a higher sample size applied to EDSS 0 to maintain the correct total number of

transitions in the analysis. This approach was expected to overestimate uncertainty at lower EDSS states and underestimate uncertainty at higher EDSS states given that more observations are expected at lower than higher levels. This was however considered a pragmatic approach given the lack of sampling information provided in Palace et al (Palace 2014).

B.3.3.1.4. Natural history model - adjustment of progression rates for rapidly evolving severe and highly active relapsing remitting multiple sclerosis

The BCMS analysis was performed on a cohort of people with active RRMS that fulfilled the 2001 ABN criteria for interferon beta and glatiramer acetate use. This covers a broad patient group including those with mild and less progressive forms of RRMS, alongside people with highly active or RES-RRMS.

As highlighted in the FAD for TA441, people with RES-RRMS and SOT-RRMS are likely to progress at a faster rate than people with less active disease. For RES-RRMS, this is supported by analyses of patient-level data from the AFFIRM clinical study that showed progression in people with RES-RRMS RRMS was on average 0.06-0.08 EDSS points faster per year than in people with active RRMS (Polman 2006; Gani 2007).

To account for faster progression in RES-RRMS and SOT-RRMS, the model includes an acceleration parameter that is used to increase the probability of EDSS progression in the natural history model, prior to adjustment for the effect of DMT. This was preferred to the use of sub-group specific transition matrices derived from the placebo arms of clinical studies, as adopted in TA441, given the uncertainties of performing lifetime extrapolation using 2-year trial data. By adjusting the BCMS matrix for faster progression, the model retains the EDSS “trends” observed in the BCMS analysis, and enables sensitivity analyses of the impact of varying the sub-group progression rate on results.

The sub-group adjustment was applied to the summed probability of progression for each EDSS state, following the same methods used when adjusting for drug efficacy. It was therefore assumed that the probability of improving in EDSS were the same across subgroups. Based on advice from clinical experts, the adjustment was applied to EDSS states 0-6 as progression rates are expected to return to baseline levels once patients develop SPMS and transition to beyond EDSS 7.0.

The sub-group adjustments were estimated from the ratio of hazards for 6 month confirmed EDSS progression at week 96 in the placebo arm of CLARITY comparing each subgroup with its complement (e.g. non-subgroup):

$$\mathrm{HR} = \frac{\ln(1 - P_A)}{\ln(1 - P_B)}$$

Where HR is the hazard rate adjustment and P is the probability of 6-month progression at week 96.

A summary of the adjustment factors is shown in Table 67.

Table 67: Hazard rate adjustment for each subpopulation

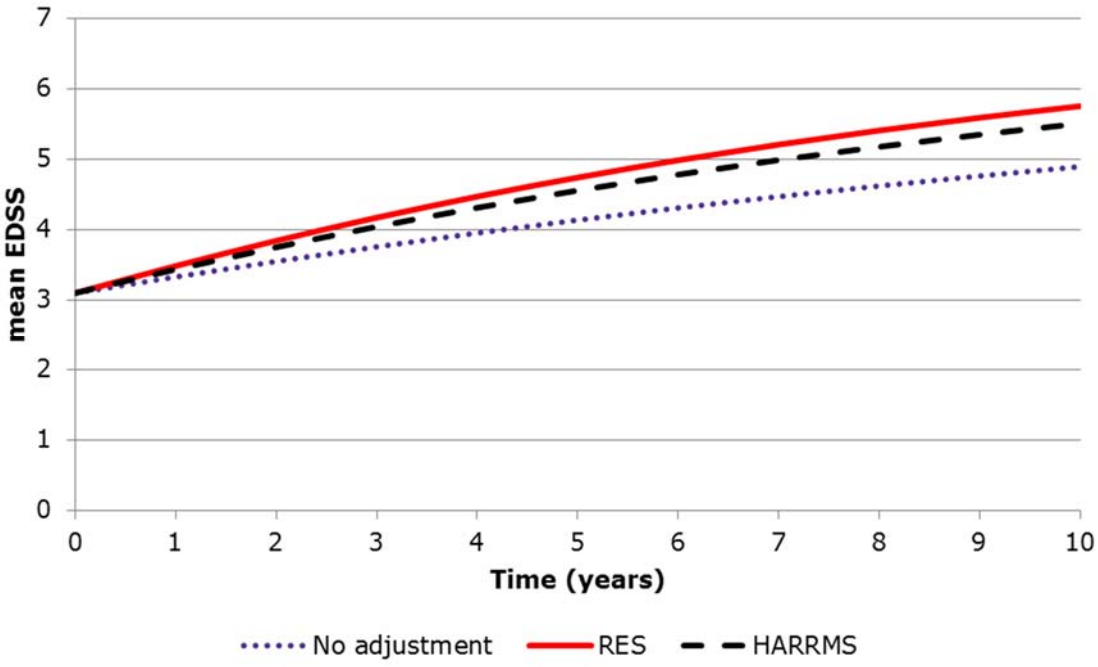
Name	Hazard rate adjustment EDSS 0-6	Hazard rate adjustment EDSS 7+	Note
RES-RRMS	[redacted]	[redacted]	[redacted] progress by week 96 in RES versus [redacted] progress in non-RES-RRMS groups of the placebo arm of CLARITY
SOT-RRMS	[redacted]	[redacted]	Progression rates were lower in the placebo SOT-RRMS group than the placebo active RRMS population which implied a slower rate of progression for SOT-RRMS than in active RRMS. This was not considered to be plausible given expert judgement provided to the Committee for TA441 indicating that people with SOT-RRMS would be expected to have a higher rate of progression than people with active disease. In the absence of data, the hazard rate adjustment for SOT-RRMS was assumed equal to the ratio of annualised relapse rates in the placebo group comparing SOT-RRMS ([redacted]) versus the active population ([redacted]). The resulting hazard rate adjustment was equal to [redacted] The rate of progression in people with SOT-RRMS was therefore assumed to be greater than in the active population (e.g. >1) but less than in the RES-RRMS population [redacted]).

Source: (Merck 2017c)

The impacts of the acceleration parameters for RES-RRMS and SOT-RRMS on the predicted mean EDSS of the population is illustrated in Figure 15.

By year 10, it is predicted that people with RES-RRMS RRMS would be an average of +0.86 EDSS points higher on the scale than people with less active disease. This equates to an average yearly increase in EDSS of +0.086, which is consistent with the results of the analysis of AFFIRM (Polman 2006; Gani 2007).

Figure 15: Illustration of the mean EDSS over time generated from the British Columbia matrix with adjustment for faster EDSS progression in RES-RRMS and SOT-RRMS, and without adjustment



The adjustment factor was sampled using a lognormal distribution in the probabilistic analysis. The standard error was assumed at 20% of the mean estimate.

B.3.3.1.5. Natural history model – Mortality risk

The probability of death was modelled as a function of time to account for the increasing risk of death associated with the increasing age of the modelled cohort over time. Transitions to the death state were assumed to be independent of EDSS state.

The annual probability of death was derived in three steps:

- A gender-averaged all-cause mortality rate was derived from Office for National statistics for population all-cause mortality
- Mortality rate was inflated for the excess mortality risk for MS using published standardized mortality ratios comparing mortality in people with RRMS against the general population
- Inflated mortality rates were converted to annual probabilities and applied during each model cycle

The standardised mortality ratio for excess MS-related mortality was obtained from a systematic literature review of mortality studies in MS (Manouchehrinia 2016). Further detail on the review is provided in the appendix.

The mortality ratio in base case analysis was modelled on data from Jick et al (Jick 2014) (1.68 [95% confidence interval: 1.38-2.05]). This study reported mortality for the largest sample of people with MS (N=1822), covered mortality across multiple regions of the UK, and had the second highest follow-up (14,295 person years) and total number of deaths (130) of the UK studies identified in the review. Sensitivity analyses were performed using data from Lalmohamed et al, which reported a mortality ratio of 3.51.

In the probabilistic analysis, the standardized mortality ratio was sampled using a log-normal distribution (Briggs 2006).

B.3.3.2. Treatment adjusted model

The following section contains a summary of the methods and data sources used to model the effect of DMT on relapse rates, EDSS progression, adverse events, and treatment persistence.

B.3.3.2.1. Treatment adjusted model – relapse rate

The relapse rate for DMT ($\widehat{R}_{DMT}$) was calculated using the following formulae:

$$\widehat{R}_{DMT} = \widehat{R}_{BSC} \text{ x } RR$$

Where RR is the rate ratio comparing DMT versus placebo and $\widehat{R}_{BSC}$ is the annualised relapse rate in the BSC population. The relapse rate ratios were obtained from the network meta-analyses outlined in the comparative efficacy section of the submission.

A summary of the relapse rate ratios used in the economic analysis is shown in Table 68.

Table 68: Ratio of annualised relapse rates comparing DMT versus placebo

Treatment, versus placebo	Median ratio of annualised relapse rates comparing treatment versus placebo [upper 95% credible to lower 95% credible value]	
	RES-RRMS	SOT-RRMS
Cladribine Tablets	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]
Preferred model type in systematic review	Fixed effects model	Fixed effects model
Note	* based on relapse rate ratio from CARE MS-II study ** assumed the same effect as Cladribine Tablets	

RES: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SOT: Sub-optimal therapy

The efficacy of alemtuzumab and daclizumab in SOT-RRMS had to be assumed due to the lack of published data for daclizumab, and the lack of studies reporting the efficacy of interferon-beta1a in SOT-RRMS to connect the alemtuzumab studies to the network. For daclizumab, it was conservatively assumed that therapy is of equivalent efficacy to Cladribine Tablets.

The efficacy of alemtuzumab was modelled using the effect size estimate from CARE MS-II (rate ratio of 0.51, 95% confidence interval 0.39 to 0.65), which compared alemtuzumab versus interferon beta-1a in a population who had experience at least 1 relapse during prior treatment. These data were thus generalised to the SOT-RRMS population and it was further assumed that interferon beta is of equivalent efficacy to placebo in SOT-RRMS; a population who had failed to respond to previous DMT including interferon. The probable lack of effect for interferon in SOT-RRMS is supported by the results of meta-analysis, which reported a rate ratio of [redacted] (95% credible interval [redacted]) for interferon beta-1a 30mcg versus placebo.

B.3.3.2.2. Treatment adjusted model – EDSS progression

The effect of DMT on disability progression was modelled using data on confirmed disability progression at 6 months, following Committee preferences in TA320 and TA441.

The hazard ratio of DMT versus placebo was estimated from a meta-regression analysis with adjustment for baseline risk, as outlined in the appendix D. The results of the analysis were in the form of the log-hazard ratio comparing DMT versus placebo and centered to the baseline risk for the RES-RRMS population of CLARITY. Following TSD3, the treatment effects were then un-centered and transformed to produce an estimate of DMT effect with the baseline risk in SOT-RRMS. Further detail is provided in appendix K.

A summary of the hazard ratios for 6 month confirmed disability progression comparing DMT versus placebo is provided in Table 69.

Table 69: Log and normalised hazard ratios on 6 month confirmed disability progression comparing DMT versus placebo after centering on baseline risk using data from the ITT populations of clinical literature

Treatment versus placebo	Log hazard ratio from the random effect model with common covariate for baseline risk (base case model)*				Normalised hazard ratio (derived from log-hazard ratio and baseline risk)	
	Mean	SD	L95%	U95%	Centered on RES-RRMS	Centered on SOT-RRMS
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Between-study standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline risk covariate (centered on baseline risk in RES-RRMS)	[redacted]	[redacted]	[redacted]	[redacted]		
Residual deviance	[redacted]					
pD	[redacted]					
DIC	[redacted]					

RES: Rapidly evolving severe; RRMS: Relapsing-remitting multiple sclerosis; SD: Standard deviation; SOT: Sub-optimal therapy

*treatment effect expected on a RES_RRMS population; logHR has been derived from a ITT population accounting for the baseline risk for disease progression in a RES-RRMS population

The log-hazard ratios reported in Table 69 correspond to the effect of DMT versus placebo for patients with a baseline probability of progression that is equal to the mean progression probability in the RES-RRMS population of CLARITY.

The results of the meta-regression analysis shows significant overlap in the credible intervals for the hazard ratios of confirmed disability progression at six months, with no therapy statistically dominating in terms of efficacy. At the point estimate level, Cladribine Tablets was predicted to be more efficacious than fingolimod (log hazard ratio relative to placebo of [redacted] Cladribine Tablets versus [redacted] for fingolimod) and alemtuzumab [redacted] versus [redacted]), but marginally less efficacious than natalizumab [redacted] versus [redacted]) and daclizumab [redacted] versus [redacted]) for the RES-RRMS population. The corresponding normalised hazard ratios were [redacted] for treatment effect of Cladribine Tablets, [redacted] for alemtuzumab[redacted] for daclizumab, in the RES-RRMS and [redacted] for natalizumab versus placebo.

The log-hazard ratios in Table 69 were un-centered and transformed to produce an estimate of DMT effect consistent with the baseline risk in SOT-RRMS. The corresponding normalised hazard ratios in this population were [redacted] for Cladribine Tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, and [redacted] for fingolimod versus placebo. Overall, the meta-regression predicted that all DMT's are less effective in the SOT-RRMS population than in RES-RRMS..

Overall, the results of the meta-regression suggest that Cladribine Tablets are of equivalent efficacy to these therapies on the endpoint of confirmed disability progression at 6 months.

B.3.3.2.3. Treatment adjusted model – Waning of drug efficacy

As in all previous appraisals since TA254, the economic model for Cladribine Tablets allows for the waning of drug effect over time to reflect uncertainty in the longer-term benefits of drug therapy, and to explore the impact of this uncertainty on the results of the economic analysis.

The waning effect was applied by adjusting the hazard ratio for drug effect via the following equation:

$$HR_w = (1 - (1 - HR_{NW}) \times W)$$

Where $\mathrm{HR_W}$ is the drug effect adjusted for waning, $\mathrm{HR_{NW}}$ is the drug effect without adjustment from the network meta-analysis described previously, and W is the proportional waning effect (e.g. 50%).

The waning effects for fingolimod, daclizumab, natalizumab and alemtuzumab were based on approaches accepted by the NICE Committee in TA441, Table 70.

Table 70: Proportion of drug effect applied to alemtuzumab, daclizumab, fingolimod and natalizumab by year

Year	Proportion of treatment effect that is assumed to apply during each period of the model
0-2	100%
2-5	75%
5+	50%

The assumptions about waning of treatment effects for Cladribine Tablets were informed by a post-hoc analysis of data collected throughout CLARITY and into CLARITY EXT.

Specifically, the analysis considered the efficacy of cladribine in CLARITY followed by placebo in EXT (LLPP) versus four years of placebo (PPPP), to provide an estimate of the potential comparative efficacy of Cladribine Tablets over a longer follow-up than CLARITY. The aim of the analysis was to demonstrate whether the treatment effect observed in CLARITY (LL versus PP) persists in the absence of additional treatment (LLPP versus PPPP), and hence understand whether the effect of Cladribine Tablets wanes over this extended period.

The outcomes for LLPP were available from the pooling of patient data in CLARITY and CLARITY EXT. The outcomes of PPPP were not available from the pooled data because CLARITY placebo patients who entered CLARITY EXT were re-randomized to Cladribine Tablets (e.g. PPLL). To estimate PPPP, a “treatment switching” analysis was performed using data from the LLPP group and data from patients who had received placebo in CLARITY and switched to Cladribine Tablets in CLARITY EXT (PPLL). This is the first known “evidence-based” attempt to justify the waning of drug efficacy in RRMS submitted to NICE, using novel methods typically applied in oncology appraisals. The University of Sheffield was contracted to conduct this analysis, which was carried out by Helen Bell-Gorrod and Nicholas Latimer, lead author of the DSU guidance on switching methods in NICE appraisals.

The rank preserving structural failure time (RPSFT) model and the iterative parameter estimation (IPE) algorithm were used to estimate the effect of patients switching from PP to LL in the PPLL group of CLARITY EXT. As all placebo treated patients from CLARITY who entered EXT had switched to LL, other recommended methods such as the inverse probability of censoring weights and the two-stage adjustment method were not considered as they require follow-up of those who did not switch from PP to LL.

The RPSFT and IPE methods use the same counterfactual survival model but use different estimation procedures. For completeness, both methods were considered and results reported. Sensitivity analyses were also performed with and without re-censoring and when assuming “on treatment” or “treatment group” effect, as recommended in TSD16.

The results of the switching analysis for 6 month confirmed disability progression are shown in Table 71.

Table 71: Summary results after adjustment for switching from PP to LL in the CLARITY EXT study

Method	Hazard ratio (HR)			Acceleration factor			CF HR test
	Mean	Lower 95% CI	Upper 95% CI	Mean	Lower 95% CI	Upper 95% CI	
ITT (LLPP vs. PPLL)	[redacted]	[redacted]	[redacted]	-	-	-	-
CLARITY ITT (LL vs. PP)	[redacted]	[redacted]	[redacted]	-	-	-	-
LLPP vs. PPPP treatment switching adjustment analyses with re-censoring							
RPSFTM treatment group with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM on treatment with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE treatment group with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE on treatment with re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LLPP vs. PPPP treatment switching adjustment analyses without re-censoring							
RPSFTM treatment group no re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM on treatment no re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE treatment group no re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPE on treatment no re-censoring	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: RPSFTM: Rank Preserving Structural Failure Time Model; IPE: Iterative Power Estimation

The point estimates of the hazard ratio for RFPST and IPE ranged from [redacted], depending on choice of model, and the use of re-censoring and "on treatment" versus "treatment group" effects.

As expected, each of the adjusted analyses showed a numerically lower hazard ratio than for the unadjusted comparison of LLPP versus PPLL ([redacted] 95% confidence intervals of [redacted]). In CLARITY, the point estimate of the hazard ratio was [redacted] for LL versus PP, and was largely comparable to results from the analysis of LLPP versus PPPP.

These analyses suggest that the effect of Cladribine Tablets were approximately constant over CLARITY and CLARITY EXT, and hence supports the assumption of a durable drug effect during the 2 years of treatment and first 2 years of follow-up. The efficacy of Cladribine Tablets beyond 4-years remains uncertain, and in the absence of data, it was conservatively assumed that the same waning assumptions from previous NICE appraisals were applied from this period thereafter.

A summary of the waning effects applied to Cladribine Tablets is provided in Table 72.

Table 72: Proportion of drug effect applied to Cladribine Tablets

Year	Proportion of treatment effect that is assumed to apply during each period of the model	Rationale
0-2	100%	Evidence of limited to no waning of drug efficacy over the first four years of treatment based on the treatment switching analysis of CLARITY and CLARITY EXT
2-4	100%	
4-5	75%	In line with NICE precedent and applying same assumptions across therapies
5+	50%	

B.3.3.2.4. Treatment adjusted model – Safety and tolerability

The probability of experiencing drug-related adverse events or tolerability issues was modelled based on clinical trial data identified in the systematic literature review, and from published literature sources.

Infusion and injection site reactions were assumed to apply to therapies administered by infusion (e.g. natalizumab and alemtuzumab) or injection (daclizumab) only. The risk of PML was assumed to apply to fingolimod and natalizumab only, given that no PML events have been reported for Cladribine Tablets, daclizumab and alemtuzumab. The risk of macular oedema was applied to fingolimod only as it is the only drug in scope that includes a warning for such events in its summary of product characteristics. Similarly, the risk of immune thrombocytopenic purpura was assumed to apply to alemtuzumab only as treatment has been linked to an increased risk, as outlined in its summary of product characteristics.

The risk of hypersensitive reaction was applied to natalizumab only and modelled based on data from the AFFIRM study (Polman 2006). No events were reported for the placebo or active groups of CLARITY, and SELECT (Gold 2013), and hence the risk of hypersensitivity reaction for all other comparators was assumed at 0%.

Malignancy events have been reported in clinical trials for Cladribine Tablets, Alemtuzumab, Natalizumab and Fingolimod (Pakpoor 2015), and in the Decide and SELECT trials for daclizumab (Gold 2013; Kappos 2015). A network meta-analysis was attempted but failed to converge due to a high number of studies reporting zero events for cancer. Instead, the risk of malignancy was modelled based on data from Pakpoor et al, which reported a cancer risk of 0.34% in the pooled treatment group of CLARITY, and 0.60% in a pooled treatment group comprising outcome data for dimethyl fumarate, fingolimod, teriflunomide, natalizumab, alemtuzumab and glatiramer acetate (Pakpoor 2015). In the absence of a clear trend towards higher or lower risks of malignancy across different DMT, it was conservatively assumed that the cancer risk was 0.60% across all treatment groups.

The risk of gastrointestinal disorder, thyroid related events, serious infections and influenza like illness were modelled using a pooled event probability in placebo patients combined with the odds ratios for treatment versus placebo obtained from a series of network meta-analyses of studies identified in the clinical review. Where it was not possible to derive the odds ratio for an individual treatment versus placebo, the odds ratio was set equal to 1, which conservatively assumed parity with the placebo risk.

A summary of the absolute probabilities of adverse events by DMT is provided in Table 73.

Table 73: Absolute probabilities of adverse events by DMT and event type

Event type	Cladribine Tablets	Alemtuzumab	Fingolimod	Natalizumab	Daclizumab	Event
Recurring events that apply to each year treated in the model						
Infusion site reaction	0%	90.1%	0%	23.6%	0%	(1)
Injection site reaction	0%	0%	0%	0%	2.0%	(2)
One-off events that apply at the start of the model time horizon						
PML	0%	0%	0.001%	0.213%	0%	(3)
Macular Oedema	0%	0%	0.394%	0%	0%	(4)
Malignancy	0.60%	0.60%	0.60%	0.60%	0.60%	-
Hypersensitivity reaction	0%	0%	0%	4.0%	0%	(5)
Gastrointestinal disorder	24.5%	22.8%	30.4%	22.8%	22.8%	(6)
Thyroid related events	5.1%	11.3%	1.2%	1.2%	1.2%	(7)
Immune thrombocytopenic purpura	0%	1.8%	0%	0%	0%	(8)
Serious infection	2.8%	2.3%	2.2%	1.9%	10.1%	(9)
Influenza like illness	1.3%	1.1%	0.5%	0.1%	1.5%	(10)

B.3.3.2.5. Treatment adjusted model – discontinuation

The probability of discontinuation was derived from all-cause discontinuation rates reported in trials used in the network meta-analysis for 6-month confirmed disability progression (appendix K).

Of the 18 studies included in the network meta-analysis, 15 had reported discontinuation data that were used to derive the discontinuation probabilities. The all-cause discontinuation probabilities reported in the individual studies (Table 74) were converted to annualized probabilities using the following equation:

$$P = 1 - e^{\left(-\left(-\frac{52}{t}\times\ln(1-p)\right)\right)}$$

Where t is study follow-up time in weeks and p is the probability of discontinuation. For each therapy, a weighted mean probability was calculated based on the number of patients in each study (Table 74).

A summary of the annualized probabilities are presented in Table 74.

Table 74: Summary of comparator discontinuation probabilities across included trials

Trial number	Clinical trial	Treatment	Patients	All-cause discontinuations	Study duration (weeks)	Proportion discontinuing	Annualised probability of discontinuing	Study weight
Cladribine Tablets – discontinuation probability: 4.854%								
1	CLARITY	Cladribine 3.5 mg/kg	433	38	96	8.8%	4.9%	100%
Alemtuzumab – weighted discontinuation probability: 2.266%								
1	CAMMS223	Alemtuzumab, 12 mg, qd	113	14	156	12.4%	4.3%	12.1%
2	CARE-MS I	Alemtuzumab, 12 mg, qd	386	5	104	1.3%	0.6%	41.3%
3	CARE-MS II	Alemtuzumab, 12 mg, qd	436	27	104	6.2%	3.1%	46.6%
Fingolimod - weighted discontinuation probability: 13.595%								
1	FREEDOMS	Fingolimod, 0.5 mg, qd	425	80	104	18.8%	9.9%	54.3%
2	FREEDOMS II	Fingolimod, 0.5 mg, qd	358	116	104	32.4%	17.8%	45.7%
Natalizumab – discontinuation probability: 6.4%								
1	AFFIRM	Natalizumab, 300 mg, q4w	627	73	104	11.6%	6.4%	100.0%
Daclizumab – discontinuation probability: 11.609%								
1	Decide	Daclizumab HYP, 150 mg, q4w	919	266	144	28.9%	11.6%	100.0%

B.3.4 Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

EQ-5D-3L questionnaires were collected at regular intervals throughout CLARITY and CLARITY EXT, including at study day 1, weeks 24, 48, 72, at the week 96/early termination visit, and at each relapse evaluation. As required in the NICE methods guide, completed EQ-5D questionnaires were mapped to health state utility (HSU) index values using the UK social tariff.

5763 HSU values were generated from the EQ-5D data collected in the Cladribine Tablets studies; CLARITY (n=3518) and CLARITY EXT (n=2245). Summary statistics from across both studies indicate no evidence of a meaningful difference in HSU across patient subgroups, and no difference in HSU by treatment group when stratified by EDSS. To reduce uncertainty in the analysis, the HSUs by EDSS were pooled across treatment and patient subgroups to provide inputs to the cost-effectiveness analysis.

A summary of HSU by EDSS state at baseline is provided in Table 75.

Table 75: Summary statistics of HSU in CLARITY (baseline)

Health state	Mean	Standard error	Number of HSU
EDSS 0	0.906	0.026	20
EDSS 1.0	0.845	0.046	24
EDSS 2.0	0.804	0.012	221
EDSS 3.0	0.701	0.012	171
EDSS 4.0	0.655	0.013	167
EDSS 5.0	0.565	0.026	62
EDSS >5.0	0.573	0.225	32

EDSS: Expanded disability status scale; HSU: Health state utility

Only baseline HSU were applied in the model as HSU captured during the study may be impacted by the effects of adverse events, which are accounted for separately in the analysis.

B.3.4.2. Mapping

No mapping analyses were performed as EQ-5D HSU were available from the CLARITY and CLARITY EXT studies.

B.3.4.3. Health-related quality-of-life studies

Published health related quality of life studies in RRMS were identified via a systematic literature review (search date January 4th 2017) of biomedical literature databases in accordance with the NICE methods guide (NICE 2013), and TSD8, TSD9 and TSD10. The review covered:

- published peer-reviewed health related quality of life studies
- health related quality of life data used in models submitted to the NICE STA process
- unpublished data held by the company

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix H.

In summary, 133 unique published studies (from 160 publications) and 3 HTA submission documents were included. Of the 133 published studies, 61 reported HSU data considered applicable to the health state structure of the cost-effectiveness model, including HSU by EDSS (52 studies), and HSU for relapse (28 studies). The remaining studies reported HSU that were unrelated to EDSS or relapses,

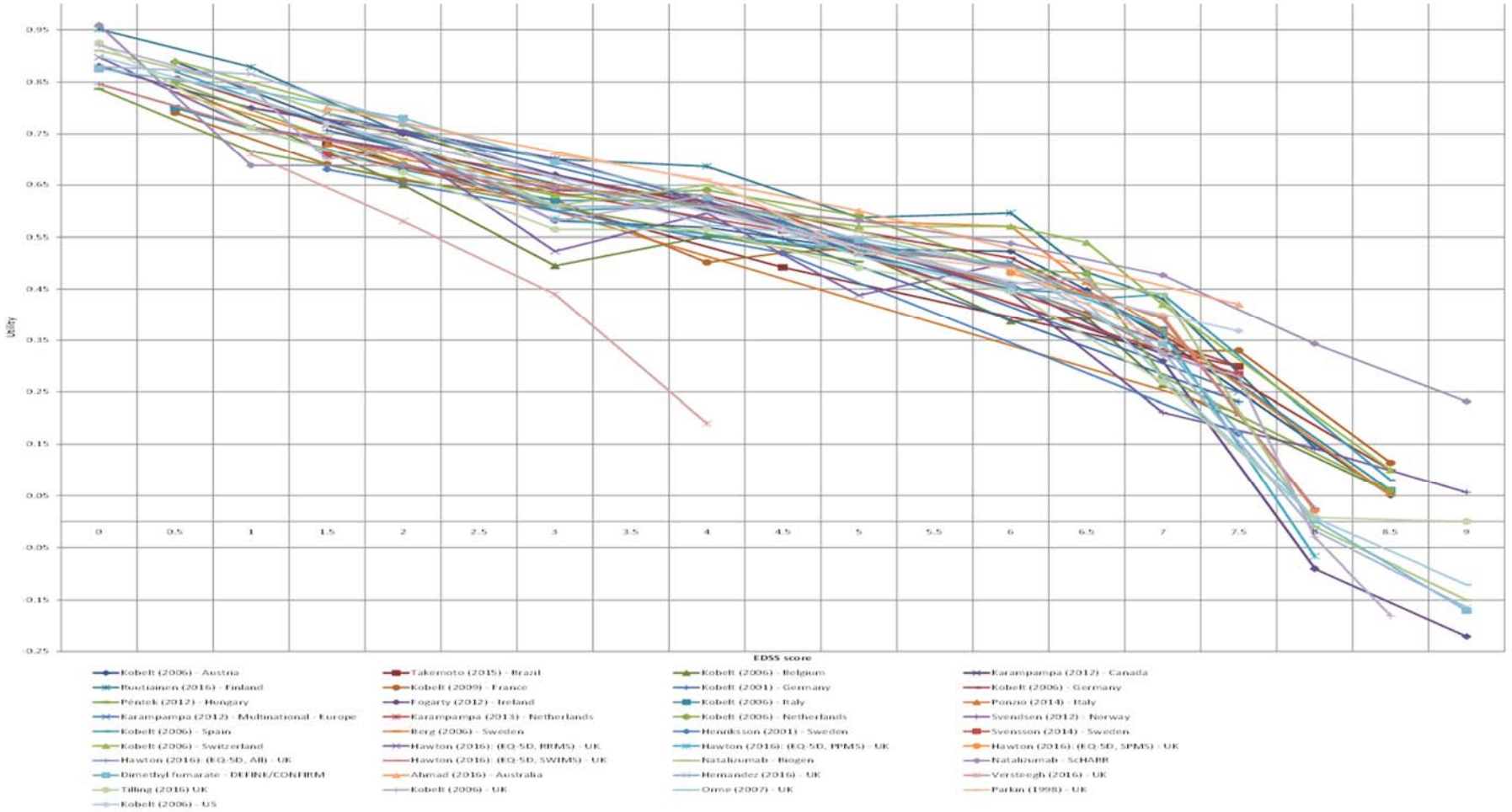
including studies of the direct effects of treatment or intervention on HSU, and studies reporting HSU for walking speed, walking distance and numerical rating scores for spasticity.

B.3.4.3.1. Health state utility by EDSS state for persons with MS

EDSS-related HSUs were reported in 52 studies and 3 HTA documents included in the review. Thirty-two of the 52 studies and all 3 of the HTA documents reported EQ-5D HSU derived using UK social preferences (Berg 2006; Kobelt 2006i; Kobelt 2006e; Kobelt 2006d; Kobelt 2006c; Kobelt 2006g; Kobelt 2006f; Kobelt 2006h; Kobelt 2006b; Kobelt 2006a; Takemoto 2015; Karampampa 2012b; Ruutiainen 2016; Kobelt 2009; Pentek 2012; Fogarty 2013; Ponzio 2015; Karampampa 2013; Svendsen 2012; Svensson 2014a; Svensson 2014b; Henriksson 2001; Hawton 2016a; Orme 2007; Parkin 1998; Forbes 1999; Karampampa 2012a) in line with the NICE reference case. From these studies, 41 unique sets of EQ-5D HSU data were reported, of which, 25 covered the range of EDSS levels in the economic model (e.g. EDSS 0-1 to EDSS 8.5-9.5).

A global comparison of the mean EQ-5D HSU by EDSS state based on UK societal preferences is presented in Figure 16.

Figure 16: HSU by EDSS state for all studies reporting EQ-5D HSU valued using UK social preferences



The preferred data source for the base case was selected based on the quality of the included studies, by considering how patients were recruited, the rate of recruitment and response, and how HSU and disease severity were assessed across the literature. Preference was given to studies reporting large sample sizes, high response rates and used clinician assessed EDSS.

Based on this assessment, Hawton et al (Hawton 2016a) was selected as the preferred literature source for EDSS-related HSU given that it includes a large patient sample (1406 participants and 6066 completed EQ-5D questionnaires) that is representative of the UK MS population, a high recruitment rate (75% contacted had participated) and response rate (90% of those recruited had responded at 3.5 year follow-up), and used clinician-assessed EDSS.

Other literature sources that were considered relevant to this analysis include Orme et al (large sample, low response rate, self-assessed EDSS that was used in previous NICE appraisals) (Orme 2007), and HSU data from the CONFIRM and DEFINE trials reported in TA320 (large sample, unknown response rate, clinician-assessed EDSS and used in previous NICE appraisals) (CRD and CHE Technology Assessment Group 2013; NICE Technology appraisal guidance 2014b).

A summary of the literature sources is provided in Appendix H. A summary of the HSU data from CLARITY and the preferred literature sources is provided in Table 76.

Table 76: Summary of mean EQ-5D HSU from UK social preferences in CLARITY, and key HSU publications

Health state	CLARITY	Hawton et al	Orme et al	DEFINE/CONFRIM values
Age	38.3	50.7	51.4	Not available
EDSS 0	0.906 (0.026)	0.846 (0.026)	0.87 (0.045)	0.875 (0.175)
EDSS 1.0	0.845 (0.046)	0.762 (0.025)	0.799 (0.093)	0.834 (0.167)
EDSS 2.0	0.804 (0.012)	0.711 (0.019)	0.705 (0.093)	0.78 (0.156)
EDSS 3.0	0.701 (0.012)	0.608 (0.029)	0.574 (0.097)	0.695 (0.139)
EDSS 4.0	0.655 (0.013)	0.609 (0.028)	0.61 (0.093)	0.625 (0.125)
EDSS 5.0	0.565 (0.026)	0.531 (0.031)	0.518 (0.092)	0.544 (0.109)
EDSS 6.0	Not available	0.496 (0.012)	0.46 (0.093)	0.456 (0.091)
EDSS 7.0	Not available	0.392 (0.032)	0.297 (0.094)	0.344 (0.069)
EDSS 8.0	Not available	0.025 (0.038)	-0.049 (0.109)	0.002 (0.002)
EDSS 9.0	Not available	Not available	-0.195 (0.119)	-0.17 (0.034)

Note: n.r. – not reported; * Derived from the DEFINE and CONFIRM clinical trials

The mean HSU by EDSS in CLARITY were generally higher than values reported in Hawton et al (Hawton 2016a), Orme et al (Orme 2007), and the pooled CONFIRM and DEFINE trial data from TA320 (CRD and CHE Technology Assessment Group 2013). This may be due to the different age profile of patients in the studies, with patients in CLARITY being on average 12 years younger than individuals in Hawton et al (Hawton 2016a) and Orme et al (Orme 2007) (Table 76). Increasing age is a predictor of lower HSU in the general population, and has been shown to be a predictor of HSU in MS patients independent of EDSS. The CLARITY HSUs were generally comparable to the trial data from CONFIRM and DEFINE (CRD and CHE Technology Assessment Group 2013), which is suspected to have a similar age profile to CLARITY.

In line with TA254, TA303, TA312, TA320 and TA441, the HSU data from CLARITY were used for EDSS 0-5.0, and were supplemented by HSU data from Hawton et al for EDSS 6.0-8.0, and Orme et al for EDSS 9.0. All other relevant HSU sources were considered in sensitivity analyses.

Table 77: Summary of literature sources for HSU related to EDSS chosen for economic analyses

Author: Study name	Country of respondents	Study design	N	Baseline age	Baseline disease severity	Baseline relapse history	Form of MS	Method	Respondent selection and recruitment, data collection method and response rate
(Hawton 2016a): Health utilities for multiple sclerosis	UK	Regional patient/research organisation longitudinal, prospective study	1441 (total) (EQ-5D: 1406 SF-36: 1357)	Mean (SD) 50.7 (11.7)	Mean EDSS (SD/range) 4.3 (2.3 /0-9) [n=289]	Relapse during last 12-months: Yes: 53.6% No: 33.3% Don't know: 13.2% Number of relapses in the previous 12 months mean (SD) 1.1 (1.2)	RRMS: 42% PPMS: 19.4% SPMS: 17.0% Benign: 3.3% Unknown: 18.4%	EQ-5D (UK tariff), SF-6D	Adult patients (>18-years old) with a clinically definite diagnosis of MS (McDonald or Poser criteria), or clinically isolated syndrome (CIS), and resident in Devon or Cornwall, England, were identified from attendances to neurology outpatient clinics, hospital case notes, a survey of general practitioners, and self-referrals from public awareness campaigns Data were collected on patient health status, including self-assessment of quality of life (EQ-5D). EDSS were assessed by clinicians, and identified from data collected at routine visits, where available. Study response rate: 75%
(Orme 2007): The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK	UK	National patient/research organisation observational, cross-sectional study	2048	Mean 51.4	EDSS 0-3: 21.3% EDSS 4-6.5: 59.6% EDSS 7-9.5: 19.1%	Relapse during last 3-months: Yes 28.9% No 71.1%	RRMS: 35.3% SPMS: 37.2% PPMS: 27.3%	EQ-5D (UK tariff)	Questionnaires were mailed to 12,968 patients with MS registered with the UK MS trust. Data were collected on patient health status, including self-assessment of quality of life (EQ-5D), and patients determined disease steps, used as proxy for EDSS. Study response rate: 15.8%

B.3.4.3.2. Health state utility by EDSS state for caregiver of person with MS

The review identified one study that reported the impact of MS on the HSU of caregivers of people with MS.

Acaster et al (Acaster 2013) was a cross-sectional observational online survey study of the EQ-5D of 200 caregivers and 200 matched controls (e.g. non-caregiver). The study reported an assessment of differences in HSU between caregiver and non-caregivers, including stratified by severity of MS.

Table 78: Difference in mean HSU between caregivers and controls stratified by Patient Determined Disease Steps (PDDS) state

State	Mean	SE (standard error)	95% CI (Confidence interval)
PDDS 0-1	-0.002	0.053	(-0.106607, 0.102512)
PDDS 2-3	-0.045	0.057	(-0.157389, 0.0675467)
PDDS 4	-0.142	0.062	(-0.26265, -0.0201414)
PDDS 5	-0.16	0.055	(-0.267741, -0.0515924)
PDDS 6	-0.173	0.054	(-0.278105, -0.0672276)
PDDS 7	-0.03	0.038	(-0.103954, 0.0454175)
PDDS 8	-0.095	0.075	(-0.240843, 0.0526273)

Source:(Acaster 2013); 95% confidence interval estimated by digitisation of study graphs

Acaster et al reported lower HSUs in caregivers when compared to matched controls (0.74 [Standard deviation (SD) = 0.28] versus 0.8 [SD = 0.25], p =0.003), with lower HSU being associated with lower levels of functioning in the person with MS (Table 78). Between PDDS 0 and 6, increasing disability was associated with an increasing loss in HSU for the caregiver, when compared to the matched control. This overall trend ceases at PDDS 7 and 8 (wheel chair use and bedridden), where the loss in HSU declines versus PDDS 6 with an overall HSU decrement that is comparable to losses estimated at PDDS 0-3.

Data from Acaster et al were used to model the impact of disability progression on caregiver HSU by mapping PDDS 0-1 to EDSS 0-2, PDDS 2-3 to EDSS 3, PDDS 4 to EDSS 4, PDDS 5 to EDSS 5, PDDS 6 to EDSS 6, PDDS 7 to EDSS 7 and PDDS 8 to EDSS 8-9.

B.3.4.3.3. Health state utility by relapse state

The review identified 28 studies that reported the effect of relapses on HSU, of which 20 were derived using UK social preferences. The loss in HSU associated with each relapse event ranged from 0.014 to 0.8.

The preferred literature sources for modelling the impact of relapses on HSU were Ruutiainen et al (Ruutiainen 2016) and Orme et al (Orme 2007) as they reported HSU effects from regression analyses that adjusted for EDSS staging.

The same disutility values were applied to hospitalised and non-hospitalised events on the basis that neither preferred source reported data by hospital status.

Table 79: Summary of the HSU impact of relapse events in the model

Health state	Duration (days)	Orme et al	Ruutiainen et al
Relapse requiring hospitalisation	34.41	-0.071 (0.013)	-0.066 (0.013)
Relapse not requiring hospitalisation	38.64		

B.3.4.4. Adverse reactions

The systematic review of HSU failed to identify studies reporting the HSU for treatment-related adverse events in people with MS.

Additional ad-hoc searches were therefore performed to identify relevant data from previous RRMS appraisals and from other chronic conditions. These data were supplemented with estimates of the duration of adverse events to provide estimates of the QALY loss from each event.

A summary of the duration and disutility impact of treatment-related adverse events is reported in Table 80.

The QALY loss from treatment-related adverse events ranged from -0.0002 (infusion site reaction) to -0.116 (malignancy). Events that had a large impact on total QALY were malignancy (-0.116), PML (-0.510) and thyroid related events (-0.110). Severe infections, influenza-like symptoms and gastrointestinal disease had a significant impact on the person's HSU but persisted for a shorter period of time (e.g. 14 days) than malignancy, PML and thyroid events, and hence had a reduced impact on total QALYs.

Table 80: Duration and quality of life impact of adverse events

Adverse event	Duration of event (days)	Source for duration	Disutility	Source for disutility	QALY impact
Infusion site reaction - alemtuzumab	5	Alemtuzumab NICE submission (NICE Technology appraisal guidance 2014a)	-0.011	Same as injection site reaction	-0.0002
Infusion site reaction – natalizumab	5		-0.011		-0.0002
Injection site reaction (monthly)	13	Assumption: Every month lasting the full day	-0.011	Utilities and disutilities for attributes of injectable treatments for type 2 diabetes, Boye et al (Boye 2011)	-0.0004
PML	93.1	Assumption: based on mean 13.3 weeks of steroid treatment for immune reconstitution syndrome associated with PML	-0.200	Alemtuzumab NICE submission (NICE Technology appraisal guidance 2014a)	-0.0510
Severe infection	14	Assumption: Severe infection lasts for 2 weeks	-0.190	Utilities for treatment-related adverse events in type 2 diabetes, Shingler et al (Shingler 2015)	-0.0073
Macular oedema	84	Manufacturer submission for TA312	-0.040	Alemtuzumab NICE submission (NICE Technology appraisal guidance 2014a)	-0.0092
Gastrointestinal	8	Phillips et al (Phillips 2015)	-0.240	Utilities for treatment-related adverse events in type 2 diabetes, Shingler et al (Shingler 2015)	-0.0053
Hypersensitivity	7	Manufacturer submission for TA312	-1.000	Alemtuzumab NICE submission (NICE Technology appraisal guidance 2014a)	-0.0192
Autoimmune thyroid-related event	365.25	Manufacturer submission for TA312	-0.110	Alemtuzumab NICE submission (NICE Technology appraisal guidance 2014a)	-0.1100
Influenza-like symptoms	7	Assumption: influenza like symptoms persist for one week	-0.210	Health state utilities associated with attributes of treatments for hepatitis C	-0.0040
Malignancy	365.25	Assumption	-0.116	Breast Cancer in Young Women: Health State Utility Impacts by Race/Ethnicity, Trogdon et al (Trogdon 2016)	-0.1160
Immune thrombocytopenic purpura	28	Manufacturer submission for TA312	-0.090	Manufacturer submission for TA312 (NICE Technology appraisal guidance 2014a)	-0.0069

Source: (Boye 2011) (NICE Technology appraisal guidance 2014a) (Trogdon 2016) (Phillips 2015)

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the health state utilities used in the base case model is shown in Table 81.

Table 81: Summary of health state utilities in base case and sensitivity analysis for EDSS and relapse events

Health state	Base case	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
	Orme et al (Orme 2007)	Ruutiainen et al (Ruutiainen 2016)	-	-
Relapse (hospital)	-0.071 (0.013)	-0.066 (0.013)	-	-
Relapse (non-hospital)			-	-
EDSS	CLARITY plus Hawton (Hawton 2016a)	Hawton et al (Hawton 2016a)	Orme et al (Orme 2007)	DEFINE/CONFRIM values (CRD and CHE Technology Assessment Group 2013)
EDSS 0	0.906 (0.026)	0.846 (0.026)	0.87 (0.045)	0.875 (0.175)
EDSS 1.0	0.845 (0.046)	0.762 (0.025)	0.799 (0.093)	0.834 (0.167)
EDSS 2.0	0.804 (0.012)	0.711 (0.019)	0.705 (0.093)	0.78 (0.156)
EDSS 3.0	0.701 (0.012)	0.608 (0.029)	0.574 (0.097)	0.695 (0.139)
EDSS 4.0	0.655 (0.013)	0.609 (0.028)	0.61 (0.093)	0.625 (0.125)
EDSS 5.0	0.565 (0.026)	0.531 (0.031)	0.518 (0.092)	0.544 (0.109)
EDSS 6.0	0.496 (0.012)		0.46 (0.093)	0.456 (0.091)
EDSS 7.0	0.392 (0.032)		0.297 (0.094)	0.344 (0.069)
EDSS 8.0	0.025 (0.038)		-0.049 (0.109)	0.002 (0.002)
EDSS 9.0	-0.195 (0.119)			-0.17 (0.034)
Adverse events	**QALY loss associated with each adverse event**			
Infusion site reaction - alemtuzumab	-0.011			
Infusion site reaction – natalizumab	-0.011			
Injection site reaction (monthly)	-0.011			
PML	-0.200			
Severe infection	-0.190			
Macular oedema	-0.040			
Gastrointestinal	-0.240			
Hypersensitivity	-1.000			
Autoimmune thyroid-related event	-0.110			
Influenza-like symptoms	-0.210			
Malignancy	-0.116			

Source: in table

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A summary of the aggregated costs applied in the economic analysis is provided in Table 82.

The total number of Cladribine Tablets administered to each individual patient is dependent on the patient's weight. As a result, the annual drug costs applied in the RES-RRMS analysis differ slightly to the cost used for SOT-RRMS because of small differences in the weight distribution of the two cohorts in CLARITY.

Table 82: Summary of cost inputs to the economic analysis for Cladribine Tablets in RES-RRMS and SOT-RRMS

Resource item	Treatment	Cost	Standard error of cost (if relevant)	Reference in submission
Annual acquisition cost All years unless specified	Cladribine Tablets – SOT-RRMS	£26,373	Not relevant	B 3.5.1
	Cladribine Tablets - RES-RRMS	£25,917	Not relevant	
	Alemtuzumab	£35,225 – year 1 £21,135 – year 2+	Not relevant	
	Fingolimod	£19,176	Not relevant	
	Natalizumab	£14,690	Not relevant	
	Daclizumab	£19,160	Not relevant	
Annual administration cost All years unless specified	Cladribine Tablets - RES-RRMS	£0	Not relevant	
	Cladribine Tablets - SOT-RRMS	£0	Not relevant	
	Alemtuzumab	£2,782 – year 1 £1,681 – year 2+	Not relevant	
	Fingolimod	£551 – year 1 £0 – year 2+	Not relevant	
	Natalizumab	£7,159	Not relevant	
	Daclizumab	£204 – year 1 £0 – year 2+	Not relevant	
Annual monitoring cost All years unless specified	Cladribine Tablets - RES-RRMS	£584 – year 1 £215 – year 2+	Not relevant	
	Cladribine Tablets - SOT-RRMS	£584 – year 1 £215 – year 2+	Not relevant	
	Alemtuzumab	£444 – year 1 £267 – year 2+	Not relevant	
	Fingolimod	£821 - year 1 £169 – year 2+	Not relevant	
	Natalizumab	£540 – year 1 £547 - year 2+	Not relevant	
	Daclizumab	£349 – year 1 £187 – year 2+	Not relevant	
EDSS direct medical costs	EDSS 0	£1,054	290	B 3.5.2
	EDSS 1.0	£941	174	

Resource item	Treatment	Cost	Standard error of cost (if relevant)	Reference in submission
	EDSS 2.0	£740	95	
	EDSS 3.0	£691	84	
	EDSS 4.0	£1,036	114	
	EDSS 5.0	£1,040	124	
	EDSS 6.0	£1,348	97	
	EDSS -7.0	£1,360	186	
	EDSS 8.0	£3,432	409	
	EDSS 9.0	£3,432	409	
EDSS direct non-medical costs	EDSS 0	£1,675	738	
	EDSS 1.0	£1,675	738	
	EDSS 2.0	£1,675	738	
	EDSS 3.0	£1,675	738	
	EDSS 4.0	£8,589	968	
	EDSS 5.0	£8,589	968	
	EDSS 6.0	£8,589	968	
	EDSS 7.0	£35,392	9,759	
	EDSS 8.0	£35,392	9,759	
	EDSS 9.0	£35,392	9,759	
Relapse costs	Relapse requiring hospitalisation	£526	49	
	Relapse not requiring hospitalisation	£3,463	162	
Adverse events	Infusion site reaction	£0	Not available	B 3.5.3
	Injection site reaction	£6.79	Not available	
	PML	£1268.11	Not available	
	Severe infection	£3287.62	Not available	
	Macular oedema	£245.46	Not available	
	Gastrointestinal	£707.28	Not available	
	Hypersensitivity	£156.68	Not available	
	Autoimmune thyroid-related event	£543.63	Not available	
	Influenza-like symptoms	£6.79	Not available	
	Malignancy	£11,427.59	Not available	
	Immune thrombocytopenic purpura	£939.54	Not available	

Relevant cost and health resource use data were identified from various sources including previous NICE appraisals, a systematic review of published costing studies, the British National formulary, NHS reference costs, PSS research unit reports, and the summary of product characteristics for in-scope comparators. Further detail on the methods used to estimate costs is provided in the following sections.

B.3.5.1. Intervention and comparators' costs and resource use

The total cost of intervention and comparator treatment comprises three components:

- drug acquisition
- drug administration,
- drug monitoring

The costs of acquisition, administration and monitoring were assumed to apply for the duration that people remain on therapy. For daclizumab, fingolimod and natalizumab, the number of people on therapy was estimated from the EDSS status of the population taking into account those that discontinue (e.g. develop SPMS or discontinue for other reasons) in the previous cycle. All patients were assumed to adhere to therapy and take their full course in a given year.

For alemtuzumab and Cladribine Tablets, drug costs were estimated based on the proportion of patients eligible for therapy (EDSS <7.0 and RRMS) at the start of each cycle multiplied by the proportion treated, Table 83. Re-initiation of treatment was permitted up to year 10 of the simulated time horizon.

The proportion of patients treated with Cladribine Tablets and alemtuzumab was set to 100% in years 1 and 2. This was applied to all patients eligible for treatment after excluding persons who progressed to EDSS 7.0 or greater, developed SPMS, or were intolerant to therapy. In CLARITY, an estimated 91.2% of all randomized patients completed two courses of therapy. Reasons for not completing the course included disease progression, and intolerance, which are accounted for separately in the model calculation.

After year 2, it was assumed that a proportion of patients will require re-initiation with alemtuzumab in line with Committee preferences for TA441, and TA312. This was modelled based on the data used in TA441, where it was assumed that 28% received an additional course in year 3, 11% in year 4, and 1% in year 5.

Similarly, for Cladribine Tablets, it is conceivable that a proportion of patients may require re-initiation of treatment after completion of their first 2-courses.

While long-term follow-up data for Cladribine Tablets are available from CLARITY EXT, the study does not provide clear evidence on the expected rate of re-initiation of treatment as patients who entered the extension study were randomised to either Cladribine Tablets (e.g. 100% re-initiation) or placebo (e.g. 0% re-initiation). Re-initiation of Cladribine Tablets was therefore modelled on the expected proportion of patients who experience their first relapse between years 2 and 6, estimated from data on the time to first relapse in the LLPP arm of CLARITY and CLARITY EXT. After year 6, no further re-initiation was assumed given uncertainty over the rate of relapse beyond this time period.

It was assumed that all patients who relapse will be re-initiated on a single course of Cladribine Tablets, regardless of lymphocyte status or other factors that may preclude re-initiation. This is a conservative assumption that likely overestimates re-initiation costs for Cladribine Tablets.

A summary of the alemtuzumab and Cladribine Tablets re-initiation rates are provided in Table 83.

Table 83: Base case assumptions on the proportion of eligible patients treated with Cladribine Tablets and alemtuzumab

Year(s)/course of therapy	Proportion of eligible patients treated with Cladribine Tablets	Proportion of eligible patients treated with alemtuzumab
1	100%	100%
2	100%	100%
3	9.3%	28%
4	4.2%	11%
5	3.2%	1%
6	13.4%	0%

Source: Data on file, (NICE Technology appraisal guidance 2014a) (Willis 2016)

B.3.5.1.1. Drug acquisition

The annual cost of drug acquisition was calculated from the list price of medication and the mean total dose of therapy administered in each year of the simulation. The list price of each medication was

obtained from the British National Formulary. The total dose of therapy was modelled based on the posology stated in the summary of product characteristic for each individual drug in scope.

A summary of the total cost of drug acquisition by therapy is shown in Table 84.

Table 84: Total drug acquisition cost by therapy in the model (list price)

Therapy	Pack	Unit per pack	Unit cost	Dose based on summary of product characteristic	Units consumed per year Year 1 / year 2+	Total annual cost Year 1	Total annual cost Year 2+
Cladribine Tablets (Weight distribution and number of tablets per category is shown in Appendix I1.1)	1 x 10 mg tab	1	£2,047	0.875 mg/kg per dose	2 / 2	£26,373 (SOT-RRMS) £25,917 (RES-RRMS)	£26,373 (SOT-RRMS) £25,917 (RES-RRMS)
Alemtuzumab	12mg vial	1	£7,045	12mg per infusion	5 / 3	£35,225	£21,135
Fingolimod – List price	28-cap	28	£1,470	1 tab per day	365.25	£ 19,176	
Natalizumab	15ml- vial	1	£1,130	Once every 4 weeks (300mgs equating to 1x 15ml-vial)	13.0	£ 14,690	
Daclizumab – List price	1-syringe	1	£1,597	Once monthly	12.0	£ 19,160	

The annual drug cost of Cladribine Tablets varies between the RES-RRMS and SOT-RRMS populations due to small differences in the weights distributions of the two cohorts in CLARITY. A summary of the weight distribution of the RES-RRMS and SOT-RRMS populations is provided in Appendix D, and the recommended number of tablets per category is outlined in the draft summary of product characteristics.

A standard course of alemtuzumab is administered in two courses over two years, and involves the administration of five single 12 mg vials over five consecutive days (one vial per day) in the first year followed by three 12 mg vials over three consecutive days in year 2. The re-initiation of alemtuzumab beyond year 2 was assumed to involve 3 12mg vials given over three consecutive days.

The total number of doses per year of daclizumab and natalizumab treatment was 12.0 and 13.0 respectively. This follows the recommended dosing for each individual DMT stated in the summary of product characteristics; Monthly dosing for daclizumab or every 4 weeks dosing for natalizumab. This follows the approach accepted in TA441.

The annual drug costs of fingolimod and daclizumab were calculated based on their respective list prices. Both therapies are available on the NHS at a discounted price, as agreed in the manufacturer's patient access schemes. The discounts provided are commercial in confidence, and are therefore not available to the company.

Given uncertainty over the discount rates applied to fingolimod and daclizumab, the list prices for each treatment were used in the base case analysis. To assess the potential impact of each scheme on the cost-effectiveness of Cladribine Tablets, a series of sensitivity analyses were performed assuming discount rates of 20% and 40% on the list price.

B.3.5.1.2. Drug administration

The annual cost of drug administration was calculated from the unit cost of each administration resource multiplied by the number of resources consumed in a year of treatment.

Administration costs comprise admissions for infusions, additional medications provided alongside therapy, and any additional district nurse or neurologist visits required to support drug administration. The unit costs of drug administration are summarised in Table 85.

The number of resources consumed in the administration of DMT is presented in Table 85.

Table 85: Total costs of administration of DMT in people with multiple sclerosis

Therapy	Administration	Source	Administration resources consumed per year of therapy	Total cost Year 1	Total cost Year 2+
Cladribine Tablets	Oral	Draft summary of product characteristics	No administration requirements	£0	£0
Alemtuzumab	Infusion	Manufacturer submission for TA312	5x admissions in first year plus 3 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of Aciclovir (200mg) 3x admissions in subsequent years plus 3 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of Aciclovir (200mg)	£2,782	£1,681
Fingolimod	Oral	Manufacturer submission for TA312	Admission during first year to monitor ECG	£551	£0
Natalizumab	Infusion	Summary of product characteristics	Monthly admissions for infusions (13 in total)	£7,159	£7,159
Daclizumab	Subcutaneous	Assumption in line with administration costs applied to other subcutaneous injectables in previous RRMS appraisals	Training for self-administration of device	£204	£0

B.3.5.1.3. Drug monitoring

The annual cost of drug monitoring was calculated from the unit cost of monitoring resources multiplied by the number of resources consumed in a year of treatment.

Monitoring costs comprise drug-related biochemistry, urinalysis, and thyroid function tests, complete blood counts, MRI scans, tests for human papilloma virus (HPV), tuberculosis, hepatitis B and C, and John Cunningham's (JC) virus, and visits to health care practitioners to support the monitoring of DMT.

A summary of the resource use and associated total costs of DMT monitoring is provided in Table 86.

The costs of drug monitoring were assumed to vary between the first and subsequent years to account for the increased testing typically required on initiation of therapy. With the exception of natalizumab, which has an associated high risk of PML that requires ongoing MRI monitoring, the costs of monitoring were lower in subsequent years than in the first year.

Table 86: Costs of DMT monitoring

Therapy	Form	Source	Administration resources consumed in first year	Total cost Year 1	Administration resources consumed in subsequent year	Total cost Year 2+
Cladribine Tablets	Oral	Draft summary of product characteristics	1 x MRI scan 3 x complete blood counts 2x neurology visits 1x tuberculin skin test 1x HBV test 1xHCV test	£584	3 x complete blood counts 1x neurology visits 1x HBV test 1xHCV test	£215
Alemtuzumab	Infusion	Alemtuzumab summary of product characteristics Manufacturer submission for TA312	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 1x tuberculin skin test 0.65x human papilloma virus test (females only – assumption 65%) 2x neurology visits	£444	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 0.65 x human papilloma virus test (females only – assumption 65%) 1x neurology visits	£267
Fingolimod	Oral	Manufacturer submission for TA312 Fingolimod summary of product characteristics	1x MRI scan 4 x complete blood count 6 x biochemistry tests (month 0,1,3, 6,9 and 12) 1 x Ophthalmology assessment 3 x neurology visits	£821	2 x complete blood count 2 x biochemistry test 1 x neurology visits	£169
Natalizumab	Infusion	(McGuigan 2016) Alemtuzumab NICE submission	1 x JC virus test 2 x biochemistry test 1 x MRI scan 2 x neurologist visit	£540	2 x JC virus test (six monthly) 2 x biochemistry test 1 x MRI scan 2 x neurology visits	£547
Daclizumab	S/C	Manufacturer submission for TA441	13 x biochemistry tests 4 x complete blood count 2 x neurology visit	£349	12 x biochemistry tests 4 x complete blood count 1 x neurology visit	£187

B.3.5.2. Health-state unit costs and resource use

Published costing studies in RRMS were identified via a systematic literature review (search date January 4th 2017) of biomedical literature databases in accordance with the NICE methods guide (NICE 2013). The review covered:

- published peer-reviewed costing studies
- costing data used in models submitted to the NICE STA process
- unpublished data held by the company

The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix I.

In total, 122 unique published studies were included (117 from search, 4 following bibliographic searching, 1 by conference hand searching), of which six reported UK costs relevant to clinical practice in England (McCrone 2008; Karampampa 2012c; Tyas 2007; Hawton 2016b; Duddy 2014).

Three of the six UK studies reported costs by EDSS state (Hawton 2016b; Karampampa 2012c; Tyas 2007). Karampampa et al (Karampampa 2012c) and Tyas et al (Tyas 2007) reported direct medical, direct non-medical and indirect costs from patient self-assessments of resource consumption, EDSS and relapse status. Hawton et al (Hawton 2016b) reported direct costs comprising visits to health care and social work professionals, plus the use of rehabilitation and respite services estimated through patient self-assessment, and combined with clinician assessed EDSS scores. Across all three studies, the sample size of the analysed populations ranged from 119 to 2048.

Four of the six UK studies reported relapse-related costs (Hawton 2016b; Karampampa 2012c; Tyas 2007; Duddy 2014), of which three reported direct medical costs in line with the NICE reference case. One study reported costs funded by out of pocket expenses (Duddy 2014).

B.3.5.2.1. Costs by EDSS state

Direct medical costs by EDSS

A summary of the annualised direct medical costs by EDSS state from the three UK studies is provided in Table 87.

Table 87: Annualised costs by EDSS state for medical direct costs/health care and social worker costs

	Hawton et al* Mean (standard deviation)	Karampampa et al (Excluding DMT costs) Mean	Tyas et al Mean (standard deviation)
Sample size	289 (with EDSS)	119	2048
Cost year	2012	2009	2005
EDSS 0	£1020 (281)	£1345	£250 (1975)
EDSS 1.0	£910 (168)	£1345	£85 (899)
EDSS 2.0	£716 (92)	£1345	£213 (868)
EDSS 3.0	£668 (81)	£1345	£850 (1237)
EDSS 4.0	£1002 (110)	£2602	£806 (884)
EDSS 5.0	£1006 (120)	£2602	£1419 (823)
EDSS 6.0	£1304 (94)	£2602	£2162 (851)
EDSS 7.0	£1316 (180)	£2602	£6583 (995)
EDSS 8.0	£3320 (395)	£3961	£10,761 (1069)
EDSS 9.0	Not reported	£3961	£15,121 (2656)
Costs included	Contact with chiropodist, clinical psychologist, continence advisor, district nurse, dietician, GP, MS specialist nurse, neurologist, occupational therapist, ophthalmologist, physiotherapist, rehabilitation doctor, social worker, speech therapist, pain management service and/or rehabilitation/respite care	Inpatient and outpatient care, consultations with specialists and other medical professionals, investigations/tests, and other prescribed medication, and over-the-counter medication	Not clearly stated in publication
Assumptions	Annual costs are six monthly costs multiplied by 2	The total direct medical costs included disease modifying treatment. These costs are accounted for separately in the economic analysis, and therefore had to be excluded from the total cost. The study provided a breakdown of cost categories by EDSS state, which was used to estimate the total direct medical costs excluding drug therapy, by subtracting the mean drug costs from the mean total cost. EDSS costs were also reported in bands of EDSS (0-3.5, 4.0-6.5 7.0 – 9.0); a constant fixed cost was assumed to apply across individual states within each band.	-

Note: * Costs reported per six months in original study. Costs increased by a factor of 2 to give annualised costs

Source: (Hawton 2016b; Karampampa 2012c; Tyas 2007)

The costs reported in Hawton et al, Karampampa et al, and Tyas et al were inflated to a 2015/2016 cost year using the hospital and community health services indices reported by the PSSRU (Curtis 2016). Inflation indices up to 2016/2017 were not available at the time of analysis.

Based on the 2016 PSSRU report (Curtis 2015; Curtis and Burns 2016), the inflation indices for Tyas et al (2005 cost year), Karampampa et al (2009 cost year), and Hawton et al (2012 cost year) were 23%, 11% and 3%, respectively.

After inflation, the annual costs of direct medical care in Hawton et al ranged from £691 for EDSS 3.0 to £3,432 for EDSS 8.0 (data not reported for EDSS 9.0). The annual costs in EDSS 0, 1.0 and 2.0 were £1,054, £941, and £740, respectively. As noted in Hawton et al (Hawton 2016a), the reduction in costs from EDSS 0 to EDSS 3 may be reflective of an initial peak in resource consumption around the time of diagnosis followed by a period of stabilisation. As MS deteriorates and walking impairment develops (EDSS > 4.0), the costs increase as greater medical support is needed.

In general, higher costs were reported in both Karampampa et al and Tyas et al when compared to Hawton et al. In Karampampa et al (Karampampa 2012c), inflated annual costs of direct medical care were £1,658 for EDSS 0-3.0, £3,208 for EDSS 4.0-6.5 and £4,883 for EDSS 7.0-9.0. In Tyas et al (Tyas 2007), annual costs ranged from £94 (EDSS 1.0) to £16,720 (EDSS 9.0). Both studies include a broader range of medical costs including inpatient and outpatient services that may not be captured in Hawton et al. The lack of detail reported on the costs included in either study precludes the robust comparison of these data.

It is noted that costs from Karampampa et al and Tyas et al are uncertain given the need to inflate costs from 2005 for Tyas et al, and the relatively small sample of patients in Karampampa et al (N=194) (Karampampa 2012c). On this basis, a conservative approach was taken by using the direct medical costs by EDSS from Hawton et al (Hawton 2016b) in the base case.

Direct non-medical costs

Direct non-medical and indirect costs were reported in both Karampampa et al (Karampampa 2012c) and Tyas et al (Tyas 2007).

In Karampampa et al (Karampampa 2012c), direct non-medical costs included resources described as professional, informal care, investments and utensils required by the patient. In Tyas et al (Tyas 2007), direct non-medical costs comprised costs funded by the government and costs funded as out of pocket, although no information is provided on how these costs were defined. Only costs funded by the NHS and PSS are included in the base case analysis. Indirect costs comprised lost productivity from sickness or early retirement due to MS. These costs are also excluded from the NHS perspective.

A summary of the annualised direct non-medical costs by EDSS state is provided in Table 87.

Table 88: Annualised costs by EDSS state for non-medical direct and indirect costs for Karampampa et al and Tyas et al

	Karampampa et al Mean (standard deviation)		Tyas et al (direct non-medical costs borne by the government) Mean (standard deviation)	
	Direct non-medical	**Indirect**	**Direct non-medical**	**Indirect**
Sample size	119		2048	
Cost year	2009		2005	
EDSS 0	£1,913 (843)	£3,214 (763)	£2,536 (2,183)	£11,509 (1,633)
EDSS 1.0	£1,913 (843)	£3,214 (763)	£3,462 (1,314)	£12,857 (1,034)
EDSS 2.0	£1,913 (843)	£3,214 (763)	£4,414 (1,314)	£17,068 (1,010)
EDSS 3.0	£1,913 (843)	£3,214 (763)	£6,212 (1,585)	£19,450 (1,191)
EDSS 4.0	£10,299 (1,161)	£7,494 (865)	£4,028 (1,320)	£16,049 (1,013)
EDSS 5.0	£10,299 (1,161)	£7,494 (865)	£6,333 (1,338)	£21,116 (1,029)
EDSS 6.0	£10,299 (1,161)	£7,494 (865)	£6,580 (1,338)	£21,338 (1,042)
EDSS 7.0	£41,242 (11,371)	£11,717 (3,649)	£10,808 (1,485)	£22,736 (1,161)
EDSS 8.0	£41,242 (11,371)	£11,717 (3,649)	£15,339 (1,514)	£23,088 (1,169)
EDSS 9.0	£41,242 (11,371)	£11,717 (3,649)	£10,166 (2,837)	£23,583 (2,107)
Costs included	Professional and informal care and investments/utensils required by patients	sick leave from work and retirement due to disability	Not stated in publication	
Assumption	EDSS costs were also reported in bands of EDSS (0-3.5, 4.0-6.5 7.0 – 9.0); a constant fixed cost was assumed to apply across individual states within each band		-	

As outlined in previous NICE appraisals (TA303, TA312, TA320 and TA441), there is uncertainty concerning the extent to which direct non-medical costs can be considered under the NHS and PSS perspective. In the most recent NICE appraisal, TA441, the Committee and evidence review group concluded that some but not all direct non-medical costs would be paid for by the NHS and PSS (NICE 2017b).

Following TA441, only direct non-medical costs from Karampampa et al were considered in the analysis given that insufficient detail was provided in Tyas et al to adjust the non-medical costs to include components covered under the NHS and PSS perspective (NICE 2017b). As considered for TA441, 80% of social and community care and 47% of investment costs were considered in the analysis.

A summary of the adjusted costs from Karampampa et al is provided in Table 89.

Table 89: Annualised costs by EDSS state for non-medical direct costs for Karampampa et al adjusted for relevant values

EDSS categories in Karampampa et al	Investment cost (unadjusted)	Professional and informal care costs (unadjusted)	Total direct non-medical (unadjusted)	Investment cost (47%)	Professional and informal care costs (80%)	Total direct non-medical (adjusted)	Total direct non-medical (adjusted and inflated to 2015/2016)
0-3.0	£48	£1865	£1913	£23	£1492	£1516	£1675
4-6.5	£1475	£8843	£10,318	£693	£7074	£7768	£8,569
7-.9.0	£2989	£38,254	£41,243	£1405	£30,603	£32,008	£35,592

The direct non-medical costs were inflated to a 2015/2016 cost year using the same indices applied for direct costs (11% inflation since 2009).

B.3.5.2.2. Costs by relapse status

Hawton et al (Hawton 2016b) reported six monthly costs associated with no relapses, relapses not treated with steroids, relapses that limited everyday activities, relapses that required steroid therapy (oral, intravenous) and relapses that resulted in hospital admission. The difference in cost between no relapse and each relapse category ranged from £152 for relapses not treated with steroids to £3,350 for relapses leading to hospitalisation (2012 cost year) (Hawton 2016b).

Karampampa et al (Karampampa 2012c) reported costs associated with no relapse, relapses requiring no steroid treatment or hospitalisation and relapses requiring steroid treatment with or without hospitalisation.

A summary of the costs of relapse events by study is reported in Table 90.

Table 90: Cost of relapse reported in individual studies

Relapse state	Hawton et al mean (standard deviation)	Karampampa et al (Excluding DMT costs) mean	Tyas et al mean
Sample size	289 (with EDSS)	119	2048
Cost year	2012	2009	2005
No relapse	£229 (366)	4793	-
Any relapse	-	-	+£1623
Relapse not treated with steroids	£381 (780)	£8365	-
Relapse limited everyday activities	£557 (993)		-
Relapse resulted in oral steroids	£738 (887)	£10,244	-
Relapse resulted in intravenous steroids	£1860 (1869)		-
Relapse resulted in hospital admission	£3579 (1727)		-

The preferred data source for the direct medical costs of relapses was Hawton et al (Hawton 2016b) in line with the data used to model the costs by EDSS state in the model.

The relapse costs were inflated to a 2015/2016 cost year using hospital and community health services index of 3%.The costs associated with hospitalised and non-hospitalised relapse events were estimated by subtracting the costs in those with a relapse from the costs in those without relapse (Table 91):

- Hospital costs = (3579 -229)x103% [inflation]
- Non-hospital costs = (738-229)*103% [inflation]

Table 91: Cost of relapse events in the model

Relapse state	Inflated cost per event
Relapse without hospitalisation	£526
Relapse with hospitalisation	£3463

B.3.5.3. Adverse reaction unit costs and resource use

A summary of the adverse reaction unit costs and resource use data is presented in Table 92.

Table 92: Adverse event unit costs and resource use

Adverse event	Total Cost	Unit costs	Resource use
Infusion site reaction	£0	£0	Assumption that infusion site reactions are treated alongside administration of infusion
Injection site reaction	£6.79	£67.89 per hour of patient-related work (PSSRU) including qualification (2015 price inflated to 2015/16 value using the HCHS Pay & Prices Index)	Assumption of 6 minute nurse consultation or call
PML	£1268.11	£4503.35 (SA13A – Single plasma exchange, 19 years or over) £26.70 (BNF) per 30-tablet pack of prednisone	80% of patients were treated with plasma exchange (Dong-Si 2014), involving an average of 3 plasma exchanges (Khatri 2009) 72.5% of patients experience immune reconstitution syndrome (Dong-Si 2014) and receive 13.3 weeks of steroid treatment (Tan 2009)
Severe infection	£3287.62	£3287.62 (DZ22L – Total HRG cost for unspecified acute lower respiratory infection, with interventions, CC 0-8)	1 x NHS reference cost for respiratory infection
Macular oedema	£245.46	£128.43 (WF02B) Multi-professional Non-Admitted Face to Face Attendance, First –Ophthalmology £117.03 (WF02A) Multi-professional Non-Admitted Face to Face Attendance, Follow-up –Ophthalmology	2 x visits to ophthalmologist based on assumptions in manufacturer submission for TA312
Gastrointestinal	£707.28	(FZ90B) Abdominal Pain without Interventions	1 x NHS reference cost for abdominal pain without interventions
Hypersensitivity	£156.68	Non-consultant led multi-professional non-admitted face-to-face meeting with allergy service (WF01B)	1 x NHS reference cost for use of allergy service
Autoimmune thyroid-related event	£543.63	Non-surgical thyroid disorders with CC Score 0-1 (KA07C)	1 x NHS reference cost
Influenza-like symptoms	£6.79	£67.89 per hour of patient-related work (PSSRU) including qualification (2015 price inflated to 2015/16 value using the HCHS Pay & Prices Index)	Assumption of 6 minute nurse consultation or call

Adverse event	Total Cost	Unit costs	Resource use
Malignancy	£11,427.59	Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (CB0A1)	Based on most expensive cancer NHS reference cost category of Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (CB0A1)
Immune thrombocytopenic purpura	£939.54	Thrombocytopenia with CC Score 5-7 (SA12H)	1 x NHS reference cost

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A summary of the variables applied in the economic model is provided in Table 93.

Table 93: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Patient characteristics	Table 58	Log-normal for age Dirichlet for weight distribution and baseline EDSS	B.3.2.1
Natural history model: annualised relapse rate year 1	Table 62	Log-normal	B.3.3
Natural history model: Change in annualised relapse by time	22.9% per 5-years	Beta (converted to annualised effect after sampling)	B.3.3
Natural history model: Duration of relapse event	Table 63	Log normal	B.3.3,
Natural history model: EDSS transition matrix	Table 66	Dirichlet	B.3.3
Natural history model: Adjustment for SOT-RRMS and RES-RRMS	Table 67	Lognormal (assumed 20% of mean)	B.3.3
Natural history model: All-cause mortality statistics	Appendix K	Not sampled	B.3.3
Natural history model: standardised mortality ratio for MS related mortality	1.68 [95% confidence interval: 1.38-2.05])	Log normal	B.3.3
Treatment adjusted model: annualised relapse rate ratio	Table 68	Log normal	B.3.3
Treatment adjusted model: hazard ratio for confirmed disability progression	Table 69	Normal (on log-scale)	B.3.3
Treatment adjusted model: Waning parameters	Table 70, Table 72	Not sampled	B.3.3
Treatment adjusted model: adverse event rates	Table 73	Beta for pooled probabilities Normal for log-odds ratios	B.3.3
Treatment adjusted model: discontinuation rates	Table 74	Beta	B.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Both models: HSU by EDSS (patient and caregiver), relapse and adverse event	Table 81	Log normal on 1-HSU for HSU by EDSS (patient) Normal for HSU loss by EDSS (caregiver) Normal for HSU loss by relapse Normal for HSU loss by adverse event	B.3.4
Both models: drug costs (acquisition, administration, monitoring), EDSS, relapse and adverse events	Table 82	Gamma for EDSS and relapse costs Drug and adverse event costs are not sampled	B.3.4

CI: confidence interval

B.3.6.2. Assumptions

A summary of the key assumptions in the base case model is outlined in Table 94.

Table 94: Summary of basic structural assumptions

Aspect	Assumption	Justification
Health states	EDSS captures the main health problems associated with MS	Numerous studies have shown a strong correlation between EDSS and resource consumption and health related quality of life. EDSS is the preferred tool for measuring disability in people with MS as recommended by the European Medicines Agency
Lifetable/half-cycle correction	EDSS and drug-related costs and QALY are modelled based on midpoint estimates assuming patients, on average, transition mid-way through the model cycle. Exceptions are the drug costs of Cladribine Tablets and alemtuzumab which are assumed to accrue at the start of the model cycle as therapy is given as a fixed course at the beginning of each treated year.	Standard approach to mitigate the risk of under or over-estimating costs and effects
Natural history of MS – disability progression	Disability progression is modelled assuming a constant transition probability matrix over time	Consistent with approaches taken in previous economic models Constant transition probability matrix shown to accurately predict EDSS status over 10-years, Figure 14
Natural history of MS – relapse	In the base case, relapses are modelled independently from EDSS state , and assumed to vary over time	Consistent with approaches taken in previous economic models This is to avoid double counting of DMT effect
Effectiveness of DMT - application	Sustained accumulation of disability and relapses are modelled independently, with independent treatment effects applied.	Consistent with approaches taken in previous economic models Some treatments may be more effective in reducing relapses than slowing disease progression

Aspect	Assumption	Justification
Discontinuation of DMT or cessation of DMT benefits	People with MS are assumed to discontinue therapy upon progression to EDSS 7.0 People treated with alemtuzumab or Cladribine Tablets are also assumed to stop benefiting from therapy once progression to EDSS 7.0 or greater. The health benefits of DMT that are accrued up to the point of discontinuation or cessation of therapy benefits is maintained with future progression rates modelled based on a natural history data set	This is consistent with approaches taken in past economic models Clinical trials in RRMS have typically focused on patients who have non-ambulatory RRMS including patients with EDSS <6.5 in study enrolment. No data are available on the effects of DMT in people with EDSS 7.0 or greater
Effectiveness of DMT – waning over time	The effectiveness of DMT is assumed to wane over time	This is consistent with approaches taken in past economic models Long-term treatment with natalizumab can lead to the development of neutralising antibodies that can reduce the effectiveness of these therapies The effectiveness of fixed course therapies such as alemtuzumab or Cladribine Tablets will wane over time due to recovery of the immune system and other factors implicated in the pathogenesis of MS
No distinction made between RR and SP forms of MS	Any difference in the transition rate between RR and SP forms of MS is accounted for in the averaged transition rates used in the model	This is consistent with approaches taken in past economic models Transition rates used in the base case analysis were sourced from Palace et al (Palace 2014), which includes data from an RRMS cohort who are followed through to SPMS.
Inclusion of adverse events	Relevant drug related adverse events include infusion and injection site reactions, PML, macular oedema, malignancy, severe infections, autoimmune-thyroid events, hypersensitivity and allergic reaction	Infusion and injectable site reactions are commonly reported adverse events across the clinical trial literature and have been incorporated in previous models Natalizumab, and fingolimod has been associated with an increased risk of PML Fingolimod has been associated with an increased risk of macular oedema and skin cancer Cladribine Tablets, fingolimod, natalizumab, teriflunomide and alemtuzumab have been associated with an increased risk of severe infection Alemtuzumab has been associated with an increased risk of autoimmune-thyroid related events including immune thrombocytopenic purpura Natalizumab has been associated with an increased risk of hypersensitivity and allergic reaction

B.3.7 Base-case results

In line with the expected marketing authorisation for Cladribine Tablets and the final scope, the base-case results of the economic analyses are presented for the following four groups:

- RES-RRMSa: RES-RRMS and able to receive to alemtuzumab
- RES-RRMSb: RES-RRMS but unable to receive to alemtuzumab
- SOT-RRMSa: SOT-RRMS and able to receive to alemtuzumab
- SOT-RRMSb: SOT-RRMS but unable to receive to alemtuzumab

The relevant comparators to Cladribine Tablets are summarised in Table 61, and reproduced in Table 95.

Table 95: Comparators by population in the base case analysis

Population	Description	Comparators
RES-RRMSa	RES-RRMS and able to receive to alemtuzumab	Natalizumab Alemtuzumab
RES-RRMSb	RES-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Natalizumab Daclizumab
SOT-RRMSa	SOT-RRMS and able to receive to alemtuzumab	Fingolimod Alemtuzumab
SOT-RRMSb	SOT-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Fingolimod Daclizumab

All analyses are presented for a lifetime horizon of 50-years.

B.3.7.1. Base-case incremental cost-effectiveness analysis results

B.3.7.1.1. RES-RRMSa

The results of the deterministic base case analysis for the RES-RRMSa population are provided in Table 96.

Table 96: Base-case results for RES-RRMSa at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	480,441	22.176	8.098					
Alemtuzumab	499,575	22.176	7.916	-19,134	0.000	0.182	Cladribine dominant	Cladribine dominant
Natalizumab	611,117	22.176	7.586	-130,676	0.000	0.512	Cladribine dominant	Cladribine dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Cladribine Tablets were dominant (e.g. less costly and more effective) versus alemtuzumab and natalizumab in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets were the least costly treatment in the RES-RRMSa population with a total discounted lifetime cost of £480,441. The next most expensive strategies were alemtuzumab (£499,575) followed by natalizumab (£611,117). Cladribine Tablets were cost-saving versus both alemtuzumab and natalizumab, with incremental costs of -£19,134 (alemtuzumab) and -£130,676 (natalizumab).

Cladribine Tablets were the most effective strategy in the population with a total discounted QALY of 8.098, and compared with total QALYs of 7.916 for alemtuzumab and 7.586 for natalizumab. The incremental QALYs comparing Cladribine Tablets versus alemtuzumab was +0.182, and versus natalizumab was +0.512.

B.3.7.1.2. RES-RRMSb

The results of the deterministic base case analysis for the RES-RRMSb population are provided in Table 97.

Table 97: Base-case results for RES-RRMSb at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	480,441	22.176	8.098					
Daclizumab – at list price	569,623	22.176	7.174	-89,182	0.000	0.924	Cladribine dominant	Cladribine dominant
Natalizumab	611,117	22.176	7.586	-130,676	0.000	0.512	Cladribine dominant	Cladribine dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Cladribine Tablets were dominant (e.g. less costly and more effective) versus alemtuzumab and natalizumab in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets were the least costly treatment in the population with a total discounted cost of £480,441. The next most expensive strategies were daclizumab (£569,623) followed by natalizumab (£611,117). Cladribine Tablets were cost-saving versus both alemtuzumab and natalizumab, with incremental costs of -£89,182 (daclizumab) and -£130,676 (natalizumab).

Cladribine Tablets were the most effective strategy in the population with a total discounted QALY of 8.098, and compared with total QALYs of 7.174 for daclizumab and 7.586 for natalizumab. The incremental QALYs comparing Cladribine Tablets versus daclizumab was +0.924, and versus natalizumab was +0.512.

B.3.7.1.3. SOT-RRMSa

The results of the deterministic base case analysis for the SOT-RRMSa population are provided in Table 98.

Table 98: Base-case results for SOT-RRMSa at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	467,361	21.318	7.570					
Alemtuzumab	484,910	21.318	7.417	-17,549	0.000	0.153	Cladribine dominant	Cladribine dominant
Fingolimod – list price	539,427	21.318	6.626	-72,066	0.000	0.944	Cladribine dominant	Cladribine dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Cladribine Tablets were dominant (e.g. less costly and more effective) versus alemtuzumab and fingolimod in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets were the least costly and most effective treatment in the population with a total discounted cost of £467,361, and a total discounted QALY of 7.570. The next most expensive strategy was alemtuzumab (£484,910) with a total discounted QALY of 7.417. Fingolimod was the most expensive (£539,427) and least effective strategy with a total QALY of 6.626.

B.3.7.1.4. SOT-RRMSb

The results of the deterministic base case analysis for the SOT-RRMSb population are provided in Table 99.

Table 99: Base-case results for SOT-RRMSb at list price

Technologies (from least to most expensive)	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Cladribine Tablets	467,361	21.318	7.570					
Daclizumab	533,758	21.318	7.022	-66,397	0.000	0.548	Cladribine dominant	Cladribine dominant
Fingolimod	539,427	21.318	6.626	-72,066	0.000	0.944	Cladribine dominant	Cladribine dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Cladribine Tablets were dominant (e.g. less costly and more effective) versus daclizumab and fingolimod in the pairwise comparisons, and the dominant strategy in the fully incremental analyses.

Cladribine Tablets were the least costly and most effective treatment in the population with a total discounted cost of £467,361, and a total discounted QALY of 7.570. The next most expensive strategy was daclizumab (£533,758) with a total discounted QALY of 7.022. Fingolimod was the most expensive (£539,427) and least effective strategy with a total QALY of 6.626.

B.3.8 Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

A summary of the probabilistic distributions used in the sensitivity analysis is provided in Table 93. Further details on the derivation of sampling parameters (e.g. alpha and beta for individual distributions) are available in the Excel model.

Separate probabilistic analyses were conducted in the four groups of interest; RES-RRMSa, RES-RRMSb, SOT-RRMSa, and SOT-RRMSb. For each analysis, a run of 1000 Monte-Carlo simulations was performed. This number of iterations was judged to be sufficient to achieve convergence in the expected cost and QALY for each intervention. This was confirmed by plotting the cumulative mean net monetary benefit of Cladribine Tablets, alemtuzumab and natalizumab over 1000 iterations for RES-RRMSa, Figure 17.

Figure 17: Plot showing cumulative mean net monetary benefit by number of samples from the probabilistic analysis (RES-RRMSa)

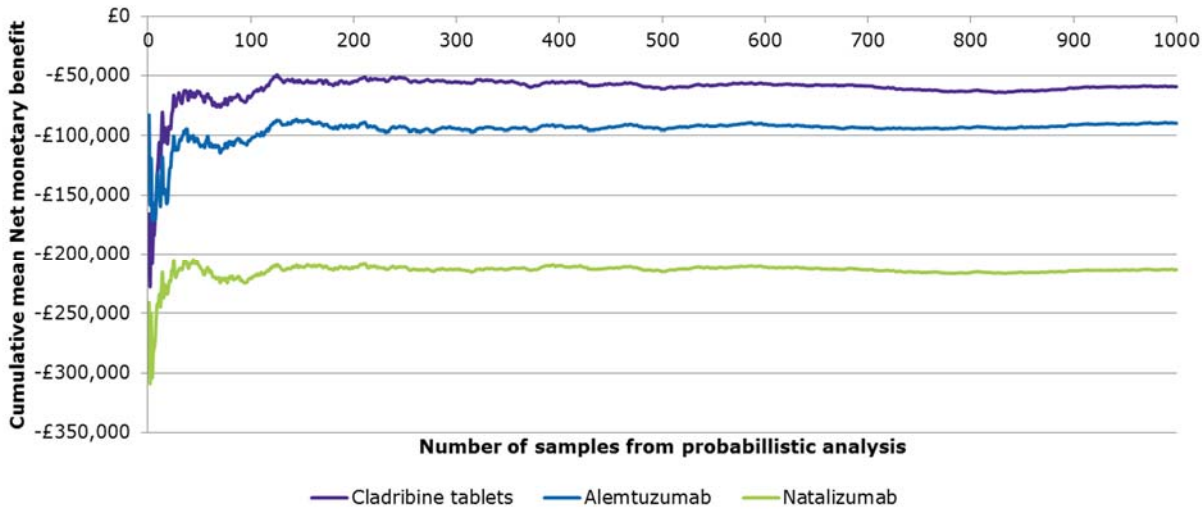


Figure 17 shows that the mean net monetary benefit is stable after approximately 500 iterations, and shows that it has converged to its expected value by 1000 iterations. Hence, a sample of 1000 iterations was judged to be sufficient, although the Excel model has the flexibility to conduct up to 10,000 iterations, if required.

Results were summarised based on expected (e.g. mean) and 95% confidence intervals for total costs and QALY. The mean incremental total cost, QALY and associated incremental cost-effectiveness ratios were estimated from the difference in mean values from each set of sampled values. Multi-way cost-effectiveness acceptability curves were plotted for each population of interest. The expected probability of cost-effectiveness at thresholds of £20,000 and £30,000 were obtained and presented alongside the expected probabilistic results.

In summary, the results of the PSA are broadly consistent with those of the deterministic analysis, providing confidence in the base-case results presented in Section B.3.7.

B.3.8.1.1. RES-RRMSa

The results of the probabilistic sensitivity analysis for the RES-RRMSa population are summarised in Table 100 and Figure 18.

Cladribine Tablets were the dominant strategy in the probabilistic analysis as a result of being both less costly and more effective than alemtuzumab and natalizumab. The results of the probabilistic analysis are consistent with the results of the deterministic analysis summarised in Table 96.

The probability that Cladribine Tablets are cost-effective versus alemtuzumab and natalizumab in the RES-RRMSa population was 64.5% at a threshold of £20,000 per QALY gained. The corresponding probability for Cladribine Tablets at £30,000 per QALY gained was 63.7%. At the same thresholds, the probability that alemtuzumab is the optimal cost-effective strategy in RES-RRMSa ranged from 35.5% to 36.3%. Alemtuzumab and Cladribine Tablets were dominant versus natalizumab in RES-RRMSa; the probability that natalizumab is cost-effective versus either therapy was 0% for thresholds of less than £30,000 per QALY.

B.3.8.1.2. RES-RRMSb

The results of the probabilistic sensitivity analysis for the RES-RRMSb population are summarised in Table 101 and Figure 19.

As in the deterministic analysis, Cladribine Tablets were less costly and more effective than daclizumab and natalizumab in the RES-RRMSb probabilistic analysis. The probabilities that Cladribine Tablets are cost-effective in RES-RRMSb at thresholds of £20,000 and £30,000 were in excess of 96%.

B.3.8.1.3. SOT-RRMSa

The results of the probabilistic sensitivity analysis for the SOT-RRMSa population are summarised in Table 102 and Figure 20.

Similar results were observed in SOT-RRMSa as reported for RES-RRMSa, with Cladribine Tablets being the dominant strategy as a result of it being both less costly and more effective than alemtuzumab and fingolimod. The probability that Cladribine Tablets are cost-effective at thresholds of £20,000 and £30,000 was 61.6% and 60.8% respectively.

B.3.8.1.4. SOT-RRMSb

The results of the probabilistic sensitivity analysis for the SOT-RRMSb population are summarised in Table 103 and Figure 21.

In SOT-RRMSb, Cladribine Tablets were dominant versus daclizumab and fingolimod. The probability that Cladribine Tablets are cost-effective at thresholds of £20,000 and £30,000 was 86.5% and 84.5% respectively.

Table 100: Probabilistic results for RES-RRMSa at list price

Treatment	Costs Mean	Lower 95% limit	Upper 95% limit	QALY Mean	Lower 95% limit	Upper 95% limit	Incremental cost (mean)	Incremental QALY (mean)	Probabilistic ICER	Probability cost effective at £20,000 (Multi-way)	Probability cost effective at £30,000 (Multi-way)
Cladribine Tablets	475,162	322,885	700,515	8.154	5.407	11.002				64.5%	63.7%
Alemtuzumab	495,655	340,710	730,918	7.952	5.103	10.962	-20,492	0.202	Cladribine dominant	35.5%	36.3%
Natalizumab	604,411	467,522	808,947	7.663	5.243	10.148	-129,249	0.491	Cladribine dominant	0.0%	0.0%

Figure 18: Multi-way cost-effectiveness acceptability curve for RES-RRMSa at list price

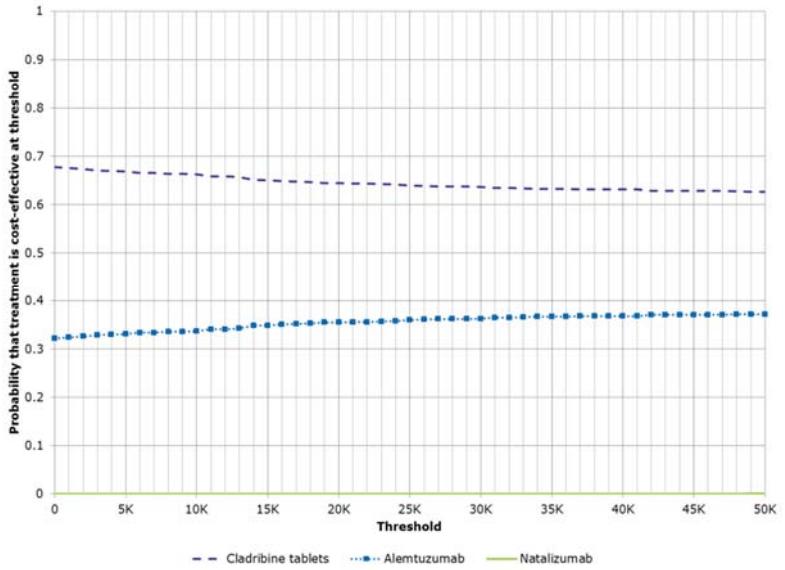


Table 101: Probabilistic results for RES-RRMSb at list price

Treatment	Costs Mean	Lower 95% limit	Upper 95% limit	QALY Mean	Lower 95% limit	Upper 95% limit	Incremental cost (mean)	Incremental QALY (mean)	Probabilistic ICER	Probability cost effective at £20,000 (Multi-way)	Probability cost effective at £30,000 (Multi-way)
Cladribine Tablets	471,594	318,242	699,831	8.249	5.350	11.024				97.5%	96.9%
Daclizumab	559,064	405,457	775,105	7.329	4.875	9.658	-87,470	0.920	Cladribine dominant	2.3%	2.6%
Natalizumab	600,923	463,227	795,561	7.751	5.360	10.105	-129,328	0.498	Cladribine dominant	0.2%	0.5%

Figure 19: Multi-way cost-effectiveness acceptability curve for RES-RRMSb at list price

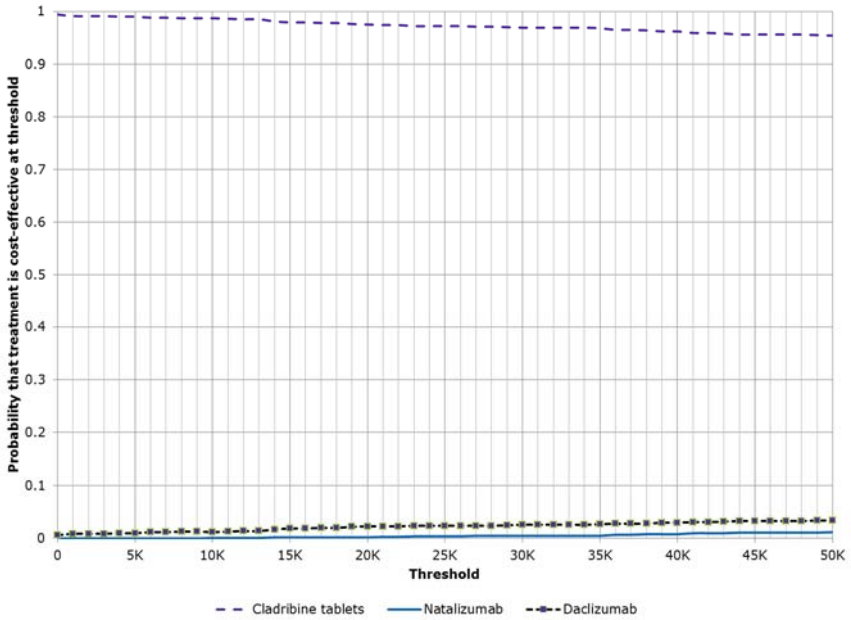


Table 102: Probabilistic results for SOT-RRMSa at list price

Treatment	Costs Mean	Lower 95% limit	Upper 95% limit	QALY Mean	Lower 95% limit	Upper 95% limit	Incremental cost (mean)	Incremental QALY (mean)	Probabilistic ICER	Probability cost effective at £20,000 (Multi-way)	Probability cost effective at £30,000 (Multi-way)
Cladribine Tablets	472,273	302,102	706,643	7.555	4.360	10.586				61.6%	60.8%
Alemtuzumab	491,914	316,157	731,764	7.357	4.305	10.600	-19,641	0.198	Cladribine dominant	35.3%	35.7%
Fingolimod	538,566	375,052	758,147	6.682	4.236	9.358	-66,293	0.873	Cladribine dominant	3.1%	3.1%

Figure 20: Multi-way cost-effectiveness acceptability curve for SOT-RRMSa at list price

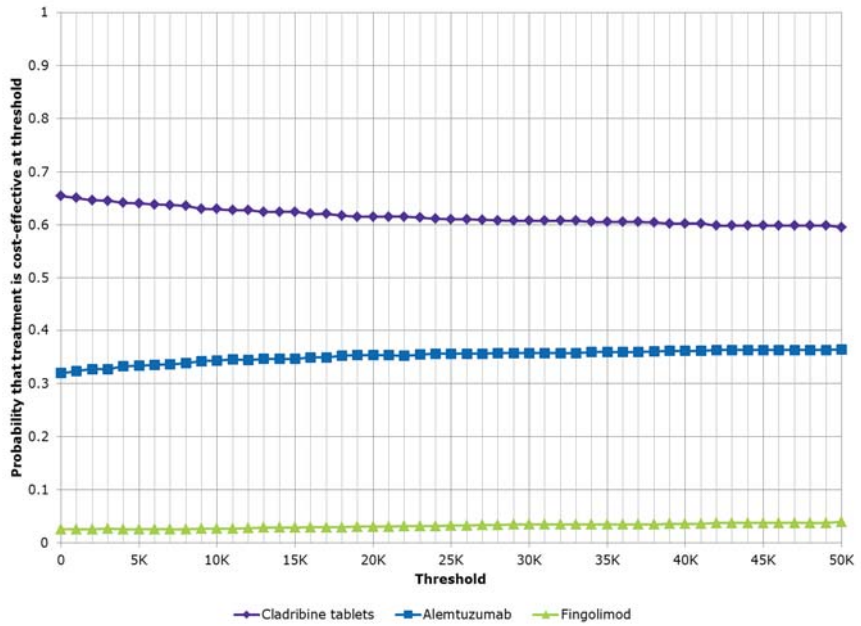
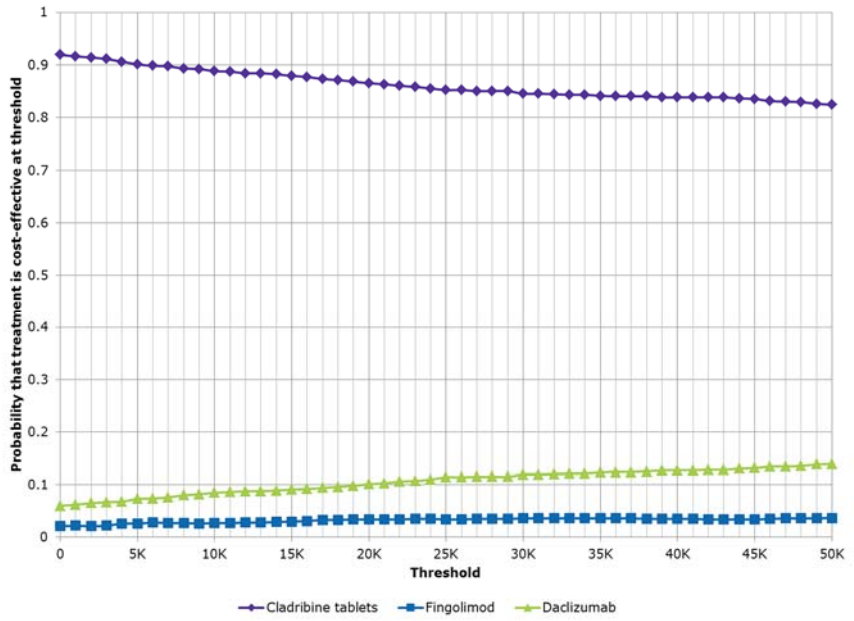


Table 103: Probabilistic results for SOT-RRMSb at list price

Treatment	Costs Mean	Lower 95% limit	Upper 95% limit	QALY Mean	Lower 95% limit	Upper 95% limit	Incremental cost (mean)	Incremental QALY (mean)	Probabilistic ICER	Probability cost effective at £20,000 (Multi-way)	Probability cost effective at £30,000 (Multi-way)
Cladribine Tablets	472,012	309,822	704,745	7.572	4.570	10.394				86.5%	84.5%
daclizumab	534,318	383,222	738,342	7.082	4.557	9.528	-62,306	0.489	Cladribine dominant	10.1%	11.9%
Fingolimod	538,296	379,940	763,761	6.727	4.485	9.011	-66,283	0.845	Cladribine dominant	3.4%	3.6%

Figure 21: Multi-way cost-effectiveness acceptability curve for SOT-RRMSb at list price



B.3.8.2. Deterministic sensitivity analysis

The results of the deterministic sensitivity analyses are summarised via a series of tornado diagrams. The aim of the analysis was to show the impact of variation in the values assigned to individual model parameters on the incremental net health effects of Cladribine Tablets versus comparators, when assessed at a fixed willingness to pay threshold of £30,000 per QALY gained.

Results were expressed in terms of net health effects in place of the incremental cost-effectiveness ratio, which is commonly used for such analyses, because in the base case Cladribine Tablets was dominant versus its comparators, and hence had a negative cost-effectiveness ratio. In this context, a negative incremental cost-effectiveness ratio cannot be directly interpreted given that this value can correspond to either the dominant (positive QALY and negative cost) or dominated (negative QALY and positive cost) quadrants of the cost-effectiveness plane.

A positive net health effect shows that Cladribine Tablets are cost-effective at a threshold of £30,000 versus its comparator in a given scenario. A negative net health effect indicates that Cladribine Tablets may not be a cost-effective option at this threshold.

Each parameter in the analysis was varied between its lower and upper 95% confidence or credible interval, or by 50% of its mean value if statistical measures of variance were not available.

B.3.8.2.1. RES-RRMSa

The results of the deterministic sensitivity analyses for RES-RRMSa are summarised in the following tornado diagrams for comparisons versus alemtuzumab (Figure 22), and natalizumab (Figure 23). The tornado diagram for Cladribine Tablets versus natalizumab applies to both RES-RRMSa and RES-RRMSb given that natalizumab is a comparator in both groups, and the same model inputs are used across both analyses.

The tornado diagrams show that the analysis is sensitive to variation in the effect of DMT on 6 month confirmed disability progression. Other key drivers include the discounting rate for costs, and the adjustment applied to the natural history model to account for faster EDSS progression in RES-RRMS patients. Factors such as the discontinuation rate, the effect of DMT on annualised relapse rate, and the baseline risk for RES-RRMS applied in the meta-regression model had a modest impact on results.

The incremental net health effects comparing Cladribine Tablets versus natalizumab was positive in all scenarios. Cladribine Tablets was therefore judged to be cost-effective versus natalizumab at a threshold of £30,000 per QALY gained. In the alemtuzumab analysis, the incremental net health effects were positive and in favour of Cladribine Tablets in most scenarios, except when varying the effect of DMT on disease progression where a negative net health effect was observed.

Figure 22: Tornado diagram for RES-RRMSa, Cladribine Tablets versus alemtuzumab

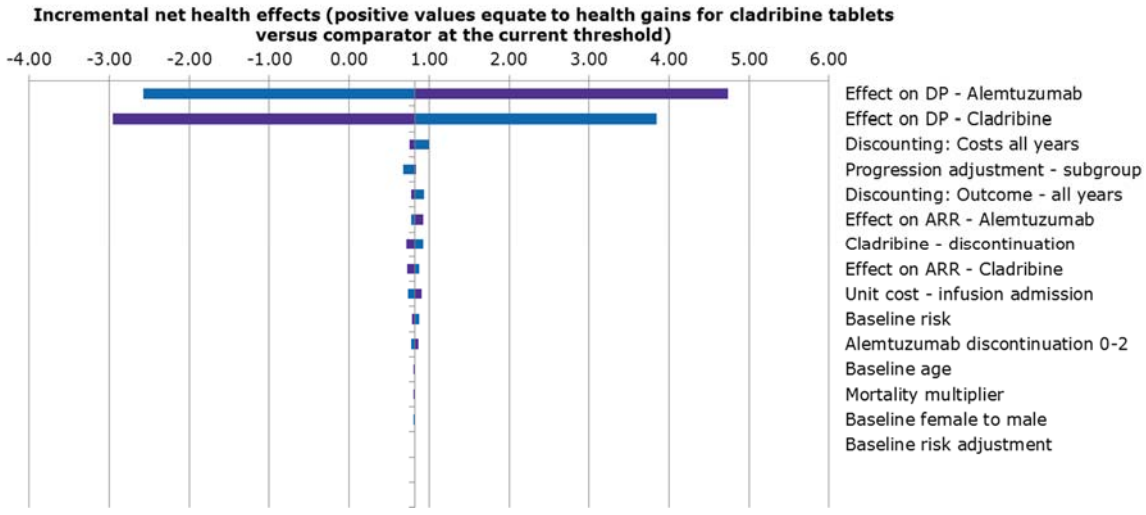
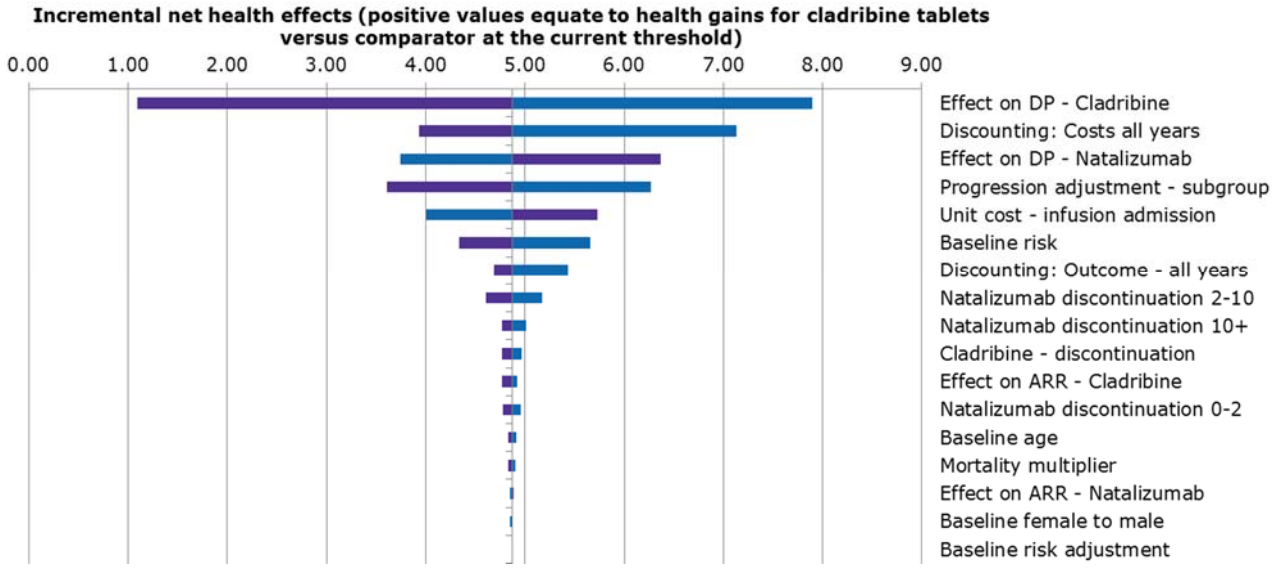


Figure 23: Tornado diagram for RES-RRMSa or RES-RRMSb, Cladribine Tablets versus natalizumab



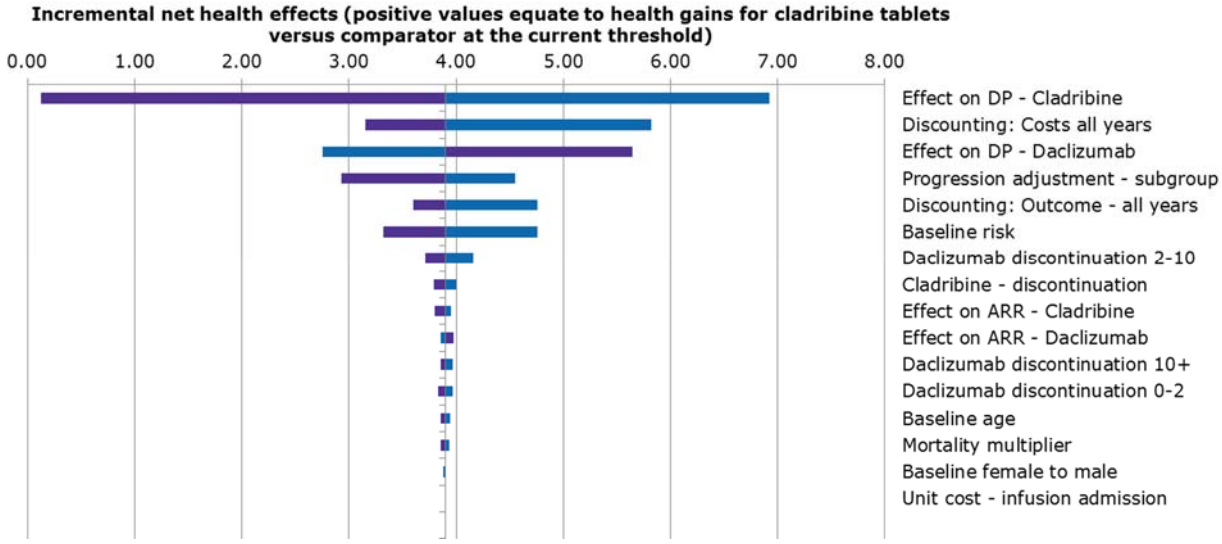
B.3.8.2.2. RES-RRMSb

The results of the deterministic sensitivity analyses for RES-RRMSb are summarised in Figure 24 for the comparison of Cladribine Tablets versus daclizumab, and in Figure 23 for the comparison to natalizumab.

As with RES-RRMSa, the tornado diagrams for RES-RRMSb shows that the analysis is most sensitive to variation in the effect of DMT on confirmed disability progression, followed by discounting rate for costs, and the adjustment for faster EDSS progression in RES-RRMS patients. Similarly, discontinuation rates, the effect of DMT on relapse rate, and the baseline risk for RES-RRMS applied in the meta-regression model had a modest impact on results.

The incremental net health effects of Cladribine Tablets versus daclizumab were positive in all scenarios. Cladribine Tablets were therefore judged to be cost-effective versus daclizumab at a threshold of £30,000 per QALY gained.

Figure 24 Tornado diagram for RES-RRMSb, Cladribine Tablets versus daclizumab



B.3.8.2.3. SOT-RRMSa

The results of the deterministic sensitivity analyses for SOT-RRMSa are summarised in the following tornado diagrams for comparisons versus alemtuzumab (Figure 25), and fingolimod (Figure 26). The tornado diagram for Cladribine Tablets versus fingolimod applies to both SOT-RRMSa and SOT-RRMSb as fingolimod is a comparator in both groups, and the same model inputs are used in both analyses.

As in the RES-RRMS analysis, the tornado diagrams for SOT-RRMSa show that the analysis is sensitive to variation in the effect of DMT on confirmed disability progression. Factors such as discounting rate for costs, the covariate for baseline risk and the baseline risk value applied in the meta-regression model, and the adjustment for faster EDSS progression in SOT-RRMS were also important drivers of results in the comparison to fingolimod.

Figure 25: Tornado diagram for SOT-RRMSa, Cladribine Tablets versus alemtuzumab

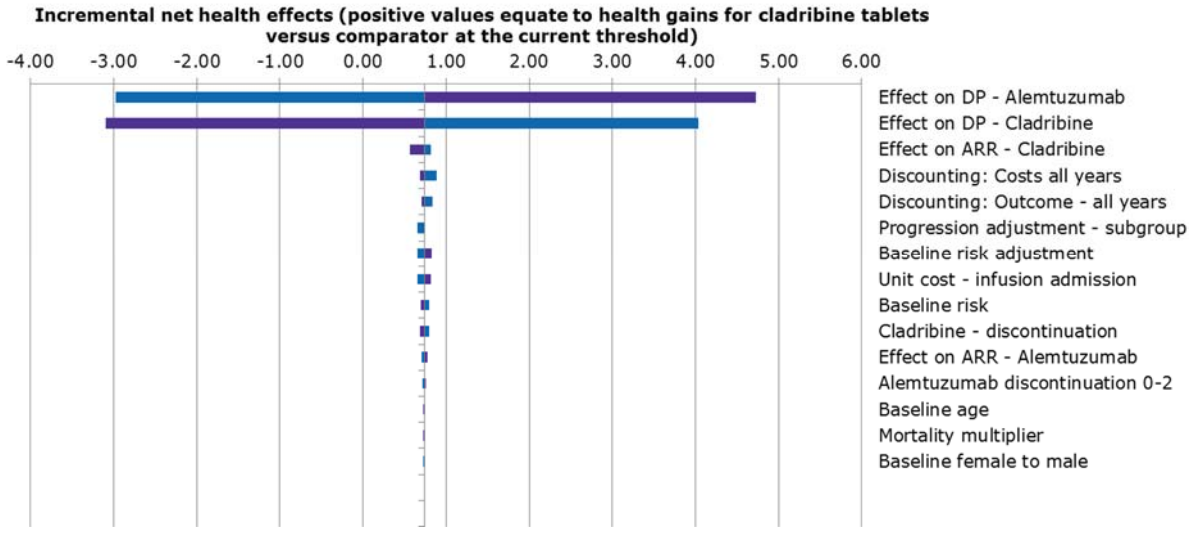
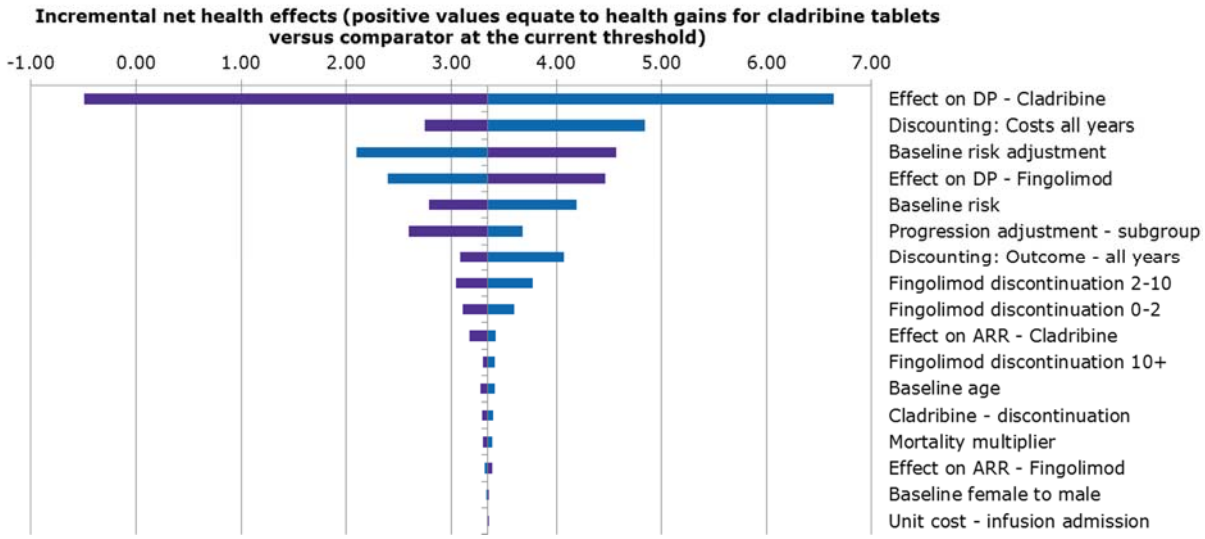


Figure 26: Tornado diagram for SOT-RRMSa, Cladribine Tablets versus fingolimod



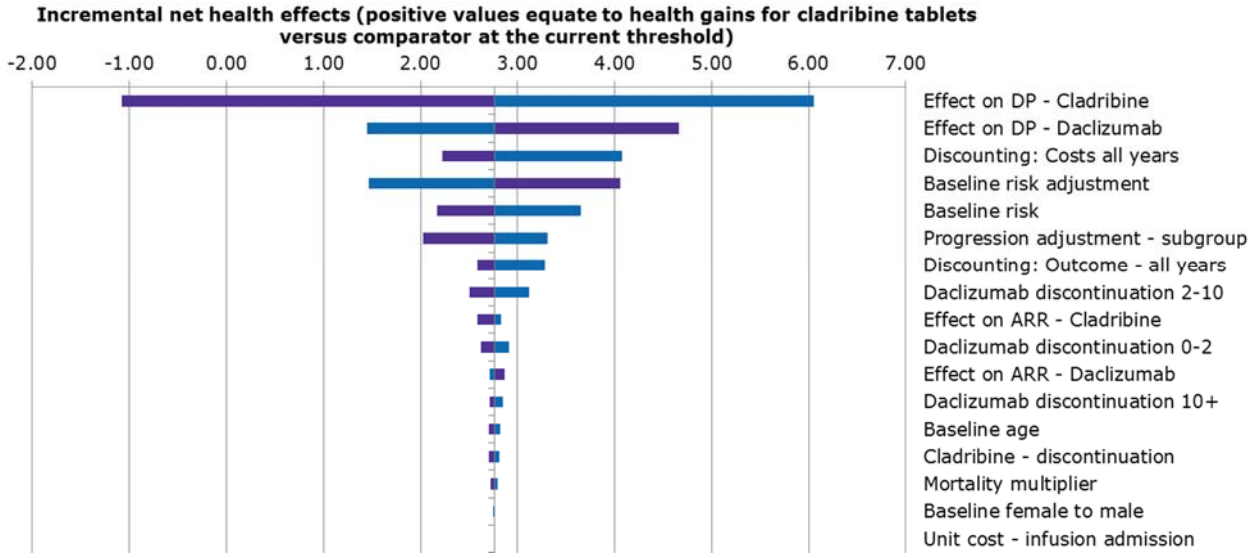
B.3.8.2.4. SOT-RRMSb

The results of the deterministic sensitivity analyses for SOT-RRMSb are summarised in Figure 27 for the comparison of Cladribine Tablets versus daclizumab, and in Figure 26 for the comparison to fingolimod.

As with SOT-RRMSa, the tornado diagrams for SOT-RRMSb show that the analysis is most sensitive to variation in the effect of DMT on confirmed disability progression, followed by discounting rate for costs, the baseline risk for SOT-RRMS applied in the meta-regression model, and the adjustment for faster EDSS progression in SOT-RRMS patients. Factors such as discontinuation rates, and the effect of DMT on relapse rate had a modest impact on results.

The incremental net health effects comparing Cladribine Tablets versus daclizumab were positive in all but one scenario. Where the net health effects were positive, Cladribine Tablets was therefore judged to be cost-effective versus daclizumab at a threshold of £30,000 per QALY gained.

Figure 27 Tornado diagram for SOT-RRMSb, Cladribine Tablets versus daclizumab



B.3.8.3. Scenario analysis

Scenario analyses were performed to test the robustness of the analysis to variations in underlying model assumptions and to the use of alternative input parameters (e.g. different utility sets or transition matrices for the natural history of disease). This included the utilisation of a societal perspective (including both direct non-medical and indirect costs), alternative time horizons, assumptions on the durability of drug effect, and the core model state structure (11 versus 21 states). The incremental cost-effectiveness ratios were generated for each scenario and then compared against the base case results.

B.3.8.3.1. RES-RRMSa

The results of the scenario analyses for RES-RRMSa are summarised in Table 104.

Across the majority of scenario analyses, Cladribine Tablets were the dominant treatment strategy yielding cost-savings for additional QALYs when compared to alemtuzumab and natalizumab. In comparison to natalizumab, incremental costs ranged from -£77,359 to -£198,586 with QALY gains ranging from 0.073 to 1.075. The corresponding incremental costs and incremental QALYs for Cladribine Tablets versus alemtuzumab were more uncertain; incremental costs ranging from -£54,406 (savings) to +£43,513 and incremental QALY ranging from -1.217 to 0.944.

The only scenario where Cladribine Tablets was not the dominant strategy was in comparison to alemtuzumab in the scenario that used a conventional network meta-analysis and unpublished RES-

RRMS subgroup data from PRISMS (interferon beta-1a versus placebo) to link alemtuzumab (alemtuzumab versus interferon beta-1a) trial data to the RES-RRMS subgroup data for CLARITY (Cladribine Tablets versus placebo) and AFFIRM (natalizumab versus placebo). In this scenario, Cladribine Tablets was more costly (+£36,519) but less effective (-1.071) than alemtuzumab as a result of the alemtuzumab effect size (hazard ratio of [redacted] versus placebo) being numerically superior to the effect size for Cladribine Tablets (hazard ratio of [redacted] versus placebo). As with the meta-regression analysis, there was significant overlap in the 95% credible intervals of the conventional meta-analysis, and hence no individual DMT was statistically superior over its comparators in terms of 6 month confirmed disability progression.

Cladribine Tablets were cost-saving and more efficacious than natalizumab in all scenarios tested, including when modelling the efficacy of therapy using the conventional network meta-analysis. In this scenario, natalizumab was more efficacious than Cladribine Tablets (hazard ratio of [redacted] for Cladribine Tablets versus placebo compared to [redacted] for natalizumab versus placebo) but required ongoing initiation of therapy to sustain a durable effect. Treatment with Cladribine Tablets is expected to yield sustained health benefits without the need for regular re-initiation of therapy. The discontinuation of natalizumab due to factors such as tolerability reduced the overall effectiveness of natalizumab, leading to fewer QALYs when compared to Cladribine Tablets.

B.3.8.3.2. RES-RRMSb

The results of the scenario analyses for RES-RRMSb are summarised in Table 104.

Across all scenarios tested, Cladribine Tablets were the dominant treatment strategy yielding cost-savings for additional QALYs when compared to daclizumab and natalizumab. In comparison to daclizumab, incremental costs ranged from -£48,749 to -£146,956 with QALY gains ranging from 0.585 to 1.789. This included scenarios where the list price for daclizumab was discounted at rates of 20 and 40%.

The results of the scenario analysis for natalizumab in RES-RRMSb are identical to those reported for RES-RRMSa as the same input parameters are used across RES-RRMS groups. The scenario analyses for natalizumab are therefore summarised in the previous section.

B.3.8.3.3. SOT-RRMSa

The results of the scenario analyses for SOT-RRMSa are summarised in Table 106.

Across all scenarios tested, Cladribine Tablets were the dominant treatment strategy yielding cost-savings for additional QALYs when compared to alemtuzumab and fingolimod. The incremental costs comparing Cladribine Tablets versus alemtuzumab ranged from -£11,342 to -£54,723, and from -£30,081 to -£117,023 versus fingolimod. This included scenarios where the list price for fingolimod was discounted at rates of 20 and 40%.

B.3.8.3.4. SOT-RRMSb

The results of the scenario analyses for SOT-RRMSb are summarised in Table 107.

Across all scenarios tested, Cladribine Tablets were the dominant treatment strategy yielding cost-savings for additional QALYs when compared to daclizumab and fingolimod. The incremental costs comparing Cladribine Tablets versus daclizumab ranged from -£28,685 to -£105,811, and from -£30,081 to -£117,023 versus fingolimod. This included scenarios where the list price for fingolimod and daclizumab were discounted at rates of 20 and 40%.

Table 104: Results of scenario analyses for RES-RRMSa population

Scenario	Cladribine Tablets versus alemtuzumab			Cladribine Tablets versus natalizumab		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Base case	-19134	0.182	Cladribine dominant	-130676	0.512	Cladribine dominant
Time horizon -20 years	-17319	0.144	Cladribine dominant	-112706	0.281	Cladribine dominant
Time horizon -80 years	-19157	0.183	Cladribine dominant	-130893	0.516	Cladribine dominant
Societal perspective	-21276	0.182	Cladribine dominant	-136871	0.512	Cladribine dominant
Discounting 1 (0% cost, 6% QALY)	-24399	0.137	Cladribine dominant	-198586	0.330	Cladribine dominant
Discounting 2 (6% cost, 0% QALY)	-17198	0.301	Cladribine dominant	-102712	1.075	Cladribine dominant
Stopping rule 6	-18077	0.165	Cladribine dominant	-77359	0.332	Cladribine dominant
Stopping rule 8	-18881	0.181	Cladribine dominant	-161770	0.656	Cladribine dominant
Natural history Transition (alternative British Columbia)	-19332	0.192	Cladribine dominant	-129190	0.531	Cladribine dominant
Natural history Transition (AFFIRM RES-RRMS with BC)	-15886	0.121	Cladribine dominant	-157891	0.570	Cladribine dominant
21 state with British Columbia data for RRMS	-18785	0.182	Cladribine dominant	-106354	0.427	Cladribine dominant
21 state with London Ontario data for RRMS	-17480	0.150	Cladribine dominant	-104777	0.351	Cladribine dominant
Mortality By EDSS	-18417	0.184	Cladribine dominant	-127709	0.518	Cladribine dominant
Mortality by Lalmohamed et al	-18776	0.174	Cladribine dominant	-126481	0.469	Cladribine dominant
Relapse by EDSS	-18849	0.179	Cladribine dominant	-130653	0.512	Cladribine dominant
Meta-regression: Fixed common	-23319	0.274	Cladribine dominant	-131186	0.522	Cladribine dominant
Meta-regression: Random Exchangeable	-41632	0.668	Cladribine dominant	-129009	0.473	Cladribine dominant
Meta-regression: Fixed Exchangeable	-54406	0.944	Cladribine dominant	-132237	0.545	Cladribine dominant
Analysis with Network Meta-analysis*	36,519	-1.071	Cladribine dominated	-130549	0.367	Cladribine dominant
Same Waning assumptions	-12256	0.033	Cladribine dominant	-123799	0.363	Cladribine dominant
Exclude non-medical costs	-11543	0.182	Cladribine dominant	-107462	0.512	Cladribine dominant

Scenario	Cladribine Tablets versus alemtuzumab			Cladribine Tablets versus natalizumab		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Direct medical costs - Karampampa	-19302	0.182	Cladribine dominant	-131077	0.512	Cladribine dominant
Direct medical costs - Tyas	-21112	0.182	Cladribine dominant	-136728	0.512	Cladribine dominant
Utility (Hawton plus Orme)	-19134	0.161	Cladribine dominant	-130676	0.457	Cladribine dominant
Utility (Orme only)	-19134	0.181	Cladribine dominant	-130676	0.513	Cladribine dominant
Utility (DEFINE/CONFIRM)	-19134	0.185	Cladribine dominant	-130676	0.518	Cladribine dominant
Utility - Relapse (Ruutin)	-19134	0.183	Cladribine dominant	-130676	0.511	Cladribine dominant
Exclusion of caregiver utility	-19134	0.165	Cladribine dominant	-130676	0.480	Cladribine dominant
Average weight (versus dist.)	-20917	0.182	Cladribine dominant	-132459	0.512	Cladribine dominant
Baseline EDSS (Hawton)	-18624	0.170	Cladribine dominant	-127891	0.504	Cladribine dominant
Baseline EDSS and age (Hawton)	-17679	0.149	Cladribine dominant	-116170	0.386	Cladribine dominant

Note: * hazard ratios for six month confirmed disability progression of 0.460 (95% credible interval: 0.153 to 1.380) for Cladribine Tablets versus placebo, 0.246 (0.085 to 0.716) for alemtuzumab, and 0.360 (0.170 to 0.761) for natalizumab.

Table 105: Results of scenario analyses for RES-RRMSb population

Scenario	Cladribine Tablets versus daclizumab			Cladribine Tablets versus natalizumab		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Base case	-89182	0.924	Cladribine dominant	-130676	0.512	Cladribine dominant
Time horizon -20 years	-71391	0.585	Cladribine dominant	-112706	0.281	Cladribine dominant
Time horizon -80 years	-89423	0.929	Cladribine dominant	-130893	0.516	Cladribine dominant
Societal perspective	-100047	0.924	Cladribine dominant	-136871	0.512	Cladribine dominant
Discounting 1 (0% cost, 6% QALY)	-146956	0.630	Cladribine dominant	-198586	0.330	Cladribine dominant
Discounting 2 (6% cost, 0% QALY)	-66795	1.789	Cladribine dominant	-102712	1.075	Cladribine dominant
Stopping rule 6	-51234	0.648	Cladribine dominant	-77359	0.332	Cladribine dominant
Stopping rule 8	-108287	1.126	Cladribine dominant	-161770	0.656	Cladribine dominant
Natural history Transition (alternative British Columbia)	-88744	0.960	Cladribine dominant	-129190	0.531	Cladribine dominant
Natural history Transition (AFFIRM RES-RRMS with BC)	-97197	0.943	Cladribine dominant	-157891	0.570	Cladribine dominant
21 state with British Columbia data for RRMS	-73465	0.818	Cladribine dominant	-106354	0.427	Cladribine dominant
21 state with London Ontario data for RRMS	-69997	0.688	Cladribine dominant	-104777	0.351	Cladribine dominant
Mortality By EDSS	-84422	0.933	Cladribine dominant	-127709	0.518	Cladribine dominant
Mortality by Lalmohamed et al	-85367	0.861	Cladribine dominant	-126481	0.469	Cladribine dominant
Relapse by EDSS	-88847	0.920	Cladribine dominant	-130653	0.512	Cladribine dominant
Meta-regression: Fixed common	-89335	0.924	Cladribine dominant	-131186	0.522	Cladribine dominant
Meta-regression: Random Exchangeable	-85444	0.820	Cladribine dominant	-129009	0.473	Cladribine dominant
Meta-regression: Fixed Exchangeable	-85700	0.797	Cladribine dominant	-132237	0.545	Cladribine dominant
Analysis with Network Meta-analysis*	NA	NA	NA	-130549	0.367	Cladribine dominant
Same Waning assumptions	-82305	0.775	Cladribine dominant	-123799	0.363	Cladribine dominant
Exclude non-medical costs	-48749	0.924	Cladribine dominant	-107462	0.512	Cladribine dominant

Scenario	Cladribine Tablets versus daclizumab			Cladribine Tablets versus natalizumab		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Drug cost - list price discount of 20% for daclizumab	-69639	0.924	Cladribine dominant	-130676	0.512	Cladribine dominant
Drug cost - list price discount of 40% for daclizumab	-50095	0.924	Cladribine dominant	-130676	0.512	Cladribine dominant
Direct medical costs - Karampampa	-89898	0.924	Cladribine dominant	-131077	0.512	Cladribine dominant
Direct medical costs - Tyas	-99734	0.924	Cladribine dominant	-136728	0.512	Cladribine dominant
Utility (Hawton plus Orme)	-89182	0.825	Cladribine dominant	-130676	0.457	Cladribine dominant
Utility (Orme only)	-89182	0.923	Cladribine dominant	-130676	0.513	Cladribine dominant
Utility (DEFINE/CONFIRM)	-89182	0.935	Cladribine dominant	-130676	0.518	Cladribine dominant
Utility - Relapse (Ruutin)	-89182	0.922	Cladribine dominant	-130676	0.511	Cladribine dominant
Exclusion of caregiver utility	-89182	0.864	Cladribine dominant	-130676	0.480	Cladribine dominant
Average weight (versus dist.)	-90965	0.924	Cladribine dominant	-132459	0.512	Cladribine dominant
Baseline EDSS (Hawton)	-86603	0.901	Cladribine dominant	-127891	0.504	Cladribine dominant
Baseline EDSS and age (Hawton)	-76063	0.727	Cladribine dominant	-116170	0.386	Cladribine dominant

Note: * hazard ratios for six month confirmed disability progression of 0.460 (95% credible interval: 0.153 to 1.380) for Cladribine Tablets versus placebo, 0.246 (0.085 to 0.716) for alemtuzumab, and 0.360 (0.170 to 0.761) for natalizumab.

Table 106: Results of scenario analyses for SOT-RRMSa population

Scenario	Cladribine Tablets versus alemtuzumab			Cladribine Tablets versus fingolimod		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Base case	-17549	0.153	Cladribine dominant	-72066	0.944	Cladribine dominant
Time horizon -20 years	-16042	0.121	Cladribine dominant	-58787	0.678	Cladribine dominant
Time horizon -80 years	-17558	0.153	Cladribine dominant	-72140	0.946	Cladribine dominant
Societal perspective	-19257	0.153	Cladribine dominant	-83378	0.944	Cladribine dominant
Discounting 1 (0% cost, 6% QALY)	-21893	0.117	Cladribine dominant	-117023	0.679	Cladribine dominant
Discounting 2 (6% cost, 0% QALY)	-15935	0.249	Cladribine dominant	-54067	1.673	Cladribine dominant
Stopping rule at EDSS 6	-15970	0.128	Cladribine dominant	-37205	0.700	Cladribine dominant
Stopping rule at EDSS 8	-17723	0.161	Cladribine dominant	-88792	1.098	Cladribine dominant
Natural history Transition (alternative British Columbia)	-17692	0.160	Cladribine dominant	-71922	0.986	Cladribine dominant
21 state with British Columbia data for RRMS	-17121	0.150	Cladribine dominant	-61900	0.888	Cladribine dominant
21 state with London Ontario data for RRMS	-16134	0.125	Cladribine dominant	-58322	0.737	Cladribine dominant
Mortality By EDSS	-16805	0.155	Cladribine dominant	-66554	0.955	Cladribine dominant
Mortality by Lalmohamed et al	-17136	0.144	Cladribine dominant	-68001	0.873	Cladribine dominant
Relapse by EDSS	-17583	0.154	Cladribine dominant	-72210	0.946	Cladribine dominant
Meta-regression: Fixed common	-22023	0.250	Cladribine dominant	-72815	0.958	Cladribine dominant
Meta-regression: Random Exchangeable	-41123	0.659	Cladribine dominant	-74873	0.985	Cladribine dominant
Meta-regression: Fixed Exchangeable	-54723	0.938	Cladribine dominant	-70793	0.916	Cladribine dominant
Same Waning assumptions	-13475	0.067	Cladribine dominant	-67992	0.858	Cladribine dominant
Exclude non-medical costs	-11342	0.153	Cladribine dominant	-30081	0.944	Cladribine dominant
Drug cost - list price discount of 20% for daclizumab	-17549	0.153	Cladribine dominant	-55874	0.944	Cladribine dominant
Drug cost - list price discount of 40% for daclizumab	-17549	0.153	Cladribine dominant	-39682	0.944	Cladribine dominant

Scenario	Cladribine Tablets versus alemtuzumab			Cladribine Tablets versus fingolimod		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Direct medical costs - Karampampa	-17669	0.153	Cladribine dominant	-72793	0.944	Cladribine dominant
Direct medical costs - Tyas	-19171	0.153	Cladribine dominant	-83043	0.944	Cladribine dominant
Utility (Hawton plus Orme)	-17549	0.137	Cladribine dominant	-72066	0.838	Cladribine dominant
Utility (Orme only)	-17549	0.152	Cladribine dominant	-72066	0.939	Cladribine dominant
Utility (DEFINE/CONFIRM)	-17549	0.155	Cladribine dominant	-72066	0.956	Cladribine dominant
Utility - Relapse (Ruutin)	-17549	0.153	Cladribine dominant	-72066	0.943	Cladribine dominant
Exclusion of caregiver utility	-17549	0.142	Cladribine dominant	-72066	0.879	Cladribine dominant
Average weight (versus dist.)	-20284	0.153	Cladribine dominant	-74801	0.944	Cladribine dominant
Baseline EDSS (Hawton)	-17125	0.148	Cladribine dominant	-71709	0.940	Cladribine dominant
Baseline EDSS and age (Hawton)	-16433	0.133	Cladribine dominant	-64622	0.815	Cladribine dominant

Table 107: Results of scenario analyses for SOT-RRMSb population

Scenario	Cladribine Tablets versus daclizumab			Cladribine Tablets versus fingolimod		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Base case	-66397	0.548	Cladribine dominant	-72066	0.944	Cladribine dominant
Time horizon -20 years	-55361	0.342	Cladribine dominant	-58787	0.678	Cladribine dominant
Time horizon -80 years	-66465	0.550	Cladribine dominant	-72140	0.946	Cladribine dominant
Societal perspective	-72984	0.548	Cladribine dominant	-83378	0.944	Cladribine dominant
Discounting 1 (0% cost, 6% QALY)	-105811	0.371	Cladribine dominant	-117023	0.679	Cladribine dominant
Discounting 2 (6% cost, 0% QALY)	-50363	1.065	Cladribine dominant	-54067	1.673	Cladribine dominant
Stopping rule at EDSS 6	-32987	0.361	Cladribine dominant	-37205	0.700	Cladribine dominant
Stopping rule at EDSS 8	-83019	0.680	Cladribine dominant	-88792	1.098	Cladribine dominant
Natural history Transition (alternative British Columbia)	-65848	0.570	Cladribine dominant	-71922	0.986	Cladribine dominant
21 state with British Columbia data for RRMS	-55008	0.483	Cladribine dominant	-61900	0.888	Cladribine dominant
21 state with London Ontario data for RRMS	-53273	0.395	Cladribine dominant	-58322	0.737	Cladribine dominant
Mortality By EDSS	-62739	0.556	Cladribine dominant	-66554	0.955	Cladribine dominant
Mortality by Lalmohamed et al	-62865	0.495	Cladribine dominant	-68001	0.873	Cladribine dominant
Relapse by EDSS	-66895	0.554	Cladribine dominant	-72210	0.946	Cladribine dominant
Meta-regression: Fixed common	-66785	0.551	Cladribine dominant	-72815	0.958	Cladribine dominant
Meta-regression: Random Exchangeable	-67083	0.518	Cladribine dominant	-74873	0.985	Cladribine dominant
Meta-regression: Fixed Exchangeable	-60258	0.366	Cladribine dominant	-70793	0.916	Cladribine dominant
Same Waning assumptions	-62323	0.462	Cladribine dominant	-67992	0.858	Cladribine dominant
Exclude non-medical costs	-41773	0.548	Cladribine dominant	-67992	0.858	Cladribine dominant
Drug cost - list price discount of 20% for daclizumab	-47541	0.548	Cladribine dominant	-30081	0.944	Cladribine dominant
Drug cost - list price discount of 40% for daclizumab	-28685	0.548	Cladribine dominant	-55874	0.944	Cladribine dominant

Scenario	Cladribine Tablets versus daclizumab			Cladribine Tablets versus fingolimod		
	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio	Incremental Cost	Incremental QALY	Incremental cost-effectiveness ratio
Direct medical costs - Karampampa	-66821	0.548	Cladribine dominant	-39682	0.944	Cladribine dominant
Direct medical costs - Tyas	-72817	0.548	Cladribine dominant	-72793	0.944	Cladribine dominant
Utility (Hawton plus Orme)	-66397	0.488	Cladribine dominant	-83043	0.944	Cladribine dominant
Utility (Orme only)	-66397	0.548	Cladribine dominant	-72066	0.838	Cladribine dominant
Utility (DEFINE/CONFIRM)	-66397	0.555	Cladribine dominant	-72066	0.939	Cladribine dominant
Utility - Relapse (Ruutin)	-66397	0.547	Cladribine dominant	-72066	0.956	Cladribine dominant
Exclusion of caregiver utility	-66397	0.513	Cladribine dominant	-72066	0.943	Cladribine dominant
Average weight (versus dist.)	-69132	0.548	Cladribine dominant	-72066	0.879	Cladribine dominant
Baseline EDSS (Hawton)	-66931	0.559	Cladribine dominant	-74801	0.944	Cladribine dominant
Baseline EDSS and age (Hawton)	-60727	0.464	Cladribine dominant	-71709	0.940	Cladribine dominant

B.3.9 Subgroup analysis

No further subgroup analyses were performed on the RES-RRMS or SOT-RRMS groups.

B.3.10 Validation

Validation of the cost-effectiveness analysis included consideration of its face validity, internal validity, cross validity, and external validity.

Face validity covers four aspects; model structure, data sources, problem formulation and results. The model structure and data sources used in the model were tested with clinical experts and external health economists familiar with RRMS, who validated the choice of structure (11 versus 21 states), and choice of inputs to the natural history model. The meta-regression model used to simulate the effect of DMT in RES-RRMS and SOT-RRMS for all comparators in scope was conceptualised and reviewed by an external meta-analysis expert.

Internal validity, which is otherwise known as verification, considers the implementation of the mathematical calculations required in the model, and includes consideration of whether the equations used to inform the model are specified and implemented correctly. This was tested through the application of extreme value testing, and by examination of the model calculations by an independent modeller. Any discrepancies identified in this review were corrected prior to submission.

Cross validity can be assessed by comparing the results of the base case analysis to different models that address the same problem. It is not feasible to exactly replicate the results of other models given differences in model inputs, state structure and modelling methodology (e.g. 21 versus 11 states). In addition, models published prior to January 2014 would not have access to the British Columbia Natural history model, which includes backward transitions to EDSS. Models published prior to this date typically used the London Ontario data for predicting lifetime EDSS status. This data set had censored for backward transitions resulting in models that predicted a faster overall rate of progression and an implausibly low accumulation of QALY relative to life years (discussed in TA312). The inclusion of backward transitions within the natural history models precludes any attempt to compare the results of this analysis to existing published studies. Hence, no formal cross validation of the model was performed.

External validation compare's a model results with actual event data. There is limited data on the natural history of RES-RRMS and SOT-RRMS; this limits the opportunity for testing the external validity of the model. As noted previously (Figure 15), the model for RES-RRMS predicts an average yearly increase in EDSS of +0.086, which is consistent with the results of a post-hoc analysis of the AFFIRM study which predicted that people with RES-RRMS would progress on average by additional 0.06-0.08 EDSS points per year versus those with less active disease (Polman 2006; Gani 2007).

No comparable data are available for SOT-RRMS. A UK clinical expert consulted during development of the model stated that the rate of progression in SOT-RRMS was likely to be similar but slightly less than in RES-RRMS, given that RES-RRMS patients tend to have greater relapse frequency at baseline indicating more active disease than in people with SOT-RRMS. This is reflected in the adjustments made to the model for SOT-RRMS, as documented in Table 67.

To further validate the model, the predicted change in mean EDSS shown in appendix J, was visually compared to predictions from the British Columbia registry (Figure 14), to ensure the correct implementation of the natural history model. It can be seen by comparing these two sets of figures that the model correctly captures the trajectory of EDSS in patients with RRMS.

B.3.11 Interpretation and conclusions of economic evidence

A de novo economic analysis was performed to assess the incremental cost-effectiveness of Cladribine Tablets versus alternative treatments within its expected marketing authorisation for highly active RRMS. In line with the final scope for this appraisal, the economic analysis focused on the use of Cladribine Tablets in people with RES-RRMS and SOT-RRMS, which included those who are able to

receive alemtuzumab and those who are unable to receive alemtuzumab, in line with the daclizumab FAD. Closely following precedent set in previous NICE appraisals, a comprehensive set of economic analyses were performed using the best available evidence currently available on the costs, and clinical outcomes of treatment in RRMS.

The results of the base case analysis demonstrate that Cladribine Tablets is dominant (e.g. cost-saving and more effective) versus alemtuzumab, daclizumab and natalizumab in RES-RRMS, and dominant versus alemtuzumab, fingolimod and daclizumab in SOT-RRMS. Over a lifetime horizon, the model predicts discounted cost-savings with Cladribine Tablets that range from £130,676 versus natalizumab to £17,549 for alemtuzumab in SOT-RRMS. In most scenarios, the cost-savings result from a lower lifetime drug acquisition cost for Cladribine Tablets due to its unique fixed course posology (versus continuously administered treatments), plus cost-savings from delaying EDSS progression and the additional care required at more severe EDSS states. The associated QALY gains from Cladribine Tablets ranged from +0.153 (alemtuzumab in SOT-RRMS) to +0.944 (fingolimod in SOT-RRMS).

In the probabilistic analysis, the probability that Cladribine Tablets is cost-effective at a threshold of £20,000 was in excess of 60% across all populations rising to 96% in comparison to fingolimod and daclizumab (both at list price) in SOT-RRMSb. Overall, the probabilistic analysis is characterised by wide credible intervals surrounding the total costs and QALYs of each intervention. This uncertainty is borne out of the credible intervals surrounding the effect of DMT on 6 month confirmed progression where none of the available DMTs, including alemtuzumab, demonstrated statistical superiority over other DMTs. The influence of DMT efficacy on 6 month confirmed progression on the results of the analysis is further demonstrated in the deterministic sensitivity analysis.

In view of the various concerns raised over the assumptions and model inputs used in previous NICE appraisals (summarised in B.3), a comprehensive set of scenario analyses were performed to assess the robustness of the economic analysis. This included analyses that excluded direct non-medical costs, a conservative assumption that applied the same waning assumptions across all comparators following NICE precedent, and the consideration of alternative input parameters. In all but one scenario analysis, Cladribine Tablets remained dominant (less costly and more effective) versus its comparators in RES-RRMS and SOT-RRMS. This demonstrates the overall robustness of the economic analysis.

The only scenario where Cladribine Tablets were not the dominant strategy was in comparison to alemtuzumab in RES-RRMSa in the scenario that used a conventional network meta-analysis for 6 month confirmed disability progression. In this scenario, Cladribine Tablets was more costly (+£36,519) but less effective (-1.071) than alemtuzumab as a result of the alemtuzumab effect size (hazard ratio of [redacted] versus placebo) being numerically superior to the effect size for Cladribine Tablets (hazard ratio of [redacted] versus placebo). As with the meta-regression, there was significant overlap in the 95% credible intervals of DMT effect in the conventional meta-analysis, and hence no single strategy was statistically superior to its comparators in terms of 6 month confirmed disability progression.

In summary, Cladribine Tablets offer a unique posology of two fixed oral courses of treatment given over 2-years leading to sustained benefits over at least a four year period. The total cost of Cladribine Tablets over a 4 year period is approximately £52,000, which is equivalent to an annualised cost of £13,000. These costs compare favourably to the annualised costs of daclizumab (£19,160 – list price), fingolimod (£19,176 – list price), natalizumab (£14,690 for acquisition plus £7,159 for administration), and alemtuzumab (£14,090 based on £56,360 for 2 courses), and hence support the prediction of cost-savings in the model. In terms of efficacy, Cladribine Tablets has demonstrated comparable efficacy on 6 month confirmed progression to comparators in RES-RRMS and SOT-RRMS, and has potential for health gains when allowing for a sustained effect over the first four years. The results of the economic analysis support the case that Cladribine Tablets are a cost-effective treatment in the RES-RRMS and SOT-RRMS population.

Consistency with published economic literature

None of the studies identified in the systematic literature review of economic evaluations in RRMS included Cladribine Tablets as a comparator. The results of this analysis cannot be directly compared with other studies.

As outlined in B.3.10, differences in the cost and clinical inputs, and the natural history model used to model EDSS progression in RRMS (e.g. with versus without backward transitions) precludes any attempt to reliably compare the results of the present analysis to results from the literature.

Relevance to all groups of patients who could potentially use the technology

In line with the expected marketing authorisation for Cladribine Tablets and the final scope for this appraisal, the economic analysis focused on the use of Cladribine Tablets in people with RES-RRMS and SOT-RRMS.

Relevance of the analysis to clinical practice in England

Where possible, the analyses have used input values from literature sources and/or previous NICE appraisals that have been considered generalizable to clinical practice in England. This includes the selection of cost inputs corresponding to the NHS and PSS perspective from patients with RRMS in England, where available, and the inclusion of HSU values derived from UK social preferences. In addition, the natural history model used to generate EDSS progression was based on the model used in the UK risk sharing scheme, which was developed with the intention of modelling the EDSS of the UK RRMS population.

Strengths and weaknesses

The key strengths of the analysis are shown below:

- Includes the long-term waning in drug efficacy for all therapies including Cladribine Tablets
- Allows for mprovements and progression in EDSS as modelled using the preferred BC natural history data set
- A faster rate of progression in those with highly active disease or rapidly evolving MS when compared to less active disease
- Use of the European Medicines Agency preferred endpoint of 6 month confirmed disability progression
- Use of health state utility values from the CLARITY clinical study
- Considers the re-initiation of alemtuzumab and Cladribine Tablets
- The use of a meta-regression approach to predict the efficacy of DMT in people with RES-RRMS and SOT-RRMS given the lack of data reported for comparator DMTs (e.g. daclizumab)
- The use of novel treatment switching techniques to estimate the durability of the effect of Cladribine Tablets over a four year period using data collected in the CLARITY and CLARITY EXT studies

The key weaknesses of the analysis are:

- The lack of published data for in scope DMT in the RES-RRMS and SOT-RRMS group has resulted in the need to predict their efficacy using a meta-regression approach.
- The analysis does not consider the cost-effectiveness of Cladribine Tablets when given in a sequence of therapies. This is in line with NICE precedent.
- DMT are assumed to only impact on EDSS progression and relapse rate. There is no effect of DMT on mortality.
- The health benefits of an oral drug are not fully captured in the QALY estimates given the need to assume the same utilities across different formulations. Similarly, in TA303 and TA320 it was recognized that oral drugs provide quality of life benefits other than those captured in the QALY calculations

Further analyses

The discounts agreed in the patient access schemes for fingolimod and daclizumab are commercial in confidence and are hence unknown to the company. All base case analyses presented here are based

on the list price for these therapies. Sensitivity analyses were performed assuming discounting rates of 20 and 40%. Further analyses should be performed using the actual discounts agreed with these therapies, as available to the evidence review group and NICE Committee.

B.4. References

Acaster S, Perard R, Chauhan D, Lloyd AJ. (2013) A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. BMC Health Serv Res. 13, 346.

Ahlgren C, Oden A, Lycke J. (2012) A nationwide survey of the prevalence of multiple sclerosis in immigrant populations of Sweden. Mult Scler. 18(8): 1099-1107.

Berg J, Lindgren P, Fredrikson S, Kobelt G. (2006) Costs and quality of life of multiple sclerosis in Sweden. Eur J Health Econ. 7 Suppl 2, S75-S85.

Boye KS, Matza LS, Walter KN, Van BK, Palsgrove AC, et al. (2011) Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 12(3): 219-230.

Briggs A, Claxton K, Sculpher M. (2006) Decision modelling for health economic evaluation.

Chilcott J, McCabe C, Tappenden P, O'Hagan A, Cooper NJ, 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. 326(7388): 522.

Compston A, Coles A. (2002) Multiple sclerosis. Lancet. 359(9313): 1221-1231.

Cook S, Comi G, Rieckmann P, Rammohan K, Soelberg-Sorensen P, et al. (2016) Safety and Tolerability of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS): Final Results from the 120-Week Phase IIIb Extension Trial to the CLARITY Study. Presented at the AAN, 15-21 April. Abstract No. 3326

CRD and CHE Technology Assessment Group. (2013) Dimethyl fumarate for treating relapsing-remitting multiple sclerosis [Evidence Review Group's report].

Curtis, Burns. Unit Costs of Health and Social Care 2016. <http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php>

Curtis L,Burns A. (2015) Unit costs of health and social care 2015, Personal Social Services Research Unit, University of Kent, Canterbury. http://www.pssru.ac.uk/project-pages/unit-costs/2015/index.php,

Department of Health. (2017) Price application for MAVENCLAD.

Department of Health. (2002) Cost effective provision of disease modifying therapies for people with multiple sclerosis. Health Service Circular 2002/004 London. Stationery Office,

Devonshire V, Havrdova E, Radue EW, O'Connor P, Zhang-Auberson L, 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.

Dong-Si T, Richman S, Wattjes MP, Wenten M, Gheuens S, et al. (2014) Outcome and survival of asymptomatic PML in natalizumab-treated MS patients. Ann Clin Transl Neurol. 1(10): 755-764.

Duddy M, Lee M, Pearson O, Nikfekr E, Chaudhuri A, et al. (2014) The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies. Mult Scler Relat Disord. 3(4): 450-456.

Ebers GC. (2001) Natural history of multiple sclerosis. J Neurol Neurosurg Psychiatry. 71 Suppl 2, ii16-ii19.

European Medicines Agency. (2017a) Data on file: Marketing authorisation.

European Medicines Agency. (2017b) Data on file: Scientific Advice from the CHMP.

European Medicines Agency. Gilenya Summary of Product Characteristics. <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002202/human_med_001433.jsp&mid=WC0b01ac058001d124> Accessed June 2017c.

Fazekas F, Bajenaru O, Berger T, Fabjan TH, Ledinek AH, et al. (2013) How does fingolimod (gilenya((R))) fit in the treatment algorithm for highly active relapsing-remitting multiple sclerosis? Front Neurol. 4, 10.

Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, et al. (2008) Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain. 131(Pt 3): 808-817.

Fogarty E, Walsh C, Adams R, McGuigan C, Barry M, et al. (2013) Relating health-related Quality of Life to disability progression in multiple sclerosis, using the 5-level EQ-5D. Mult Scler. 19(9): 1190-1196.

Forbes RB, Lees A, Waugh N, Swingler RJ. (1999) Population based cost utility study of interferon beta-1b in secondary progressive multiple sclerosis. BMJ. 319(7224): 1529-1533.

Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, 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. 26(7): 617-627.

Gani R, Nixon R, Hughes S, Jackson C. (2007) Estimating the rates of disability progression in people with active relapsing-remitting multiple sclerosis. J Med Econ. 10(2): 79-89.

Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, et al. (2010) A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 362(5): 416-426.

Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sorensen PS, et al. (2011) Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol. 10(4): 329-337.

Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, et al. (2013) Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. Lancet. 381(9884): 2167-2175.

Gold R, Wolinsky JS, Amato MP, Comi G. (2010) Evolving expectations around early management of multiple sclerosis. Ther Adv Neurol Disord. 3(6): 351-367.

Hauser SL, Oksenberg JR. (2006) The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron. 52(1): 61-76.

Hawton A, Green C. (2016a) Health Utilities for Multiple Sclerosis. Value Health. 19(4): 460-468.

Hawton AJ, Green C. (2016b) Multiple sclerosis: relapses, resource use, and costs. Eur J Health Econ. 17(7): 875-884.

Henriksson F, Fredrikson S, Masterman T, Jonsson B. (2001) Costs, quality of life and disease severity in multiple sclerosis: a cross-sectional study in Sweden. Eur J Neurol. 8(1): 27-35.

Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. (2014) Mortality of patients with multiple sclerosis: a cohort study in UK primary care. J Neurol. 261(8): 1508-1517.

Joint Formulary Committee. British National Formulary (online). <https://www.evidence.nhs.uk/formulary/bnf/current/> Accessed Mar. 2017.

Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, et al. (2010) A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 362(5): 387-401.

Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, et al. (2015) Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 373(15): 1418-1428.

Karampampa K, Gustavsson A, Miltenburger C, Eckert B. (2012a) Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Mult Scler. 18(2 Suppl): 7-15.

Karampampa K, Gustavsson A, Miltenburger C, Kindundu CM, Selchen DH. (2012b) Treatment experience, burden, and unmet needs (TRIBUNE) in multiple sclerosis: the costs and utilities of MS patients in Canada. J Popul Ther Clin Pharmacol. 19(1): e11-e25.

Karampampa K, Gustavsson A, Miltenburger C, Tyas D. (2012c) Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. Mult Scler. 18(2 Suppl): 41-45.

Karampampa K, Gustavsson A, van Munster ET, Hupperts RM, Sanders EA, et al. (2013) Treatment experience, burden, and unmet needs (TRIBUNE) in Multiple Sclerosis study: the costs and utilities of MS patients in The Netherlands. J Med Econ. 16(7): 939-950.

Khatri BO, Man S, Giovannoni G, Koo AP, Lee JC, et al. (2009) Effect of plasma exchange in accelerating natalizumab clearance and restoring leukocyte function. Neurology. 72(5): 402-409.

Kobelt G. (2006a) Costs and quality of life for patients with multiple sclerosis in Belgium. Eur J Health Econ. 7 Suppl 2, S24-S33.

Kobelt G, Berg J, Atherly D, Hadjimichael O. (2006b) Costs and quality of life in multiple sclerosis: a cross-sectional study in the United States. Neurology. 66(11): 1696-1702.

Kobelt G, Berg J, Lindgren P, Anten B, Ekman M, et al. (2006c) Costs and quality of life in multiple sclerosis in The Netherlands. Eur J Health Econ. 7 Suppl 2, S55-S64.

Kobelt G, Berg J, Lindgren P, Battaglia M, Lucioni C, et al. (2006d) Costs and quality of life of multiple sclerosis in Italy. Eur J Health Econ. 7 Suppl 2, S45-S54.

Kobelt G, Berg J, Lindgren P, Elias WG, Flachenecker P, et al. (2006e) Costs and quality of life of multiple sclerosis in Germany. Eur J Health Econ. 7 Suppl 2, S34-S44.

Kobelt G, Berg J, Lindgren P, Gerfin A, Lutz J. (2006f) Costs and quality of life of multiple sclerosis in Switzerland. Eur J Health Econ. 7 Suppl 2, S86-S95.

Kobelt G, Berg J, Lindgren P, Izquierdo G, Sanchez-Solino O, et al. (2006g) Costs and quality of life of multiple sclerosis in Spain. Eur J Health Econ. 7 Suppl 2, S65-S74.

Kobelt G, Berg J, Lindgren P, Kerrigan J, Russell N, et al. (2006h) Costs and quality of life of multiple sclerosis in the United Kingdom. Eur J Health Econ. 7 Suppl 2, S96-104.

Kobelt G, Berg J, Lindgren P, Plesnilla C, Baumhackl U, et al. (2006i) Costs and quality of life of multiple sclerosis in Austria. Eur J Health Econ. 7 Suppl 2, S14-S23.

Kobelt G, Jonsson L, Henriksson F, Fredrikson S, Jonsson B. (2000) Cost-utility analysis of interferon beta-1b in secondary progressive multiple sclerosis. Int J Technol Assess Health Care. 16(3): 768-780.

Kobelt G, Texier-Richard B, Lindgren P. (2009) The long-term cost of multiple sclerosis in France and potential changes with disease-modifying interventions. Mult Scler. 15(6): 741-751.

Kurtzke JF. (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 33(11): 1444-1452.

Larochelle C, Metz I, Lecuyer MA, Terouz S, Roger M, et al. (2017) Immunological and pathological characterization of fatal rebound MS activity following natalizumab withdrawal. Mult Scler. 23(1): 72-81.

Leist TP, Comi G, Cree BA, Coyle PK, Freedman MS, et al. (2014) Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol. 13(3): 257-267.

Leist TP, Weissert R. (2011) Cladribine: mode of action and implications for treatment of multiple sclerosis. Clin Neuropharmacol. 34(1): 28-35.

Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. (2016) Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. J Neurol Neurosurg Psychiatry. 87(3): 324-331.

Martinelli V, Colombo B, Dalla CG, Dalla LD, Moiola L, et al. (2016) Recurrent disease-activity rebound in a patient with multiple sclerosis after natalizumab discontinuations for pregnancy planning. Mult Scler. 22(11): 1506-1508.

McCrone P, Heslin M, Knapp M, Bull P, Thompson A. (2008) Multiple sclerosis in the UK: service use, costs, quality of life and disability. Pharmacoeconomics. 26(10): 847-860.

McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, et al. (2016) Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. 87(2): 117-125.

Merck. (2017a) Data on file: Baseline characteristics of patients who did and did not enter CLARITY-EXT.

Merck. (2017b) Data on file: CLARITY clinical trial report.

Merck. (2017c) Data on file: CLARITY GEVD subgroup analyses.

Merck. (2017d) Data on file: CLARITY-EXT clinical trial report.

Merck. (2017e) Data on file: CLARITY-EXT GEVD subgroup analyses.

Merck. (2017f) Data on file: Clinical overview.

Merck. (2017g) Data on file: DCE results.

Merck. (2017h) Data on file: ONWARD clinical trial report.

Merck. (2017i) Data on file: PREMIERE protocol.

Merck. (2017j) Summary of Product Characteristics for Cladribine tablets [DRAFT].

National Institute for Health and Care Excellence. (2014) CG186 - Multiple sclerosis in adults: management. Available at: https://www nice org uk/guidance/cg186. [Accessed March 2017]

NICE. NICE - Guide to the methods of technology appraisal 2013. <https://www.nice.org.uk/article/pmg9/chapter/Foreword> Accessed July 2015.

NICE. (2014) Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS) Reference: NHS ENGLAND/ D04/P/b.

NICE. (2017a) Cladribine for treating relapsing-remitting multiple sclerosis [FINAL scope].

NICE. NICE TA 441: Daclizumab for treating relapsing–remitting multiple sclerosis. <https://www.nice.org.uk/guidance/ta441>

NICE Technology appraisal guidance. (2012) Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis.

NICE Technology appraisal guidance. (2014a) Alemtuzumab for treating relapsing-remitting multiple sclerosis.

NICE Technology appraisal guidance. (2014b) Dimethyl fumarate for treating relapsing-remitting multiple sclerosis.

NICE Technology appraisal guidance. (2014c) Teriflunomide for treating relapsing-remitting multiple sclerosis [TA303].

Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. (2007) The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 10(1): 54-60.

Pakpoor J, Disanto G, Altmann DR, Pavitt S, Turner BP, et al. (2015) No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine. Neurol Neuroimmunol Neuroinflamm. 2(6): e158.

Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, et al. (2014) UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open. 4(1): e004073.

Palace J, Duddy M, Bregenzer T, Lawton M, Zhu F, et al. (2015) Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol. 14(5): 497-505.

Parkin D, Jacoby A, McNamee P, Miller P, Thomas S, et al. (2000) Treatment of multiple sclerosis with interferon beta: an appraisal of cost-effectiveness and quality of life. J Neurol Neurosurg Psychiatry. 68(2): 144-149.

Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, et al. (1998) A cost-utility analysis of interferon beta for multiple sclerosis. Health Technol Assess. 2(4): iii-54.

Peninsula Technology Assessment Group (PenTAG). (2007) The effectiveness and cost-effectiveness of natalizumab for multiple sclerosis: An evidence review of the submission from Biogen.

Pentek M, Gulacsi L, Rozsa C, Simo M, Iljicsov A, et al. (2012) Health status and costs of ambulatory patients with multiple sclerosis in Hungary. Ideggyogy Sz. 65(9-10): 316-324.

Phillips JT, Selmaj K, Gold R, Fox RJ, Havrdova E, et al. (2015) Clinical Significance of Gastrointestinal and Flushing Events in Patients with Multiple Sclerosis Treated with Delayed-Release Dimethyl Fumarate. Int J MS Care. 17(5): 236-243.

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, et al. (2006) A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 354(9): 899-910.

Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, et al. (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 69(2): 292-302.

Ponzio M, Gerzeli S, Brichetto G, Bezzini D, Mancardi GL, et al. (2015) Economic impact of multiple sclerosis in Italy: focus on rehabilitation costs. Neurol Sci. 36(2): 227-234.

Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. (2016) Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. J Med Econ. 19(1): 21-33.

Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, et al. (2015) Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol. 15(4): 273-279.

Shingler S, Fordham B, Evans M, Schroeder M, Thompson G, et al. (2015) Utilities for treatment-related adverse events in type 2 diabetes. J Med Econ. 18(1): 45-55.

Steinvorth SM, Rover C, Schneider S, Nicholas R, Straube S, et al. (2013) Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression. Mult Scler. 19(12): 1580-1586.

Svendsen B, Myhr KM, Nyland H, Aarseth JH. (2012) The cost of multiple sclerosis in Norway. Eur J Health Econ. 13(1): 81-91.

Svensson J, Borg S, Nilsson P. (2014a) Costs and quality of life in multiple sclerosis patients with spasticity. Acta Neurol Scand. 129(1): 13-20.

Svensson M, Fajutrao L. (2014b) Costs of formal and informal home care and quality of life for patients with multiple sclerosis in sweden. Mult Scler Int. 2014, 529878.

Takemoto ML, Lopes da SN, Ribeiro-Pereira AC, Schilithz AO, Suzuki C. (2015) Differences in utility scores obtained through Brazilian and UK value sets: a cross-sectional study. Health Qual Life Outcomes. 13, 119.

Tan K, Roda R, Ostrow L, McArthur J, Nath A. (2009) PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. Neurology. 72(17): 1458-1464.

Tappenden P, Chilcott J, O'Hagan T, McCabe C, Cooper N, et al. (2001) Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis: Final report to the National Institute for Clinical Excellence.

Tappenden P, McCabe C, Chilcott J, Simpson E, Nixon R, et al. (2009) Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population. Value Health. 12(5): 657-665.

Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. (2010) New perspectives in the natural history of multiple sclerosis. Neurology. 74(24): 2004-2015.

Trogdon JG, Ekwueme DU, Chamiec-Case L, Guy GP, Jr. (2016) Breast Cancer in Young Women: Health State Utility Impacts by Race/Ethnicity. Am J Prev Med. 50(2): 262-269.

Tyas D, Kerrigan J, Russell N, Nixon R. (2007) The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? Value Health. 10(5): 386-389.

Warwick Evidence. (2016) Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809]. https://www.nice.org.uk/guidance/GID-TAG529/documents/assessment-report,

Company evidence submission template for Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Willis MD, Harding KE, Pickersgill TP, Wardle M, Pearson OR, et al. (2016) Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. Mult Scler. 22(9): 1215-1223.

Zuvich RL, McCauley JL, Pericak-Vance MA, Haines JL. (2009) Genetics and pathogenesis of multiple sclerosis. Semin Immunol. 21(6): 328-333.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Dear [redacted]

The Evidence Review Group, LR/G, and the technical team at NICE have looked at the submission received on 26 June 2017 from Merck. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm on Monday 26 July 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Palmer, Technical Lead (thomas.palmer@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on decision problem and effectiveness data

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A1. **Priority question:** Please provide the Clinical Study Report (CSR) for the CLARITY trial referenced in the CS as Merck (2017b).

A2. **Priority question**: The company presented characteristics and results for 3 patient subgroups from the CLARITY trial: highly active relapsing-remitting multiple sclerosis (HDA-RRMS), rapidly-evolving severe relapsing-remitting multiple sclerosis (RES-RRMS) and sub-optimally treated relapsing-remitting multiple sclerosis (SOT-RRMS). The ERG noted that there is some overlap in the definitions of the RES-RRMS and SOT-RRMS subgroup populations presented in the company submission (CS). For example, a patient who has experienced two relapses in the past year whilst on DMT and has a T1 Gd+ lesion could be included in either group. Are there additional criteria that clinicians can use to assign patients to either the RES-RRMS or the SOT-RRMS subgroup?

A3. The RES-RRMS and SOT-RRMS subgroup definitions include mention of 'T1 Gd+ lesion' and 'nine T2 lesions'. Are these qualifying lesions existing lesions, new lesions or a combination of both?

A4. Please provide the mean number of relapses in the previous year experienced by patients in the RES-RRMS and SOT-RRMS subgroups (Table 14, Page 38 of CS).

A5. Please provide a breakdown of the HDA-RRMS patients by independent subgroups so that all of the numbers in the subgroups add up to the total of 180. Please present the same set of patient characteristics as shown in Table 14 and Table 15 of the CS for any currently missing subgroups.

A6. **Outcome definitions**

a. Table 11, page 36 of the CS lists the outcomes for the CLARITY trial. 'Time to use of rescue therapy' is mentioned twice in this table. The ERG noted that the 'Time to first qualifying relapse' (Section B 2.6.1.1, page 161 of the CS) is not list. Please clarify if the first entry of 'Time to use of rescue therapy' in Table 11 should read 'Time to first qualifying relapse.'

b. Please provide justification for including the following outcomes defined post-hoc:

- NEDA-3

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

- 6-month CDP

c. Please clarify the exact definition of the NEDA-3 outcome which appears to have been analysed as a time-to-event outcome within the CS (i.e. time to three months of no evidence of disease activity).

A7. **Statistical approach**

The sample size calculation (outlined in Table 16, page 39 of the CS) assumes a relative reduction of 25% in the cladribine groups compared with the placebo group; i.e. 'a mean number of 2.1 relapses would occur in the placebo group, that the standard deviation for the number of relapses in each group would be 2.02, that the proportion of patients who could not be evaluated would be 10%, and that the two-sided type I error rate for the comparison between each cladribine group and the placebo group would be 2.5%.'

a. Please justify why the assumptions used for the sample size calculate, such as the mean number of relapses. Please state whether these assumptions were based on those used in earlier trials?

b. Please clarify whether the proportional hazards assumption of the Cox proportional hazards model was checked for the secondary outcomes 'time to first qualifying relapse' and 'time to 3 month CDP.' Please include graphical evidence (such as log cumulative hazard plots or similar) for visual inspection of the assumption.

c. Please provide details of the statistical analysis approach taken for the post-hoc analyses for following outcomes. Include checks of any assumptions where applicable; such as proportional hazards for time-to-event outcomes.

- NEDA-3
- Time to 6 month CDP
- proportion of patients with 6 month CDP

A8. **Consistency of reported results**

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

a. Table 13, page 17 of the CS has different numbers for previous DMT use and mean disease duration in both the placebo and cladribine groups compared with the Giovannoni 2010 NEJM paper. Please clarify which numbers are correct.

b. Section B.2.6 of the CS states that handling of missing data of post-hoc analyses was amended between the publication of the CLARITY trial clinical study report and submission to regulatory authorities. Please clarify exactly how the statistical approach taken to handle missing data for regulatory submissions was different to the approach specified in the original statistical analysis plan for CLARITY?

c. There are some slight differences in the results presented in tables 18 to 21 of the CS compared with the equivalent results presented in Table 2 of the Giovannoni 2010 NEJM paper. Does the different approach to handling missing data (outlined in question 4b above) explain the slight differences in results between the Giovannoni 2010 NEJM paper and the CS?

A9. **Additional results**

a. The proportion of relapse-free patients, with 3-month CDP and with 6-month CDP is presented for the ITT population at 48 weeks in Table 19, Table 21 and Table 22 of the CS. Please provide equivalent results for relapse-free patients, 3-month CDP and 6-month CDP at 48 weeks for the HDA-RRMS, RES-RRMS and the SOT-RRMS subgroups?

b. Table 37, page 37 of the CS presents results for NEDA-3 status in CLARITY post-hoc subgroup analysis. Please provide the confidence intervals for the Kaplan-Meier estimates be provided (as in Table 23)?

c. **Priority question**: Section 2.6.1.4 of the CS states that analyses of other endpoints that are not relevant for the NICE Decision problem are presented in Appendix E. Appendix E presents does not present results for ‘Severity of Relapses’ or ‘Confirmed Worsening’. For completeness, please provide results for these endpoints.

d. **Priority question:** Section B.2.7 of the CS: subgroup analysis – Please provide subgroups analysis for health related quality-of-life.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

e. **Priority question**: Section B.2.7 of the CS: subgroup Analysis states that 'the full dataset is summarised in Appendix E.' Appendix E only summarises the additional results of MRI lesions for CLARITY and CLARITY-EXT. Please provide any other information from Appendix E relating to subgroup analyses.

A10. **Network meta-analysis and meta-regression (Appendix D and Appendix K)**

a. **Priority question:** Please clarify which studies contributed data to the network meta-analysis and/or meta-regression for the outcomes below. Please provide the number of patients and information for the ITT, HDA, RES and SOT analyses as applicable, ideally presented in tables similar to Table 60, page 153 (presented in Appendix K for the meta-regression).
   i. ARR
   ii. ARR hospital treated
   iii. ARR requiring steroid treatment
   iv. CDP3M 24M
   v. CDP6M 24M (with INCOMIN study)
   vi. RF12M
   vii. RF24M
   viii. NEDA-3 24M
   ix. QoL results (EQ-5D 12M, EQ-5D 24M, EQ-5D VAS 12M, EQ-5D VAS 24M)
   x. Tolerability results (Study withdrawals, treatment withdrawals, any AE, any SAE, any TRAE, any grade 3/4 AE, any CVS, any infection, any serious infection, depression, ALT increased.

b. Please state the data sources used in the network meta-analysis and meta-regression (i.e. was individual participant data used for CLARITY and results extracted from the published literature for other trials? Or was individual participant data available for any other trials – such as unpublished data from PRISMS?).

c. Section B.2.9.2 of the CS states that 'attempts were made to improve these connections, e.g. through a series of post-hoc analysis that incorporated unpublished data from the phase III PRISMS trial (details available in Appendix D).' Please provide further details of these post-hoc analyses.

d. Related to point b, do the networks presented in Figure 6, Figure 7 and Figure 8 of the CS appendix correspond to the post-hoc analyses that include the PRISMS trial

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

to incorporate a link between alemtuzumab and cladribine using data for IFN beta-1a, 44 mg 3 times a week and placebo?

e. Please provide any information on the investigations carried out for inconsistency (for networks with closed loops) or heterogeneity for these network meta-analysis?

f. The legend of the NMA results tables (Table 11 onwards of the CS appendix) states that: "-" indicates that analyses were not feasible for these comparisons considering limited evidence.

   Please clarify whether this refers to the number of studies (that is, that no studies were available for the comparison for that outcome) or whether this refers to the feasibility of the statistical methods (such as models not converging).

g. Please clarify the labelling of Table 14 to 16 of the CS appendix:
   i. Table 14: does RR stand for rate ratio (this abbreviation is not provided as a footnote)?
   ii. Table 15 and 16: should RR presented in these tables be Hazard Ratio (HR)?

h. Section B.2.9.1, page 61 of the CS states that 'results of sensitivity analyses generally found that the findings for ARR CDP3M and CDP6M at 24 months were robust'. Appendix D refers only to sensitivity analysis excluding open label studies or studies with unclear blinding. Please provide details of any other sensitivity analyses conducted.

i. Appendix K presents a meta-regression which is also referred to in this section as a 'network meta-analysis.' Usually, network meta-analysis conducted within a meta-regression framework of dummy variables do not allow for adjustments of correlation between treatment arms in multi-arm trials. Table 60, of the CS Appendix indicates that three 3-arm trials have been incorporated.

   Please clarify whether the analysis described in Appendix K is conducted using a similar hierarchical approach to the time-to-event outcome analysis described in Appendix D.1.1.4.5 using the model:

$$cloglog(p_{i,k}) = \log(T_i) + \mu_i + \delta_{i,k} + \beta * (\mu_i - \bar{x})$$

   To incorporate baseline risk rather than:

```
# model for linear predictor

      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
```

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

As specified in the WinBugs code for the time-to-event outcome?

j. Table 69 of the CS presents median ratio of annualised release rates (ARR) used within the cost-effectiveness analysis which the ERG believes to be based on the resulted presented in Table 14 of the CS Appendix D.
   i. The results presented in Table 14 of the CS appendix are produced with random effects yet the preferred model type in Table 69 in the CS is fixed effects. Please clarify or justify the difference.
   ii. Please clarify how the results within Table 14 of the CS appendix have been transformed to the results in Table 69 in the CS for the other disease modifying therapies.

k. Please provide the confidence intervals for the normalised hazard ratios centred on RES-RRMS and SOT-RRMS in Table 70.

A11. Appendix D of the CS (in the paragraph underneath Table 10) states that: "As per the review inclusion criteria, the selected trials were composed of adults patients (≥18 years) with a confirmed diagnosis of RRMS. Nonetheless, although some studies specified RRMS as an inclusion criterion, they also included a small number of patients with progressive disease. If that was the case, trials with more than 20% of progressive patients were excluded, consequently stipulating a minimum of 80% of patients with RRMS for studies subgroups that were included." Please state how many trials also included progressive patients. Please clarify if these progressive patients were included or excluded within data which contributed to NMAs.

A12. Appendix D of the CS (in the third paragraph below Table 10) states that: "apparent variations in the mean number of relapses in the previous one and two years and mean EDSS score could not be observed across studies, nevertheless, these parameters were included in covariate analysis." Please clarify whether this statement refers to a sensitivity analysis? If so, provide any relevant results to support this statement.

A13. Appendix D.1.1.4.4 of the CS suggests that a frequentist approach was also performed for network meta-analysis using generalised linear models. However, Bayesian analysis are presented within the results due to credible intervals in the results tables. Please provide the rationale for also performing a frequentist analysis

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

and if these additional analyses showed any difference in results to the Bayesian network meta-analysis.

A14. Please clarify how quality of life outcomes (change from baseline in EQ-5D) were analysed in the network-meta analysis. Please state if the outcomes were analysed as continuous outcomes rather than as poisson, time to event or binomial outcomes as specified in the WinBUGS code presented in the CS Appendix D.1.1.4.5.

A15. Appendix D1.1.4.5 of the CS states that: "In order to further validate the output of the NMA, anchor based indirect treatment comparisons were also conducted." Please provide details of this alternative approach to network meta-analysis and whether this alternative analysis showed any difference to the arm based approach.

A16. Please clarify whether the summary results (that is, the directions of effect) presented in Tables 11 to 13 and Tables 17 to 20 of the CS Appendix are from a random-effects network meta-analysis model (as specified for Tables 14 to 16).

Section B: Clarification on cost effectiveness data

B1. **Priority request:** Please repeat the analyses using CLARITY-EXT annualised relapse rate (6-month disability progression) data presented in Table 72, page 112 of the CS for the following 2 populations (2 analyses):

- RES-RRMS
- SOT-RRMS

B2. **Priority request:** Please undertake the analyses necessary to populate Table 72, page 112 of the CS using ARR data from the CLARITY-EXT trial, for the following populations (3 analyses):

- Intention to treat (ITT)
- RES-RRMS
- SOT-RRMS.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Dear [redacted]

The Evidence Review Group, LR/G, and the technical team at NICE have looked at the submission received on 26 June 2017 from Merck. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm on Monday 26 July 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Thomas Palmer, Technical Lead (thomas.palmer@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk).

Yours sincerely

Jasdeep Hayre
Technical Adviser
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on decision problem and effectiveness data

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A1. **Priority question:** Please provide the Clinical Study Report (CSR) for the CLARITY trial referenced in the CS as Merck (2017b).

This has now been provided and uploaded to NICE Docs/Appraisals.

A2. **Priority question**: The company presented characteristics and results for 3 patient subgroups from the CLARITY trial: highly active relapsing-remitting multiple sclerosis (HDA-RRMS), rapidly-evolving severe relapsing-remitting multiple sclerosis (RES-RRMS) and sub-optimally treated relapsing-remitting multiple sclerosis (SOT-RRMS). The ERG noted that there is some overlap in the definitions of the RES-RRMS and SOT-RRMS subgroup populations presented in the company submission (CS). For example, a patient who has experienced two relapses in the past year whilst on DMT and has a T1 Gd+ lesion could be included in either group. Are there additional criteria that clinicians can use to assign patients to either the RES-RRMS or the SOT-RRMS subgroup?

While definitions for RRMS patients with high disease activity (HDA) vary between different HTA bodies, regulatory agencies, and clinical practice, definitions for RES-RRMS and SOT-RRMS are standardised. NICE define RES-RRMS and SOT-RRMS as follows:

- RES-RRMS: Patients with two or more relapses in the prior year whether on treatment or not, and at least one T1 Gd+ lesion or a significant increase in T2 lesion load compared with a previous MRI.
- SOT-RRMS: Patients with at least one relapse in the previous year while on DMT therapy, and at least one T1 Gd+ lesion or nine T2 lesions

To the best of our knowledge, there are no additional criteria used in clinical practice to further segment patients into either subgroup.

A3. The RES-RRMS and SOT-RRMS subgroup definitions include mention of ‘T1 Gd+ lesion’ and ‘nine T2 lesions’. Are these qualifying lesions existing lesions, new lesions or a combination of both?

The number of lesions are established at baseline to inform diagnosis.

A4. Please provide the mean number of relapses in the previous year experienced by patients in the RES-RRMS and SOT-RRMS subgroups (Table 14, Page 38 of CS).

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Mean number of relapses in the previous year is unavailable. However, number of patients experiencing 0, 1, 2, or greater than 3 relapses in the prior 12 months is available and presented in Table 1:

Table 1: Comparative characteristics of patient subgroups in CLARITY

CLARITY	Placebo subgroups			Cladribine Tablets 3.5 mg/kg subgroups		
	HDA-RRMS (n=149)	RES-RRMS ([redacted])	SOT-RRMS [redacted])	HDA-RRMS (n=140)	RES-RRMS ([redacted])	SOT-RRMS ([redacted])
Relapses in prior 12 months ; n (%)						
0	0	[redacted]	[redacted]	0	[redacted]	[redacted]
1	18 (12.1)	[redacted]	[redacted]	10 (7.1)	[redacted]	[redacted]
2	110 (73.8)	[redacted]	[redacted]	105 (75.0)	[redacted]	[redacted]
≥3	21 (14.1)	[redacted]	[redacted]	25 (17.9)	[redacted]	[redacted]

HDA-RRMS: High disease activity; RES-RRMS: Rapidly evolving severe; SD: Standard deviation; SOT-RRMS: Sub-optimal therapy

A5. Please provide a breakdown of the HDA-RRMS patients by independent subgroups so that all of the numbers in the subgroups add up to the total of 180. Please present the same set of patient characteristics as shown in Table 14 and Table 15 of the CS for any currently missing subgroups.

HDA-RRMS is defined as:

- Patients with ≥1 relapse while on DMT therapy and who have at least 1 T1 Gd+ lesion or at least 9 T2 lesions OR
- Patients with at least 2 relapses in the previous year

While the definition of HDA-RRMS comprises RES-RRMS and SOT-RRMS, it is not solely comprised of these two subgroups (Table 2). Therefore, the patient numbers for RES-RRMS and SOT-RRMS do not add up to the total number of HDA-RRMS patients. Merck has not conducted analyses on the additional subgroups of HDA-RRMS outside of RES-RRMS and SOT-RRMS.

Table 2: Criteria for HDA-RRMS, RES-RRMS, and SOT-RRMS

Criteria	HDA-RRMS		RES-RRMS	SOT-RRMS
≥1 T1 Gd+ or ≥ 9 T2 lesions	✓			✓
≥1 T1 Gd+			✓	
Patients with ≥1 relapse while on DMD therapy	✓			✓
Patients with ≥2 relapses regardless of treatment		✓	✓	

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A6. **Outcome definitions**

a. Table 11, page 36 of the CS lists the outcomes for the CLARITY trial. 'Time to use of rescue therapy' is mentioned twice in this table. The ERG noted that the 'Time to first qualifying relapse' (Section B 2.6.1.1, page 161 of the CS) is not list. Please clarify if the first entry of 'Time to use of rescue therapy' in Table 11 should read 'Time to first qualifying relapse.'

Yes, Merck apologises for this typo. The first entry of 'Time to use of rescue therapy' should read 'Time to first qualifying relapse'.

b. Please provide justification for including the following outcomes defined post-hoc:

- NEDA-3
- 6-month CDP

While NEDA-3 had received little attention from the neurology community at the time the CLARITY trial was planned and conducted (2005-2007), literature published after the completion of CLARITY suggested that freedom from disease activity was becoming an increasingly important endpoint in MS to measure treatment effect beyond the duration of a trial (Bevan 2014; Lublin 2012; Havrdova 2010). Therefore, to ensure that the NEDA-3 outcome was captured for Cladribine Tablets, analyses were conducted post-hoc.

Similarly, at the time of the CLARITY trial, 3-month CDP was the recommended endpoint to measure disease progression, and hence the older studies of DMDs report 3-month progression data only. Since then, there have been developments in the definition of sustained accumulation of disability (3-month versus 6-month CDP) and assumptions on the durability and magnitude of treatment benefit beyond the duration of a clinical trial. This has led the European Medicines Agency (EMA) to release guidance recommending the use of the 6-month definition of CDP:

"An accurate and reliable definition of confirmed progression is important and should include two consecutive examinations carried out by the same physician at least 6 months apart."(European Medicines Agency 2015)

In line with this, Merck conducted analyses for 6-month CDP post-hoc.

c. Please clarify the exact definition of the NEDA-3 outcome which appears to have been analysed as a time-to-event outcome within the CS (i.e. time to three months of no evidence of disease activity).

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

NEDA-3 is defined as absence of magnetic resonance imaging (MRI) activity (T2 and/or gadolinium-enhanced T1 lesions), relapses and disability progression. The primary measurement for assessment of absence of disease activity (NEDA-3) was be the Kaplan Meier estimated cumulative probability of the disease-free state by 48 and 96 weeks for the CLARITY.

While the definition of NEDA is evolving, for NEDA to occur, three conditions need to be met, the combination of which is sometimes called NEDA3. We believe the ERG has incorrectly interpreted NEDA-3 as 'time to three months of no evidence of disease activity'.

Each component (MRI activity, relapses and disability progression) were defined as follows in order to be included in the NEDA-3 analysis:

- No T1 Gd+ lesion: Patients with no new or enhancing Gd+ T1 lesion over the full time period are viewed as free of disease-activity
- No active T2: Patients with no new or enlarging T2 lesion over the full time period are viewed as free of disease-activity
- No relapse: Patients with no relapse over the full time period are viewed as free of disease-activity
- No Progression: Patients with no progression over the full time period are viewed as free of disease-activity

Time to disease activity (days) was calculated as the (date of first occurrence of disease activity – randomization date) + 1[1]

A7. **Statistical approach**

The sample size calculation (outlined in Table 16, page 39 of the CS) assumes a relative reduction of 25% in the cladribine groups compared with the placebo group; i.e. 'a mean number of 2.1 relapses would occur in the placebo group, that the standard deviation for the number of relapses in each group would be 2.02, that the proportion of patients who could not be evaluated would be 10%, and that the two-sided type I error

[1] 48 weeks is defined by:
- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experienced the second year treatment: week 48 target day is considered (336 days)

A progression observed before week 48 but confirmed after week 48 is considered in the 48 weeks analysis.
Status at 96 weeks is the status at the end of the study with the following rule:
- Patients who withdrew early (less than 587 days (83 weeks)), with no progression are considered as unknown.

Patients who withdrew after 587 days with no progression are considered as No Progression

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

rate for the comparison between each cladribine group and the placebo group would be 2.5%.'

a. Please justify why the assumptions used for the sample size calculate, such as the mean number of relapses. Please state whether these assumptions were based on those used in earlier trials?

The Clinical Trial Protocol of the CLARITY study explains that the assumption of the common standard deviation of 2.02 was based on results from the PRISMS study of Interferon β-1a in RRMS. The observed average number of relapses in two years in the placebo arm of the PRISMS study was 2.56 (Lancet 1998; 352: 1498–504), comparable to the mean number of 2.1 relapses assumed for the placebo group of CLARITY.

The relative reduction of 25% for which the study was powered was based on the effect considered clinically relevant.

b. Please clarify whether the proportional hazards assumption of the Cox proportional hazards model was checked for the secondary outcomes 'time to first qualifying relapse' and 'time to 3 month CDP.' Please include graphical evidence (such as log cumulative hazard plots or similar) for visual inspection of the assumption.

The Cox regression models have been refitted for the following outcomes: time to 3-month confirmed EDSS progression, time to 6-month confirmed EDSS progression, time to first qualifying relapse and time to first disease activity, for the ITT population and its subgroups, HDA4, RES and SOT. Plots of log(-log(Estimated Survival Distribution Function) against log(Time since Study Entry) are presented in a separate document sent to NICE in conjunction with this response. In general, the graph for the Cladribine Tablets 3.5 mg/kg and the graph for the placebo arm, both in the entire ITT and in the subgroups, are close to parallel, as expected if the constant hazards ratio assumption holds.

In addition to the plots obtained from the initial Cox regression models, new Cox regression models were fitted to the same outcomes, for the ITT population and same subgroups, that had as fixed effect, besides the treatment group, the interaction between treatment group and log(time(in days)). Evidence that group*log(time) is not zero is evidence against proportional hazards. The p-values of the interaction term are presented alongside the log(-log(Estimated Survival Distribution Function) plots (and denoted as "p-value"). All the interaction p-values are well above 0.05, except for the ITT population: time to 3-month EDSS progression ($p = 0.05$) and time to 6-month EDSS progression ($p = 0.02$). In these two instances, the estimated hazard ratios can be interpreted as an average over the entire study period.

c. Please provide details of the statistical analysis approach taken for the post-hoc analyses for following outcomes. Include checks of any assumptions where applicable; such as proportional hazards for time-to-event outcomes.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

- NEDA-3

The primary measurement for assessment of absence of disease activity (NEDA-3) was the Kaplan Meier estimated cumulative probability of the disease-free state by 48 and 96 weeks for the CLARITY and CLARITY EXT studies. A 95% confidence interval on the estimated cumulative probability (CI) of the disease-free state was also be presented. A Cox proportional hazard model produced the hazard ratio and its 95% CI, with placebo (CLARITY) and LLPP (CLARITY EXT) as reference groups. All available data through the end of study was used in the time to event models (for both CLARITY and CLARITY EXT), using the period definitions as described in the original GEVD SAP, sections 12.1.3 and 13.1.3.

Time to disease activity (days) was calculated as the (date of first occurrence of disease activity – randomisation date) + 1[2].

The censor variable was set at 1 if there is no disease event and 0 if there is a disease event, defined as any of the following:

- Qualifying relapse
- 3 month confirmed EDSS Progression
- new or enhancing Gd+ T1 lesion
- new or enlarging T2 lesion

For counts and percentages of no evidence of disease activity (NEDA-3), which constitutes the secondary measure, the following provisions are noted:

NEDA-3 is defined as absence of magnetic resonance imaging (MRI) activity (T2 and/or gadolinium-enhanced T1 lesions), relapses and disability progression. Analysis of NEDA-3 was previously conducted for the Cladribine Tablets CSE. The analytic methods are provided below.

1. No relapse

Qualifying relapse was considered.

No relapse: Patients with no relapse over the full time period are viewed as free of disease-activity

[2] 48 weeks is defined by:
- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experienced the second year treatment: week 48 target day is considered (336 days)

A progression observed before week 48 but confirmed after week 48 is considered in the 48 weeks analysis.
Status at 96 weeks is the status at the end of the study with the following rule:
- Patients who withdrew early (less than 587 days (83 weeks)), with no progression are considered as unknown.
- Patients who withdrew after 587 days with no progression are considered as No Progression.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Relapse: Patients with at least 1 relapse are viewed as not free of disease-activity

Unknown: Patients with no relapse but who withdrew from the study early are considered as unknown. In time-to-event analyses, patients who have withdrawn from the study without reporting an event are censored at the date of their last reported MRI assessment. Patients who are determined to be of unknown status at their last reported MRI assessment had the censor variable set to 1, indicating no event, and have their time, in days, calculated as (last reported MRI date – randomization date) + 1. This rule applies to any of the 4 contributing disease activity parameters cited above, and further described below.

Relapse was derived separately through week 48 and also through week 96.

48 weeks is defined by:

- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experience the second year treatment: week 48 target day is considered (336 days)
- Patients who withdrew early (less than 336 days) with no relapse are considered unknown

Status at 96 weeks is the status at the end of the study with the following rule:

- Patients who withdrew early (less than 587 days (83 weeks)), with no relapse are considered as unknown. The cutoff time is defined by the upper limit of the time window for the MRI week 72 analysis visit (Section 15.13.1 CSE SAP).
- Patients who withdrew after 587 days with no relapse are considered as No Relapse.
- For CLARITY EXT, 96 weeks is defined as the day prior to supplemental follow-up (SFU) for those moving in to this period or the maximum Last Visit Date for subjects not entering the SFU. Only relapses occurring prior to this cutoff was included in the count and percentage analysis.

No relapse-activity was be presented descriptively with the 3 possible status values (disease-free, disease and unknown).

2. No progression

3-month confirmed EDSS progression was considered.

No Progression: Patients with no progression over the full time period are viewed as free of disease-activity

Progression: Patients with at least 1 progression are viewed as not free of disease-activity

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Unknown: Patients with no progression but who withdrew from the study early are considered as unknown.

3-month confirmed EDSS progression was derived separately through week 48 and also through week 96.

48 weeks is defined by:

- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experience the second year treatment: week 48 target day is considered (336 days)
- Patients who withdrew early (less than 336 days) with no progression are considered unknown

A progression observed before week 48 but confirmed after week 48 is considered in the 48 weeks analysis.

Status at 96 weeks is the status at the end of the study with the following rule:

- Patients who withdrew early (less than 587 days (83 weeks), with no progression are considered as unknown.
- Patients who withdrew after 587 days with no progression are considered as No Progression.

For CLARITY EXT, 96 weeks is defined as the day prior to supplemental follow-up (SFU) for those moving in to this period or the maximum Last Visit Date for subjects not entering the SFU. Only progression events occurring prior to this cutoff was included in the count and percentage analysis.

No progression -activity was presented descriptively with the 3 possible status values (disease-free, disease and unknown).

3. No T1 Gd+ lesion

No Gd+: Patients with no new or enhancing Gd+ T1 lesion over the full time period are viewed as free of disease-activity

Gd+: Patients with at least 1 new or enhancing Gd+ T1 are viewed as not free of disease-activity

Unknown: Patients with no new or enhancing Gd+ T1 lesion but who withdrew from the study early are considered as unknown.

Absence of Gd+ T1 lesion was derived separately through week 48 and also through week 96.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

48 weeks is defined by:

- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experience the second year treatment: week 48 target day is considered (336 days)
- Patients who withdrew early (less than 336 days) with no new or enhancing Gd+ T1 lesion are considered unknown

Status at 96 weeks is the status at the end of the study with the following rule:

- Patients who withdrew early (less than 587 days (83 weeks)), with no new or enhancing Gd+ T1 lesion are considered as unknown.
- Patients who withdrew after 587 days with no new or enhancing Gd+ T1 lesion are considered as Gd+ T1 lesion.

For CLARITY EXT, 96 weeks is defined as the day prior to supplemental follow-up (SFU) for those moving in to this period or the maximum Last Visit Date for subjects not entering the SFU. Only new T1 lesions occurring prior to this cut-off was included in the count and percentage analysis.

No Gd+ -activity was presented descriptively with the 3 possible status values (disease-free, disease and unknown).

4. No active T2 lesion

No active T2: Patients with no new or enlarging T2 lesion over the full time period are viewed as free of disease-activity

Active T2: Patients with at least 1 new or enlarging T2 are viewed as not free of disease-activity

Unknown: Patients with no new or enlarging T2 lesion but who withdrew from the study early are considered as unknown.

Absence of T2 lesions was derived separately through week 48 and also through week 96.

48 weeks is defined by:

- for subjects who experienced the second year treatment, day of the earliest exposure ≥ (year 1 start + 308 days).
- for subjects who did not experience the second year treatment: week 48 target day is considered (336 days)
- Patients who withdrew early (less than 336 days) with no new or enlarging T2 lesion are considered unknown

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Status at 96 weeks is the status at the end of the study with the following rule:

- Patients who withdrew early (less than 587 days (83 weeks)), with no new or enlarging T2 lesion are considered as unknown.
- Patients who withdrew after 587 days with no new or enlarging T2 lesion are considered as T2 lesion.
- For CLARITY EXT, 96 weeks is defined as the day prior to supplemental follow-up (SFU) for those moving in to this period or the maximum Last Visit Date for subjects not entering the SFU. Only new or enlarging T2 lesions occurring prior to this cutoff was included in the count and percentage analysis.

No active T2 -activity was presented descriptively with the 3 possible status values (disease-free, disease and unknown).

5. NEDA-3 Composite Endpoint

NEDA: Patients with no evidence of disease activity for all 4 of the above components over the full time period are viewed as having no evidence of disease activity overall.

Not NEDA: Patients with disease activity in at least one individual component (relapse, progression, Gd+, active T2) are viewed as having evidence of disease activity overall.

Unknown: Patients with no disease activity on some components and missing data on others are reported as unknown for the overall NEDA outcome. These patients are censored at the date of their last complete MRI assessment.

For each endpoint above, descriptive statistics was presented for week 48 and 96 week evaluations.

Data was presented for the ITT population for the 3.5 mg/kg and placebo treatment groups of the CLARITY study and the LLPP, PPLL and LLLL treatment arms of the CLARITY EXT study. Analysis was repeated for each analysis population by subgroup combination for the following subgroups: HDA4, RES, and SOT. All analyses was further stratified by treatment naïve and previously treated patients.

- time to 6 month CDP

Definition of Time to 3-month confirmed EDSS Progression

A 3-month confirmed increase in a subject's EDSS score occurs when a subject's EDSS score increases from baseline and the increase is sustained over consecutive visit(s) for a period equal to or greater than 3 month (i.e., 83 days). That is, a 3-month confirmed progression means that two consecutive visits (assuming each consecutive visit is at least 3 months apart) must have the following worsening compared to the baseline visit:

1. If the baseline EDSS score is zero, the increase must be ≥ 1.5 units

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

2. If the baseline EDSS score is ≥ 0.5 or ≤ 4.5, the increase must be ≥ 1.0 units

3. If the baseline EDSS score ≥ 5.0 the increase must be ≥ 0.5 units

The date of confirmed progression is the date of 1-point (or 1.5 or 0.5 depending on the baseline EDSS score) EDSS worsening (i.e., the date when the worsening in 1-point EDSS was recorded), not the date when the worsening 1-point (or 1.5 or 0.5 depending on the baseline EDSS score) EDSS was confirmed. EDSS values obtained from both unscheduled and scheduled visits are all taken into account.

Computation rules:

If a subject experienced a 3-month sustained change in EDSS Score from start of the period date to end of the period, then

- Time to 3-month confirmed EDSS progression = (date associated with the first 3-month sustained change – start of period date) + 1
- Censor = 0 (i.e. there is an event, no censoring)

If a subject does not experience a 3-month sustained change (days) in EDSS Score time to observing such an event was censored at the end of the study date, that is

- Time to 3-month confirmed EDSS progression = (end of period date - start of period date) + 1.
- Censor = 1 (i.e. there is no event, i.e. censoring)

Statistical analysis

Kaplan-Meier estimate of time to 3-month sustained change in EDSS (survival function) was presented by treatment group in table and graphically.

Time to 3-month sustained change in EDSS score was analyzed using a Cox proportional hazards model with fixed effects for treatment group. The hazard ratio of time to 3-month sustained change in EDSS score for the contrast cladribine versus placebo and the associated 95% CI was be provided.

For the analyses by subgroup

Kaplan-Meier estimate of time to 3-month sustained change in EDSS (survival function) was presented by treatment group and subgroup in table and graphically.

1) An estimate of the interaction subgroup*treatment for the contrast of interest was provided. Time to 3-month sustained change in EDSS score was analyzed using a Cox proportional hazards model with fixed effects for treatment group, subgroup, subgroup-by-treatment interaction.

2) Estimates of treatment effect within each subgroup for the contrast of interest was provided. Time to 3-month sustained change in EDSS score was analyzed using a Cox

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

proportional hazards model with fixed effects for treatment group. The hazard ratio of time to 3-month sustained change in EDSS score for each of the contrast comparison of interest and the associated 95% CI was estimated.

A forest plot depicting the Hazard Ratio (95% CI) for the contrast of cladribine 3.5 vs placebo for each subgroup was presented.

The analysis for time to 3-month confirmed EDSS progression was repeated using the 6-month confirmation EDSS progression.

- proportion of patients with 6 month CDP

A 6-month confirmed increase in a subject's EDSS score occurs when a subject's EDSS score increases from baseline and the increase is sustained over consecutive visit(s) for a period equal to or greater than 6 month (i.e., 166 days). That is, a 6-month confirmed progression means that three consecutive visits (assuming each consecutive visit is at least 3 months apart) must have the same worsening criteria defined for the 3-month confirmed progression. The below analysis was repeated using the 6-month confirmation EDSS progression definition.

3-month confirmed EDSS progression was computed and each patient was categorized in one of the 3 categories. Number and percentage of patients for the 3 categories was provided.

- No Progression: Patients with no progression up to 48 weeks.
- Progression: Patients with at least 1 confirmed progression up to 48 weeks.
- Unknown: Patients with no progression but who withdrew from the study before 48 weeks.

48 weeks is defined by:

- for subjects who experienced the second year treatment, day of the earliest exposure >= (year 1 start + 308 days).
- for subjects who did not experienced the second year treatment: week 48 target day is considered (336 days)

A progression observed before week 48 but confirmed after week 48 is considered in the 48 weeks analysis.

The above analysis was repeated at 96 weeks.

Status at 96 weeks is the status at the end of the study with the following rule:

- Patients who withdrew early (less than 587 days (83 weeks)), with no progression are considered as unknown.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

- Patients who withdrew after 587 days with no progression are considered as No Progression.

A8. **Consistency of reported results**

a. Table 13, page 17 of the CS has different numbers for previous DMT use and mean disease duration in both the placebo and cladribine groups compared with the Giovannoni 2010 NEJM paper. Please clarify which numbers are correct.

We acknowledge the differences in numbers for previous DMT use and mean disease duration in both the placebo and cladribine groups between the Giovannoni et al., 2010 New England Journal of Medicine (NEJM) journal article and the analyses presented in the CS. Both the numbers presented in the NEJM article and in Table 13, page 17 of the CS are correct. The discrepancies between them are related to the different definitions used in the CLARITY initial analyses as reported in the CLARITY trial report in 2010 and published in the NEJM article and in re-analyses of the data presented in the CS. Specifically:

Previous DMT use: In the NEJM article, the use of any DMT was tabulated. In the re-analyses, the definition was restricted to treatments that have been approved by EMA for Multiple Sclerosis. This restricted list of medications consisted of the following preferred terms (WHODD Sept 2014): interferon beta-1a; interferon beta-1b; glatiramer acetate; fingolimod hydrochloride; fingolimod; natalizumab; fumaric acid.

Disease duration: In the NEJM initial analyses, the duration was defined as “the time (in years) from the first attack until randomization”. In the re-analyses presented in the CS, the duration was adapted to a more commonly used definition, “the time (in years) from the MS diagnosis date until randomization”.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

b. Section B.2.6 of the CS states that handling of missing data of post-hoc analyses was amended between the publication of the CLARITY trial clinical study report and submission to regulatory authorities. Please clarify exactly how the statistical approach taken to handle missing data for regulatory submissions was different to the approach specified in the original statistical analysis plan for CLARITY?

Instead of the imputation procedures implemented in the original CLARITY analyses (as detailed in the CLARITY SAP), the following approaches were taken in the data reanalyses:

	Original CLARITY analysis	CLARITY reanalysis for CS
1	Imputation of number of qualifying relapses after rescue for subjects who received rescue medications	For all subjects, including those who received rescue medications, their reported qualifying relapses were used without exclusions or alterations.
2	Imputation of missing data for the proportion of qualifying relapse-free subjects during 96 weeks (for subjects who prematurely withdrew from the study and had not had a relapse before withdrawing)	Subjects with no qualifying relapses but who withdrew from the study early were considered of unknown status and were excluded from logistic regression analyses (in the CSE analyses). In the GEVD analyses, the proportions were presented descriptively and in addition, K-M estimates were provided (in which subjects that withdrew prematurely without having had a qualifying relapse were considered censored at the time of withdrawal).
3	Imputation of missing data for the proportion of subjects without a 3-month sustained change in EDSS score (for subjects who prematurely withdrew from the study and had not had a sustained change before withdrawing)	The same approach as for the proportion of qualifying relapse-free subjects was taken.
4	Imputation of missing data for the proportion of subjects with no CU, no active T1 Gd+ or no active T2 lesions (for subjects with missing mean lesion numbers)	For proportion of subjects with no active T1 Gd+ lesions and for proportion of subjects with no active T2 lesions: the same approach as for the proportion of qualifying relapse-free subjects was taken. The proportion of subjects with no CU lesions was analyzed descriptively only in the GEVD analyses.
5	Missing MRI data	Missing data were not imputed. For the definition of HDA populations: subjects with missing baseline number of T2 lesions were considered in the <9 T2 lesions category. Subjects with missing baseline number of T1 Gd+ lesions were considered in the <1 T1 Gd+ category.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

c. There are some slight differences in the results presented in tables 18 to 21 of the CS compared with the equivalent results presented in Table 2 of the Giovannoni 2010 NEJM paper. Does the different approach to handling missing data (outlined in question 4b above) explain the slight differences in results between the Giovannoni 2010 NEJM paper and the CS?

There are two reasons for the slight discrepancies between the results presented in tables 18 to 21 of the CS compared with the equivalent results presented in Table 2 of the Giovannoni 2010 NEJM paper. The first is indeed the handling of missing data. The second reason is that the statistical models presented in NEJM included geographic region (region) as a fixed effect, whereas the same models used in the CS analyses did not include region.

Region was not included as a term in the reanalyses because of the concern that the models would not converge when fitted on small subpopulations. Therefore simpler versions of the same models were preferred.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

The reasons for the small differences are detailed below for each table:

CS Table	Estimate presented	Imputation and model used in the NEJM	Imputation and model used in the CS
18	Qualifying ARR	- Numbers of qualifying relapses were imputed for rescued subjects (after the rescue time). - The relapse count was modelled through a Poisson regression model with fixed effects for treatment group and region and with log of time on study as an offset variable.	- Numbers of qualifying relapses were not imputed. Reported numbers of qualifying relapses were used for all subjects. - The relapse count was modelled through a Poisson regression model with fixed effect for treatment group and the log of time on study as an offset variable.
	Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effect for treatment group.
19	Proportion of relapse-free patients	- Missing data was imputed for the proportion of qualifying relapse-free subjects - The proportion of relapse-free patients was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 18. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.
20	Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effect for treatment group.
21	Proportion of patients with 3-month confirmed disability progression	- Missing data was imputed for the proportion of patients without a 3-month sustained disability progression - The proportion of patients without a 3-month sustained disability progression was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 20. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A9. **Additional results**

a. The proportion of relapse-free patients, with 3-month CDP and with 6-month CDP is presented for the ITT population at 48 weeks in Table 19, Table 21 and Table 22 of the CS. Please provide equivalent results for relapse-free patients, 3-month CDP and 6-month CDP at 48 weeks for the HDA-RRMS, RES-RRMS and the SOT-RRMS subgroups?

Please see Table 3 for the proportion of patients qualifying relapse-free, Table 4 for the proportion of patients with 3-month CDP, and Table 5 for the proportion of patients with 6-month at 48 weeks for HDA-RRMS, RES-RRMS, and SOT-RRMS.

Table 3: Proportion of relapse-free patients at 48 weeks in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets			Placebo		
	HDA-RRMS (N=140)	RES-RRMS ([redacted])	SOT-RRMS ([redacted])	HD -RRMS (N=149)	RES-RRMS ([redacted])	SOT-RRMS ([redacted])
Qualifying relapse-free at 48 weeks, n (%)						
Relapse	21 (15)	10 (20.0)	3 (15.8)	50 (33.6)	[redacted]	[redacted]
Relapse-free	112 (80.0)	35 (70.0)	15 (78.9)	89 (59.7)	[redacted]	[redacted]
Unknown*	7 (5.0)	5 (10.0)	1 (5.3)	10 (6.7)	[redacted]	[redacted]

SOURCE: (Merck 2017a)

* Patients who withdrew early before week 48/96 with no relapse are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

CI: Confidence interval; L: Low-dose Cladribine Tablets over 48 weeks

Table 4: Proportion of patient with 3-month confirmed disease progression at 48 weeks in CLARITY

Outcome	3.5 mg/kg Cladribine Tablets			Placebo		
	HDA (N=140)	RES ([redacted])	SOT ([redacted])	HDA (N=149)	RES ([redacted])	SOT ([redacted])
3-month confirmed disability progression at 48 weeks, n (%)						
Progression	6 (4.3)	6 (12.0)	0	27 (18.1)	7 (17.1)	4 (12.5)
Progression -free	126 (90.0)	39 (78.0)	18 (94.7)	109 (73.2)	32 (78.0)	23 (71.9)
Unknown*	8 (5.7)	5 (10.0)	1 (5.3)	13 (8.7)	2 (4.9)	5 (15.6)

SOURCE: (Merck 2017a)

* Patients who withdrew early before week 48/96 with no 3-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

L: Low-dose Cladribine Tablets over 48 weeks

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 5: 6-month confirmed disability progression at 48 weeks in CLARITY (post-hoc analysis)

Outcome	HDA-RRMS		RES-RRMS		SOT-RRMS	
	3.5 mg/kg Cladribine Tablets (N=140)	Placebo (N=149)	3.5 mg/kg Cladribine Tablets [redacted]	Placebo ([redacted])	3.5 mg/kg Cladribine Tablets ([redacted])	Placebo ([redacted])
K-M estimate of progression-free patients, % (95% CI)	95.5 (90.2; 97.9)	77.7 (69.8; 83.8)	[redacted]	[redacted]	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	0.18 (0.08; 0.44)		[redacted]		[redacted]	[redacted]
p-value	0.0001		[redacted]		[redacted]	
6-month confirmed disability progression at 48 weeks, n (%)						
Progression	2 (1.4)	23 (15.4)	[redacted]	[redacted]	[redacted]	[redacted]
Progression -free	129 (92.1)	112 (75.2)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown*	9 (6.4)	14 (9.4)	[redacted]	[redacted]	[redacted]	[redacted]

SOURCE: (Merck 2017a)

CI: Confidence interval; HR: Hazard ratio; L: Low-dose Cladribine Tablets over 48 weeks;

* Patients who withdrew early before week 48/96 with no 6-month confirmed disability progression are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)

b. Table 37, page 37 of the CS presents results for NEDA-3 status in CLARITY post-hoc subgroup analysis. Please provide the confidence intervals for the Kaplan-Meier estimates be provided (as in Table 23)?

The Kaplan-Meier estimates and confidence intervals for NEDA-3 in HDA-RRMS, RES-RRMS and SOT-RRMS from CLARITY have been presented in Table 6.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 6: NEDA-3 status in CLARITY post-hoc subgroup analysis

Outcome	3.5 mg/kg Cladribine Tablets	Placebo
HDA-RRMS		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	43.7 (35.0; 52.0)	6.9 (2.8; 13.6)
HR for Cladribine Tablets vs. placebo (95% CI)	2.86 (2.14, 3.81)	
p-value	<0.0001	
RES-RRMS		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
[redacted]		
K-M estimate of NEDA-3 status at last event, % of patients (95% CI)	[redacted]	[redacted]
HR for Cladribine Tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	

SOURCE: (Merck 2017a)

CI: Confidence interval; HDA-RRMS: High disease activity; HR: Hazard ratio; K-M: Kaplan-Meier: L: Low-dose Cladribine Tablets treatment over 48 weeks; NEDA: No evidence of disease activity; RES-RRMS: Rapidly evolving severe: SOT-RRMS: Sub-optimal therapy

c. **Priority question**: Section 2.6.1.4 of the CS states that analyses of other endpoints that are not relevant for the NICE Decision problem are presented in Appendix E. Appendix E presents does not present results for 'Severity of Relapses' or 'Confirmed Worsening'. For completeness, please provide results for these endpoints.

Please see Table 7, Table 8, and Table 9 for data on confirmed worsening (CLARITY + CLARITY-EXT), severity of relapses from CLARITY, and severity of relapses from CLARITY-EXT.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 7: Confirmed worsening (EDSS ≥6) (CLARITY + CLARITY-EXT)

Outcome	3.5 mg/kg Cladribine Tablets (LLPP)	
	Time to 3 month Confirmed Worsening	Time to 6 month Confirmed Worsening
ITT (N=98)		
K-M estimate at last event, % confirmed worsening (95% CI)	13.8 (7.8; 23.8)	13.8 (7.8; 23.8)
HDA-RRMS (N=31)		
K-M estimate at last event, % confirmed worsening (95% CI)	13.2 (5.1; 31.4)	13.2 (5.1; 31.4)
RES-RRMS (N=13)		
K-M estimate at last event, % confirmed worsening (95% CI)	[redacted]	[redacted]
SOT-RRMS (N=4)		
K-M estimate at last event, % confirmed worsening (95% CI)	[redacted]	[redacted]

Table 8: Severity of relapses determined by those requiring hospitalisation or steroid treatment (CLARITY)

Outcome	ITT		HDA-RRMS		RES-RRMS		SOT-RRMS	
	3.5 mg/kg Cladribine Tablets (N=433)	Placebo (N=437)	3.5 mg/kg Cladribine Tablets (N=140)	Placebo (N=149)	3.5 mg/kg Cladribine Tablets ([redacted])	Placebo ([redacted])	3.5 mg/kg Cladribine Tablets ([redacted])	Placebo ([redacted])
Number of qualifying relapses requiring hospitalisation by 48 weeks								
Mean (SD)	0.07 (0.28)	0.15 (0.42)	0.09 (0.31)	0.19 (0.47)	[redacted]	[redacted]	[redacted]	[redacted]
Number of qualifying relapses not requiring hospitalisation by 48 weeks								
Mean (SD)	0.08 (0.30)	0.18 (0.51)	0.09 (0.33)	0.28 (0.64)	[redacted]	[redacted]	[redacted]	[redacted]
Number of qualifying relapses requiring hospitalisation by 96 weeks								
Mean (SD)	0.11 (0.40)	0.25 (0.64)	0.13 (0.46)	0.30 (0.78)	[redacted]	[redacted]	[redacted]	[redacted]
Number of qualifying relapses not requiring hospitalisation by 96 weeks								
Mean (SD)	0.14 (0.42)	0.32 (0.71)	0.15 (0.45)	0.48 (0.86)	[redacted]	[redacted]	[redacted]	[redacted]
Number of qualifying relapses requiring steroid treatment by 48 weeks								
Mean (SD)	0.13 (0.38)	0.28 (0.57)	0.15 (0.41)	0.40 (0.69)	[redacted]	[redacted]	[redacted]	[redacted]
Number of qualifying relapses requiring steroid treatment by 96 weeks								
Mean (SD)	0.20 (0.52)	0.47 (0.83)	0.23 (0.58)	0.64 (1.02)	[redacted]	[redacted]	[redacted]	[redacted]

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 9: Severity of relapses determined by those requiring hospitalisation or steroid treatment (CLARITY-EXT)

Outcome	ITT	HDA-RRMS	RES-RRMS	SOT-RRMS
	3.5 mg/kg Cladribine Tablets (LLPP) (N=98)	3.5 mg/kg Cladribine Tablets (LLPP) (N=31)	3.5 mg/kg Cladribine Tablets (LLPP) ([redacted])	3.5 mg/kg Cladribine Tablets (LLPP) ([redacted])
Number of qualifying relapses requiring hospitalisation by 48 weeks				
Mean (SD)	0.06 (0.28)	0.06 (0.25)	[redacted]	[redacted]
Number of qualifying relapses not requiring hospitalisation by 48 weeks				
Mean (SD)	0.05 (0.26)	0.06 (0.25)	[redacted]	
Number of qualifying relapses requiring hospitalisation by 96 weeks				
Mean (SD)	0.11 (0.45)	0.10 (0.40)	[redacted]	
Number of qualifying relapses not requiring hospitalisation by 96 weeks				
Mean (SD)	0.15 (0.62)	0.19 (0.54)	[redacted]	
Number of qualifying relapses requiring steroid treatment by 48 weeks				
Mean (SD)	0.10 (0.37)	0.10 (0.30)	[redacted]	
Number of qualifying relapses requiring steroid treatment by 96 weeks				
Mean (SD)	0.23 (0.72)	0.19 (0.54)	[redacted]	

d. **Priority question:** Section B.2.7 of the CS: subgroup analysis – Please provide subgroups analysis for health related quality-of-life.

Subgroup analysis for health related quality of life data (EQ-5D data only) are available in the appendix to the CS, and are re-summarised in **Error! Reference source not found.**.

As shown in **Error! Reference source not found.**, the mean health state utilities of patients with RES were similar to the mean utility for non-RES patients with week 1 values of 0.688 versus 0.718. At week 96, the mean health state utility of RES patients was 0.726 versus 0.693 for non-RES. Similarly, in the SOT population, mean health state utilities were 0.666 at week 1 and 0.703 at week 96, compared with 0.719 and 0.696 at weeks 1 and 96 for non-SOT patients respectively. Overall, it was concluded that there was no meaningful difference in mean utility across groups, such that data from the pooled intention to treat group could be used in the base case economic analysis.

No formal statistical testing of mean health state utility was possible in time for the clarification question. This analysis is presently being conducted and will follow this response.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 10: Summary of descriptive statistics for EQ-5D HSU from UK social preferences in CLARITY and CLARITY EXT by study visit and subgroup (pooled intention to treat)

	Week 1	Week 24	Week 48	Week 72	Week 96	Unscheduled
CLARITY						
EQ-5D HSU (UK tariff) – RES						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D HSU (UK tariff) – non-RES						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D HSU (UK tariff) – SOT						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D HSU (UK tariff) – Non-SOT						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CLARITY EXT						
EQ-5D HSU (UK tariff) – RES						
n	36	34	33	33	34	8
Mean (SD)	0.762 (0.223)	0.774 (0.191)	0.782 (0.216)	0.733 (0.329)	0.695 (0.274)	0.667 (0.199)
EQ-5D HSU (UK tariff) – non-RES						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D HSU (UK tariff) – SOT						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D HSU (UK tariff) – Non-SOT						
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

e. **Priority question**: Section B.2.7 of the CS: subgroup Analysis states that 'the full dataset is summarised in Appendix E.' Appendix E only summarises the additional results of MRI lesions for CLARITY and CLARITY-EXT. Please provide any other information from Appendix E relating to subgroup analyses.

This sentence has been mistakenly placed in section B.2.7 and should be deleted. Instead, the following sentence should be added in Section B.2.7.3: "The main efficacy outcomes in the RRMS subgroups are discussed below, with additional outcomes associated with MRI lesions summarised in Appendix E." These data have been provided in **Error! Reference source not found.** of this document.

A10. **Network meta-analysis and meta-regression (Appendix D and Appendix K)**

a. **Priority question:** Please clarify which studies contributed data to the network meta-analysis and/or meta-regression for the outcomes below. Please provide the number of patients and information for the ITT, HDA, RES and SOT analyses as applicable, ideally presented in tables similar to Table 60, page 153 (presented in Appendix K for the meta-regression).
   i. ARR
   ii. ARR hospital treated
   iii. ARR requiring steroid treatment
   iv. CDP3M 24M
   v. CDP6M 24M (with INCOMIN study)
   vi. RF12M
   vii. RF24M
   viii. NEDA-3 24M
   ix. QoL results (EQ-5D 12M, EQ-5D 24M, EQ-5D VAS 12M, EQ-5D VAS 24M)
   x. Tolerability results (Study withdrawals, treatment withdrawals, any AE, any SAE, any TRAE, any grade 3/4 AE, any CVS, any infection, any serious infection, depression, ALT increased.

The details on studies contributing in the evidence network for the NMA with the corresponding number of patients for the above-requested outcomes have been provided in Appendix A.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

b. Please state the data sources used in the network meta-analysis and meta-regression (i.e. was individual participant data used for CLARITY and results extracted from the published literature for other trials? Or was individual participant data available for any other trials – such as unpublished data from PRISMS?).

The data sources used in the network meta-analysis and meta-regression were obtained from the published clinical literature, and from unpublished study reports for CLARITY and PRISMS. Individual participant data are available for both CLARITY and PRISMS but were not included in the analyses.

c. Section B.2.9.2 of the CS states that 'attempts were made to improve these connections, e.g. through a series of post-hoc analysis that incorporated unpublished data from the phase III PRISMS trial (details available in Appendix D).' Please provide further details of these post-hoc analyses.

The existing network for ARR and CDP6M in the sub-groups, HDA_RRMS, RES-RRMS and SOT-RRMS did not allow comparison of Cladribine Tablets to all relevant comparators such as alemtuzumab. The PRISMS trial is a MERCK sponsored trial and therefore post-hoc analyses of ARR and CDP6M were conducted in order to allow these comparisons. Please find below the details of populations and outcomes assessed in the post-hoc analyses:

- HDA RRMS
    - ARR
    - CDP6M
- RES
    - ARR
    - CDP6M
- ITT
    - CDP6M

It should be noted that a post-hoc analysis of the SOT population from the PRISMS trial was not possible due to inadequate patient numbers.

d. Related to point b, do the networks presented in Figure 6, Figure 7 and Figure 8 of the CS appendix correspond to the post-hoc analyses that include the PRISMS trial

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

to incorporate a link between alemtuzumab and cladribine using data for IFN beta-1a, 44 mg 3 times a week and placebo?

Yes, Figure 6 (HDA-RRMS and RES-RRMS), and Figure 8 (ITT, HDA-RRMS, and RES-RRMS) of the CS appendix includes the post-hoc analyses of ARR and CDP6M from the PRISMS trial. SOT data from the PRISMS trial were not available. ARR and CDP3M from ITT analyses of the PRISMS trial was available from the publication. Post-hoc analysis of CDP3M data was not performed, as this outcome is not the preferred outcome for NICE and not directly used in the cost-effectiveness analysis. Therefore Figure 7 does not contain this post-hoc analysis of the PRISMS trial.

e. Please provide any information on the investigations carried out for inconsistency (for networks with closed loops) or heterogeneity for these network meta-analysis?

Inconsistency factor (ω) was calculated to test the consistency between direct and indirect results that contributed to the NMA analysis. A value of ω close to zero indicates no inconsistency between the direct and indirect comparison results. The value of ω is considered significant if $p<0.05$ (Dias 2010).

Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5 presents the results of the consistency test performed for ARR, CDP3M, CDP6M, proportion of patients relapse free at 12 month and proportion of patients relapse free at 24 month, respectively. The results of the consistency assessment indicated no significant differences between direct and indirect estimates for all the comparisons in closed loops except placebo versus IFN beta-1a 44 mcg tiw and placebo versus teriflunomide 7 mg od. Meta-regression was performed to take into account any inconsistency in the results.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Figure 1: ARR: Consistency test for closed triangular loops

ω: Inconsistency factor; CrI: Credible Interval; DAC: Daclizumab; DMF: dimethyl fumarate; FIN: Fingolimod; GA: Glatiramer acetate; IFN: Interferon; PLA: Placebo; TER: Teriflunomide

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Figure 2: CDP3M: Consistency test for closed triangular loops

ω: Inconsistency factor; CrI: Credible Interval; DMF: dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; PLA: Placebo; TER: Teriflunomide

Figure 3: CDP6M: Consistency test for closed triangular loops

ω: Inconsistency factor; CrI: Credible Interval; DMF: dimethyl fumarate; GA: Glatiramer acetate; PLA: Placebo; TER: Teriflunomide; CDP sustained for 6 months at 24 months

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Figure 4: Proportion of patients relapse-free at 12 months: Consistency test for closed triangular loops

ω: Inconsistency factor; CrI: credible Interval; DMF: dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; PLA: Placebo; TER: Teriflunomide

Figure 5:Proportion of patients relapse free at 24 month: Consistency test for closed triangular loops

ω: Inconsistency factor; CrI: credible Interval; DMF: dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; PLA: Placebo; TER: Teriflunomide

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Heterogeneity

The summary plot of covariate analysis for ARR is presented below in Figure 6. Meta-regression was conducted by adjusting different baseline characteristics i.e. mean age, % female, mean baseline EDSS score, disease duration, and relapse in prior one year and two years. EDSS score had a significant negative correlation with ARR in univariate analysis and percentage female had a significant positive correlation with ARR in univariate analysis. However, effect size (ES) and credible intervals (CrIs) for EDSS and % female were close to 0, it is unlikely that this difference would translate into any clinical relevance. No significant correlation was observed for remaining covariates and ARR in univariate analysis.

Figure 6: Summary plot of covariate analysis for annualized relapse rate

CrI: Credible Interval; EDSS: Expanded Disability Status Score; ES: Effect Size

The summary plot of covariate analysis for CDP sustained for 3 months at 24 months is presented below in Figure 7. Meta-regression was conducted by adjusting different baseline characteristics i.e. mean age, % female, mean baseline EDSS score, study duration, disease duration, and relapse in prior one year and two years. There was no significant correlation between the covariates and CDP sustained for 3 months at 24 months in univariate analysis.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Figure 7: Summary plot of covariate analysis for confirmed disability progression sustained for 3 months at 24 months

CrI: Credible Interval; EDSS: Expanded Disability Status Score; ES: Effect Size

The summary plot of covariate analysis for CDP sustained for 6 months at 24 months is presented below in Figure 8. Meta-regression was conducted by adjusting different baseline characteristics, i.e. mean age, % female, mean baseline EDSS score, study duration, disease duration, and relapse in prior one year and two years. No significant correlation was observed between covariates and CDP sustained for 6 months at 24 months in univariate analysis.

Figure 8: Summary plot of covariate analysis for confirmed disability progression sustained for 6 months at 24 months

CI: Confidence Interval; EDSS: Expanded Disability Status Score; ES: Effect Size

The summary plot of covariate analysis for proportion of patients relapse-free at 12 months is presented below in Figure 10. Meta-regression was conducted by adjusting different baseline

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

characteristics i.e. mean age, % female, mean baseline EDSS score, study duration, disease duration, and relapse in prior one year and two years. There was no significant correlation between the covariates and proportion of patients relapse-free at 12 months in univariate analysis.

The summary plot of covariate analysis for proportion of patients relapse-free at 24 months is presented below in Figure 9. Meta-regression was conducted by adjusting different baseline characteristics i.e. mean age, % female, mean baseline EDSS score, study duration, disease duration, and relapse in prior one year and two years. There was no significant correlation between the covariates and proportion of patients relapse-free at 24 months in univariate analysis.

Figure 9: Summary plot of covariate analysis for proportion of patients relapse-free at 24 months

CrI: Credible Interval; EDSS: Expanded Disability Status Score; ES: Effect Size

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Figure 10: Summary plot of covariate analysis for proportion of patients relapse-free at 12 months

CrI: Credible Interval; EDSS: Expanded Disability Status Score; ES: Effect Size

f. The legend of the NMA results tables (Table 11 onwards of the CS appendix) states that: "-" indicates that analyses were not feasible for these comparisons considering limited evidence.
Please clarify whether this refers to the number of studies (that is, that no studies were available for the comparison for that outcome) or whether this refers to the feasibility of the statistical methods (such as models not converging).

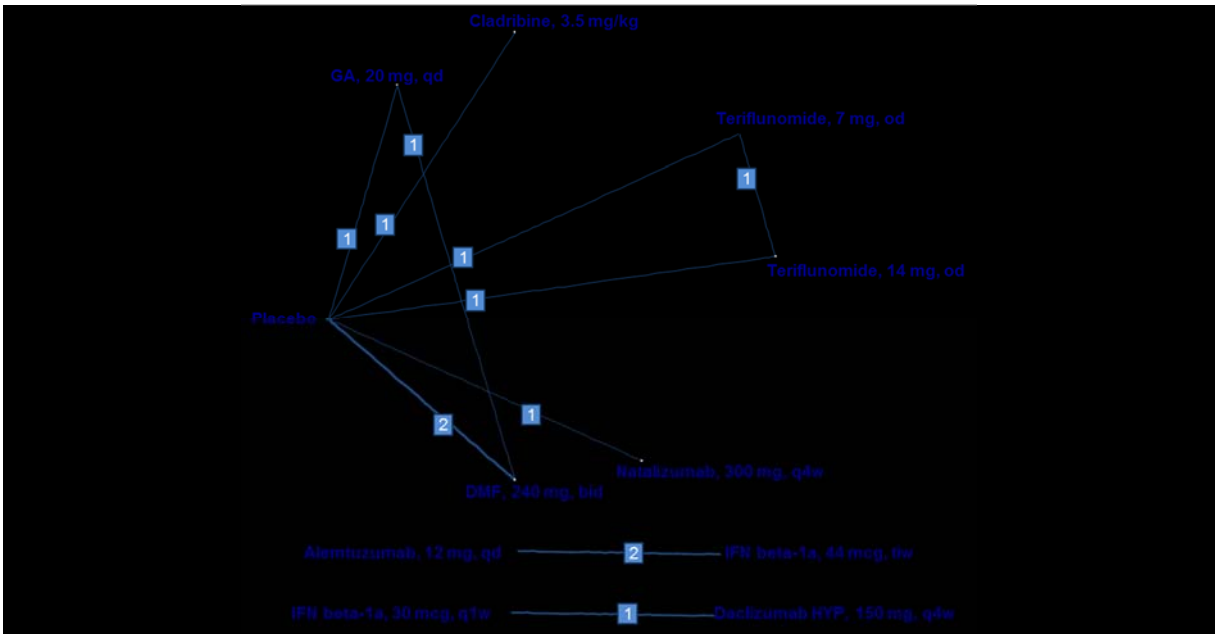
The sign "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies.

The network diagram corresponds to proportion of patients with no evidence of disease activity after 24 months of treatment (NEDA-3 at 24 months). A NMA of cladribine tablets versus alemtuzumab 12mg qd, IFN beta-1a 44mcg tiw, IFN beta-1a 30mcg q1w, and daclizumab HYP 150mg q4w could not be conducted due to absence of any connecting links in the network.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140



DMF: dimethyl fumarate; GA: Glatiramer acetate; HYP: High Yield Process; IFN: Interferon; kg: kilogram; mg: milligram; qd: per day; q1w: Once a week; q4w: every 4 weeks

g. Please clarify the labelling of Table 14 to 16 of the CS appendix:
   i. Table 14: does RR stand for rate ratio (this abbreviation is not provided as a footnote)?
   ii. Table 15 and 16: should RR presented in these tables be Hazard Ratio (HR)?

We confirm that RR stands for rate ratio. Please find below the corrected table note:

bid: twice a day; CrI: Credible Interval; DMF: dimethyl fumarate; EOD: Every other day; GA: Glatiramer acetate; IFN: Interferon; kg: kilogram; µg: microgram; mg: milligram; od: once daily; qd: per day; q1w: Once a week; q2w: every 2 weeks; q4w: every 4 weeks; tiw: thrice a week; tiw: thrice a week; SD: Standard deviation; RR: Rate ratio

Table 15 and 16 presented HR. Please find below the corrected table note:

bid: twice a day; CrI: Credible Interval; DMF: dimethyl fumarate; EOD: Every other day; GA: Glatiramer acetate; IFN: Interferon; kg: kilogram; µg: microgram; mg: milligram; od: once daily; qd: per day; q1w: Once a week; q2w: every 2 weeks; q4w: every 4 weeks; tiw: thrice a week; tiw: thrice a week; SD: Standard deviation; HR: Hazard ratio

h. Section B.2.9.1, page 61 of the CS states that 'results of sensitivity analyses generally found that the findings for ARR CDP3M and CDP6M at 24 months were robust'. Appendix D refers only to sensitivity analysis excluding open label studies or

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

studies with unclear blinding. Please provide details of any other sensitivity analyses conducted.

The results of additional sensitivity analyses conducted are provided below:

Sensitivity analyses other than the blinding status included:

- Diagnostic criteria: Studies with Poser's or unclear diagnostic criteria were excluded from the analyses
- Study phase: Phase II or studies with phase unclear were removed from the analyses
- Year of publication: Studies published prior to year 2000 were excluded from the analyses.

The results of these sensitivity analyses have been presented in Appendix B.

i. Appendix K presents a meta-regression which is also referred to in this section as a 'network meta-analysis.' Usually, network meta-analysis conducted within a meta-regression framework of dummy variables do not allow for adjustments of correlation between treatment arms in multi-arm trials. Table 60, of the CS Appendix indicates that three 3-arm trials have been incorporated.

   Please clarify whether the analysis described in Appendix K is conducted using a similar hierarchical approach to the time-to-event outcome analysis described in Appendix D.1.1.4.5 using the model:

$$cloglog(p_{i,k}) = \log(T_i) + \mu_i + \delta_{i,k} + \beta * (\mu_i - \bar{x})$$

   To incorporate baseline risk rather than:

```
# model for linear predictor

      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
```

   As specified in the WinBugs code for the time-to-event outcome?

The meta-regression analysis presented in appendix K was conducted using the same hierarchical approach to time-to-event outcome analysis as outlined in appendix D.1.4.5. As stated in the clarification question, the effect of baseline risk on drug efficacy was captured by including a dummy variable beta multiplied by the baseline risk in that study centered on the risk expected in the RES and SOT populations of CLARITY. An example of the Winbugs code is provided below:

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

```
cloglog(p[i,k]) <- log(time[i])+ mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * (mu[i]-x)
```

Where x is the fixed risk value, transformed to the cloglog scale, for the RES and SOT populations of CLARITY.

Adjustments of correlation between treatment arms in multi-arm trials was achieved using the code provided by Dias et al in Example 6 of TSD3:

```
for (k in 2:na[i]) { # LOOP THROUGH ARMS                                    delta[i,k] ~
dnorm(md[i,k],taud[i,k]) # trial-specific distributions                     md[i,k]   <-
d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of distributions (with multi-arm trial correction)

taud[i,k] <- tau *2*(k-1)/k # precision of distributions (with multi-arm trial correction)

w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs

sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for multi-arm trials
        }
```

As in example 6 of TSD3, no convergence issues were identified following correction for multi-arm trials.

j. Table 69 of the CS presents median ratio of annualised release rates (ARR) used within the cost-effectiveness analysis which the ERG believes to be based on the resulted presented in Table 14 of the CS Appendix D.
   i. The results presented in Table 14 of the CS appendix are produced with random effects yet the preferred model type in Table 69 in the CS is fixed effects. Please clarify or justify the difference.

The results for RES and SOT shown in both Table 14 and Table 69 were produced from a fixed effects model. The title for Table 69, which states “random effects model”, is in reference to the ITT analysis only. All other analyses including in the HDA population were based on a fixed effects model.

As stated in the methods section, the choice of fixed versus random effects model was based on the comparison of DIC and residual deviance statistics following guidance by Dias et al. In the case of RES, SOT and HDA, the fixed effects model had a superior or comparable goodness of fit profile to the random effects model, and hence the simpler fixed effects model was preferred. In the case of ITT, the random effects model had the superior fit compared to the fixed effects model, and hence was the preferred option

   ii. Please clarify how the results within Table 14 of the CS appendix have been transformed to the results in Table 69 in the CS for the other disease modifying therapies.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

The annualized relapse rate ratios reported in Table 14 of the CS appendix, and Table 69 of the CS were derived from the following code outlined in appendix D.1.1.4.5:

```
# Rate ratios
for (c in 1:(nt-1))
      {
      for (k in (c+1):nt)
            {
            RR[k,c] <- exp(d[k] - d[c] )
            RR[c,k] <- 1/RR[k,c]
            }
      }
```

Table 69 of the CS reports the annualized relapse rate ratio for DMT versus placebo, and was obtained from the posterior summaries of RR[k,1]. The rate ratios shown in Table 69 of the CS correspond to the comparative efficacy of Cladribine Tablets versus comparator, which were obtained from the posterior summaries of RR[2,c].

k. Please provide the confidence intervals for the normalised hazard ratios centred on RES-RRMS and SOT-RRMS in Table 70.

The normalised hazard ratios presented in table 70 were generated from the economic model using the formula presented below:

$$d_k(z) = \delta_{i,k} + \beta * (z - \bar{x})$$

Where $d_k(z)$ is the log-hazard ratio of drug k versus placebo conditional on baseline risk z, δ_i is the log hazard ratio for progression comparing DMT versus placebo centered on baseline risk $\bar{x}$, β is the covariate value for baseline risk, and $\bar{x}$ is the baseline risk used in centering the analysis. In the economic model, the normalized hazard ratio is estimated by taking the exponential of $d_k(z)$.

Only deterministic results are summarised in the economic model. While the parametric uncertainty surrounding each of the above parameters was captured within the probabilistic analysis, the series of randomly sampled normalised hazard ratios were not collected and hence it was not feasible to generate confidence/credible intervals alongside the values shown in Table 70.

Normalised hazard ratios and associated 95% credible intervals were however, recorded directly from the meta-regression analysis via the following coding:

HR_P[k,1] <- exp(d[k] - d[1])

The mean hazard ratios and 95% credible intervals for each drug of interest is summarised in Table 11.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Table 11: Normalised hazard ratios with 95% credible interval

Treatment versus placebo	Normalised hazard ratio obtained from the economic model and presented in the CS		Normalised hazard ratio and 95% credible interval obtained from the meta-regression	
	Centered on RES-RRMS	Centered on SOT-RRMS	Centered on RES-RRMS [95% credible interval]	Centered on SOT-RRMS [95% credible interval]
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]

The normalised hazard ratios generated from the meta-regression, and presented in Table 11, differ slightly to those presented in Table 70 of the CS as a result of random sampling error in the Bayesian analysis. In all cases, the results generated from the meta-regression are within 2 decimal places of the normalised hazard ratios derived in the economic model. As with the 95% credible intervals for the log hazard ratios in Table 70 of the CS, there was significant overlap in the credible intervals for the normalised hazard ratios, with no therapy statistically dominating in terms of efficacy.

A11. Appendix D of the CS (in the paragraph underneath Table 10) states that: "As per the review inclusion criteria, the selected trials were composed of adults patients (≥18 years) with a confirmed diagnosis of RRMS. Nonetheless, although some studies specified RRMS as an inclusion criterion, they also included a small number of patients with progressive disease. If that was the case, trials with more than 20% of progressive patients were excluded, consequently stipulating a minimum of 80% of patients with RRMS for studies subgroups that were included." Please state how many trials also included progressive patients. Please clarify if these progressive patients were included or excluded within data which contributed to NMAs.

Of the 44 trials included in the NMA, five trials had defined 'relapsing MS' as one of their inclusion criteria. Amongst these five trials, the highest percentage of patients with a progressive disease was 12.3% (O'Connor 2006). None of these trials reported a sub-group data for the RRMS population. Details of these five studies have been provided below:

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

Study acronym	Primary intervention	Inclusion criteria	RRMS	SPMS	Progressive relapsing MS
TEMSO trial	Teriflunomide	Patients had a relapsing clinical course, with or without progression	91%	5%	4%
TOWER trial	Teriflunomide	Patients had relapsing multiple sclerosis meeting 2005 McDonald criteria, with or without underlying progression	97.3%	0.7%	2%
O'connor 2006	Teriflunomide	Patients with MS with relapses	87.7%	12.3%	-
Saida 2012	Natalizumab	Relapsing course of the disease (relapsing–remitting or secondary progressive)	97.3%	2.7%	-
TENERE trial	Teriflunomide	Relapsing clinical course with or without progression	99%	0.3%	0.7%

A12. Appendix D of the CS (in the third paragraph below Table 10) states that: "apparent variations in the mean number of relapses in the previous one and two years and mean EDSS score could not be observed across studies, nevertheless, these parameters were included in covariate analysis." Please clarify whether this statement refers to a sensitivity analysis? If so, provide any relevant results to support this statement.

The parameters reported in the statement, i.e. mean number of relapses in the previous one and in the previous two years, and mean EDSS scores were considered as covariates in the meta-regression analyses. The results pertaining to these covariate analyses have been presented in **Error! Reference source not found.** (**Error! Reference source not found.** to **Error! Reference source not found.**).

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A13. Appendix D.1.1.4.4 of the CS suggests that a frequentist approach was also performed for network meta-analysis using generalised linear models. However, Bayesian analysis are presented within the results due to credible intervals in the results tables. Please provide the rationale for also performing a frequentist analysis and if these additional analyses showed any difference in results to the Bayesian network meta-analysis.

Frequentist analyses were performed to validate the results of Bayesian analyses. No major differences were observed between the two sets of analyses.

A14. Please clarify how quality of life outcomes (change from baseline in EQ-5D) were analysed in the network-meta analysis. Please state if the outcomes were analysed as continuous outcomes rather than as poisson, time to event or binomial outcomes as specified in the WinBUGS code presented in the CS Appendix D.1.1.4.5.

Quality of life outcomes were analysed as continuous outcomes (mean change from baseline). Please find below the WinBUGS program for the QoL NMA:

```
model{

# Loop over studies
for(s in 1:NS)
      {
      # Adjustments for comparator arms
      w[s,1] <- 0
      delta[s,trt[s,1]] <- 0

      # Loop over all arms within a study for likelihood
      for (a in 1:na[s])
            {
            # Normal likelihood

      val[s,trt[s,a]]~dnorm(val.mean[s,trt[s,a]],val.prec[s,trt[s,a]])
            val.prec[s,trt[s,a]] <- n[s,trt[s,a]] * pow(sd[s,trt[s,a]],-2)

            # Mean = study effect + treatment effect
            val.mean[s,trt[s,a]] <- mu[s] + delta[s,trt[s,a]]

            # Deviance contribution
            dev[s,a] <- pow((val[s,trt[s,a]] - val.mean[s,trt[s,a]]),2) *
val.prec[s,trt[s,a]]
```

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

```
            }

            sumdev[s] <- sum(dev[s,1:na[s]])

            # Loop over active arms for trial-specific LORs
            for (a in 2:na[s])
                  {
                  # Random effects: trial-specific mean differences
                  delta[s,trt[s,a]] ~
dnorm(md[s,trt[s,a]],taud[s,trt[s,a]])

                  # Means of trials-specific differences
                md[s,trt[s,a]] <- d[trt[s,a]] - d[trt[s,1]] + sw[s,a]
                  diff[s,trt[s,a]] <- val[s,trt[s,a]] - val[s,trt[s,1]]

                  # Precision of LOR distributions
                  taud[s,trt[s,a]] <- tau*2*(a-1)/a

                  # Adjustment for multi-arm RCTs
                  w[s,a] <- (delta[s,trt[s,a]]  - d[trt[s,a]] +
d[trt[s,1]])
            sw[s,a] <-sum(w[s,1:a-1])/(a-1)
                  }

      }

# Vague priors for the study effects (effect of treatment 1)
for(s in 1:NS)
      {
      mu[s]~dnorm(0,0.0001)
      }

# Priors for the treatment effects (mean diff. vs treatment 1)
d[1] <- 0
d[2]~dnorm(0,0.0001)
for (i in 3:NT)
      {
      prd.m[i] <- pr.m[i]+d[2]-d[1]
      d[i]~dnorm(prd.m[i],pr.prec[i])
      }

#  Vague prior for random effects standard deviation
sdr~dunif(0,10)
tau<-1/pow(sdr,2)
tau2<- 1/tau

# Absolute and relative treatment differences effect
```

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

```
for (c1 in 1:(NT-1))
      {
      for (c2 in (c1+1):NT)
            {
            diff.abs[c1,c2] <- d[c1] - d[c2]
            diff.abs[c2,c1] <- -diff.abs[c1,c2]

            }
      }

# Treatment A effect size, based on average of the trials including it.
for (s in 1:NS)
      {
      mu1[s] <- mu[s] * equals(trt[s,1],1)
      count1[s] <- equals(trt[s,1],1)
      }

# Risk estimates for each treatment and treatment ranking
for (i in 1:NT)
      {
      T[i]<- sum(mu1[])/sum(count1[]) +d[i]
      rk[i]<- rank(d[],i)
      for (j in 1:NT)
            {
            # Is treatment i the jth best, assuming lower outcomes are
good.
          best[i,j]<-equals(rk[i], j)
            # best[i,j]<-equals(rk[i], NT + 1 - j) # if higher outcomes are
good.
            }
      }
# Total deviance
resdev <- sum(sumdev[])

}
```

A15. Appendix D1.1.4.5 of the CS states that: “In order to further validate the output of the NMA, anchor based indirect treatment comparisons were also conducted.” Please provide details of this alternative approach to network meta-analysis and whether this alternative analysis showed any difference to the arm based approach.

Anchor based indirect treatment comparisons were based methods explained by Bucher et al (Bucher 1997). These analysis were performed to validate the output of Bayesian analyses. Findings from the Bucher ITC were in line with the Bayesian NMA.

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

A16. Please clarify whether the summary results (that is, the directions of effect) presented in Tables 11 to 13 and Tables 17 to 20 of the CS Appendix are from a random-effects network meta-analysis model (as specified for Tables 14 to 16).

The model selection was based on the DIC and resdev statistics. The details on the selection of the NMA model have been provided in **Error! Reference source not found.**.

Results presented in Table 11 (ITT population, except NEDA-3) and rest of the table including ITT population are from a random-effects model.

For all the sub-groups (HDA-RRMS, RES and SOT) with limited number of studies contributing in the evidence network, the results presented are from a fixed-effects model.

As the tables 17 to 20 in the CS appendix include both the ITT and the sub-groups, the caption should be modified to remove “random-effects”. For further clarity, the outcomes for which FEM results have been presented are marked with an asterisk (*) in the summary tables. The tables are presented in **Error! Reference source not found.**:

Section B: Clarification on cost effectiveness data

B1. **Priority request:** Please repeat the analyses using CLARITY-EXT annualised relapse rate (6-month disability progression) data presented in Table 72, page 112 of the CS for the following 2 populations (2 analyses):

- RES-RRMS
- SOT-RRMS

B2. **Priority request:** Please undertake the analyses necessary to populate Table 72, page 112 of the CS using ARR data from the CLARITY-EXT trial, for the following populations (3 analyses):

- Intention to treat (ITT)
- RES-RRMS
- SOT-RRMS.

Merck has contacted the School of Health and Related Research (ScHARR) who conducted the original reseach and has already provided them with the required data. After early concerns related to the small patient numbers, ScHARR concluded that it is feasible to reconduct their analysis in RES-RRMS and SOT-RRMS populations. However, this analysis is not availble at time of this response. ScHARR has informed us that it could be available by

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

the 18th of August 2017. To meet the ERG request, Merck has commisioned this further analysis and is committed to providing the results to the ERG as soon as they are obtainable.

NICE National Institute for Health and Care Excellence

10 Spring Gardens
London
SW1A 2BU
United Kingdom

+44 (0)300 323 0140

REFERENCES

Bevan CJ, Cree BA. (2014) Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA Neurol. 71(3): 269-270.

Bucher HC, Guyatt GH, Griffith LE, Walter SD. (1997) The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 50(6): 683-691.

Dias S, Welton NJ, Caldwell DM, Ades AE. (2010) Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 29(7-8): 932-944.

European Medicines Agency. (2015) Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis .

Havrdova E, Galetta S, Stefoski D, Comi G. (2010) Freedom from disease activity in multiple sclerosis. Neurology. 74 Suppl 3, S3-S7.

Lublin FD. (2012) Disease activity free status in MS. Mult Scler Relat Disord. 1(1): 6-7.

Merck. (2017a) Data on file: CLARITY GEVD subgroup analyses.

Merck. (2017b) Data on file: CLARITY-EXT GEVD subgroup analyses.

NICE National Institute for Health and Care Excellence

Patient organisation submission

[ID64] Cladribine tablets for treating relapsing-remitting multiple sclerosis

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	We're the MS Society. Our community is here for people with MS through the highs, lows and everything in between. We understand what life's like with MS. Together, we are strong enough to stop MS. We have over 32,000 members and the vast majority of our income comes from voluntary donations and legacies.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have expertise from years of experience working alongside people with MS and their carers. For this submission we have engaged directly with people with MS, asking them to get in touch with us via an online blog and social media platforms as well as contacting neurologists who prescribe cladribine off label to ask them to put us in touch with people who are currently taking it. We specifically asked people who have experience of taking cladribine or feel that cladribine would benefit their MS to contact us and tell us about what it is like to live with MS and their experiences of MS treatments.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is one of the most common disabling neurological conditions affecting young adults. Around 100,000 people in the UK have MS, 93,000 of whom live in England and Wales, and 5000 people are newly diagnosed each year.[1] MS attacks at random with many of the symptoms invisible to others. It affects almost three times as many women as men with people usually experiencing their first symptoms in their 20s or 30s. Although much progress has been made in developing disease modifying therapies (DMTs), these are not curative and even the most effective carry significant risks for people with MS. Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week[2]. Around 85% of people with MS are first diagnosed with relapsing MS. A relapse is defined as an episode of neurological symptoms, which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. In relapses, symptoms usually come on over a short period of time but often remain for a number of weeks – usually three to four – and can sometimes last for months. Our understanding of how MS attacks the body is changing. MS specialists used to think that once a relapse was over, the damage to the brain and spinal cord stops and no new damage was happening. However we now understand that even when people with MS are not having relapses, their MS can still cause damage and neurodegeneration.[3] This damage can be happening from onset and even if there are no clinical signs of MS, such as a relapse. As a result early treatment with a DMT is now considered to be the best method of slowing the disability progression by preventing unnecessary neurodegeneration.

[1] MS Society estimate based on 2010 incidence and prevalence rates (Mackenzie et al. 2013) adjusted for accuracy based on the assumption that 82% of cases from this study can be validated (estimate based on Alonso et al. 2007). These adjusted rates have been applied to 2014 population estimates (Office of National Statistics

[2]Extra Costs Commission, Driving down the costs disabled people face : Final report, June 2015, pp. 13

[3] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015

	People with MS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Relapses can vary from mild to severe, with 95% of people with MS feeling relapses left them unable to do the things they wanted to do.[4] At their worst, acute relapses may need hospital treatment, but many relapses are managed at home, with the support of a GP, MS specialist nurse and other healthcare professionals. Around half of all relapses can leave a range of residual problems. New evidence has highlighted that disability also progresses regardless of whether a person experiences relapses regularly.[5] These are further important reasons to reduce the frequency and severity of relapses through ensuring that those who are eligible find the best treatment for them as soon as possible. Due to the varied and unpredictable nature of MS, determining an 'average' relapse rate is not straight forward. Relapses can have a resonating emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family (93%). Relapses are often unpredictable and distressing, leaving most people feeling frustrated (80%) and anxious (67%) and causing a disruption to everyday life.[6] The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65% of people with relapsing MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed and 10-15% are affected by primary progressive MS. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. This progression occurs at varying rates and can lead to a worsening of symptoms resulting in a permanent loss of mobility and the need to use a wheelchair, cognitive damage and permanent sight loss. There is also a real risk of accumulating disability for those with relapsing MS who are refractory to first line treatment. Tackling disability progression is a major issue for people with MS and currently represents an unmet treatment need. Our Research Strategy (2013-17) highlights research into progression as a major priority for the MS Society going forward. The strategy was formed in consultation with people affected by MS

[4] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.
[5] Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015
[6] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.

and the MS research community. It was approved by our Board of Trustees - the majority of whom are people affected by MS. Proving DMTs slow disability progression is notoriously difficult; but without at all minimising the difficulty of living with relapses, a product that has shown significant benefit here would be greatly valued by people affected by MS. The potential to maintain function and have a greater quality of life is of critical importance, especially for a chronic, long-term and potentially debilitating condition such as MS that so often evolves from relapsing remitting MS to the secondary progressive phase.

People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life. As each person's response to DMTs is different the more effective options available on the NHS will result in more people finding a treatment which best suits them.

Impact on Carers

The progressive, fluctuating nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult.

14% of people with MS consider a family member or carer their main contact for health care support[7]. Our research also shows that 85% of people with MS who need care and support receive unpaid care, support or assistance from a friend or family member. This has increased from 71% in 2013, suggesting carers are taking on more of a role supporting people with MS relative to the state or paid support. In addition, 36% of people who need support told us they rely solely on unpaid care (2016). Based on the latest prevalence data and our research, there could be more than 54,000 people with MS in England who need care and support, indicating there are tens of thousands of carers supporting them.

Carers support people with MS with a wide variety of essential activities. Our research found 63% of people with MS who need support require help carrying out essential activities of daily living such as getting up in the morning, washing and eating. We found that severity of needs increase with age, as the

[7] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	disease progresses. Treatment's that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too. But too many carers tell us they don't get the support they need to continue caring, from respite care to social care for the person they care for, financial support and emotion support. Carers also often act as care coordinators for the person they support, overseeing complex treatment regimens and navigating disjointed health, care and welfare systems. In our survey of over 11,000 people with MS last year, 15% of respondents said a carer or member of their family was their key contact for health care and support. One carer described just how complex this support network can be: "*Between the nurse, the speech and language therapist, the neurologist and various other specialists, there is roughly a team of twenty involved in my wife's care. She relies on me as a part of this team and to co-ordinate them. It's becomes a big 'project' to manage".*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	People often experience long delays in being diagnosed with MS. Timely referral or diagnosis for people with suspected MS is hugely important, yet we know this is not always achieved. In a recent survey of people with MS, 37% of respondents waited six months or more to be diagnosed with the condition, and 17% reported waiting more than 12 months to have a consultation with a neurological specialist. [8] There are currently 12 DMTs available on the NHS in the UK, offering people with relapsing MS a variety in treatments, that, until recently did not exist. In research carried out by the MS Society in 2014, those who responded identified stopping further relapses as the most important reason to start taking DMTs (93%), followed by 84% who hoped it would reduce the severity of their relapses, and 84% who hoped it would result in less disability over the long term. [9] While many people have had positive experiences with

[8] Neurological Alliance, 2017, *Falling Short – How has neurology patient experience changed since 2014?* http://neural.org.uk/updates/278-New-Neurological-Alliance-patient-experience-report-2017

[9] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014

	DMTs, others experience negative experiences such as side effects, no treatment effect, and many people simply are not eligible for the DMTs available on the NHS. Remaining in work and engaged in wider society is an important outcome which is not always captured when evaluating a treatments cost effectiveness but is incredibly important for people with MS. For those taking first line injectable treatments that involve daily or weekly injections and those undergoing regular treatment infusions within hospital, there is a substantial impact on their lives. Planning around administering these treatments, the side effects and storage needs are too great for many which is why the adherence rates are higher for DMTs which require less frequent administration.[10] Of the 12 DMTs available, alemtuzumab and natalizumab are classified as 'high efficacy' by the Association of British Neurologists (ABN). Beta interferons, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod, are regarded as having moderate efficacy. With the latter two drugs considered the more effective within this category. Daclizumab, recently approved by NICE offers another option of good efficacy for people with relapsing MS. Decisions on which DMT to take are determined by a variety of factors including the eligibility, efficacy, related side effects, the method and frequency of taking, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. Choosing which option to take requires access to evidence-based information, and support and advice from specialist health professionals. A survey carried out by the MS Society found that the majority of people (95%) preferred the option of a pill, giving ease of use, convenience to everyday life and non-invasiveness as reasons for selecting this option. [11] There was also a clear preference for options which would allow people with MS to be in charge of their own treatments. The preference for oral treatments identified in surveys can be seen reflected in the number of people with MS who have switched to the oral DMTs which have been positively appraised in the past five years.[12]

[10] Halpern et al, 'Comparison of adherence and persistence among multiple sclerosis patients treated with disease-modifying therapies: a retrospective administrative claims analysis', Patient Prefer Adherence, 2011
[11] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[12] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	There is a clear appetite among people with MS to switch to newer, less disruptive treatments despite these carrying potential greater side effects. The latest research from the MS Society has found that the number of people on DMTs has increased significantly since the newer DMTs were made available on the NHS. [13] This highlights that the greater the option of treatments the more likely people will find a DMT suited to them, increasing adherence rates and improving efficacy of treatments overall. Our latest research indicates that in England only 56% of those who could potentially benefit from taking a DMT are doing so, which clearly implies that there is further to go in providing options that suit everyone's needs.[14] Despite oral medication being the preferred method of administration, the current available oral treatments for MS (dimethyl fumarate, fingolimod and teriflunomide) are all taken daily (twice a day in the case of dimethyl fumarate). A treatment option which consists of a pill taken over two courses without the daily side effects many people experience would be a welcome step forward in terms of available treatment options. In 2014, the MS Society found that there is a lack of understanding and communication about what treatment options are currently available, with one in five people not having heard of any DMTs, or only heard of just one.[15] While MS nurses and neurologists are reported to be the most useful sources of evidence in aiding people to make a DMT decision, our research from last year showed that, of the people who are taking or are eligible for taking a DMTs, 13% had not met with a neurologist despite needing to and 14% had not met with an MS nurse despite needing to.[16] The MS Trust has found that the increased number of DMTs has led to inefficiencies in the necessary services needed alongside them. MS nurses have to deal with increasingly stretched workloads where they are responsible for fulfilling a range of non-clinical tasks such as scheduling monitoring appointments and booking chairs for IV infusions, which could be covered by an administrator. They have also found that there are a lack of information services to assist with the planning and monitoring of care for people

[13] Ibid.
[14] Ibid.
[15] Right treatment, right time? How people with MS make decisions about disease modifying drugs, MS Society, 2014
[16] Redfern-Tofts, D., Wallace, L. and McDougal, A. (2016) My MS, My Needs 2: technical report

	undergoing treatments, a lack of integration between different providers of care and substantial difficulties with the home care delivery systems needed for many of the treatments.[17]
8. Is there an unmet need for patients with this condition?	There are several unmet treatment needs for people with MS. Currently there are no treatment options which have been proven to reverse disability and repair the damage that MS does to the myelin sheath. As yet there are also no DMTs for people with progressive forms of MS, though the first license has just been granted by the Food and Drug Administration (FDA) in the USA for primary progressive MS. These are priority research areas for the MS Society, having been identified as such by people with MS. Within the drugs pathway for relapsing MS there are unmet needs which are more specific to individuals. Many people feel that the side effects from the frequent administration of the less effective treatments are too great for them, while others are risk averse or unable to tolerate the greater risks which come with the more effective treatments. A new treatment taken in two courses of tablets with relatively low side effect risks would help to ensure some of the 44% of people who are potentially eligible for a DMT but not taking one can find a treatment suitable for them.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Reduction in relapses** The results from the phase 3 CLARITY trial for cladribine involving more than 1,300 people with relapsing MS have shown cladribine to be effective at reducing relapses. The study compared two doses of cladribine (3.5 and 5.25 mg/kg) with a placebo. They showed that the higher dose reduced relapses by 55% and the lower dose by 58%. The proportion of people who remained relapse-free during the study was significantly higher in both cladribine groups (79.7% and 78.9%) compared with placebo (60.9%).[18]

[17] Mynors, G., Roberts, M. and Bowen, A. (2016) Improving the efficiency of disease modifying drug provision

[18] Giovannoni G, et al.A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.New England Journal of Medicine 2010;362(5):416-426.

	Results from an extension study announced in April 2016, found that after two years of follow up, the effects on relapses had been maintained.[19] People who have taken cladribine injections off label for their MS have been in touch to tell us the difference they have seen to their relapses*: "Cladribine for me was life changing. It stopped my relapses"*; *"I have completed the course, feel good, no side effects and no MS symptoms I can live life as if I didn't have MS".* **Reduction in disability progression** In the CLARITY trial both doses of cladribine were found to significantly reduce the relative risk of 3-month sustained disability progression compared with placebo (by 33% with 3.5 mg/kg and 31% with 5.25 mg/kg).[20] **Brain Atrophy** A follow up study to the CLARITY trial has shown that cladribine reduces the annualised rate of brain volume loss compared to placebo.[21] **Impact on quality of life compared to first line treatments** There are a number of factors that influence a person's decision to choose one treatment over another that are not easily addressed in cost effectiveness models. Cladribine is taken as two short courses split over two years, and has minimal side effects compared with other available treatments. This makes it an appealing treatment option for many people who struggle with side effects and administration of their MS treatments.

[19] Giovannoni G, et al.Clinical efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis (RRMS): final results from the 120-week phase IIIb extension trial to the CLARITY study (P3.028)Neurology 2016;86(Suppl), P3.028
[20] Giovannoni G, et al.A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.New England Journal of Medicine 2010;362(5):416-426
[21] De Stefano N, et al.Reduced brain atrophy rates are associated with lower risk of disability progression in patients with relapsing multiple sclerosis treated with cladribine tablets.Multiple Sclerosis 2017

	The side effects that come with the currently available first line injectable treatments are often cited as a reason people move onto other drugs. The most common side effects of the first line injectable treatments include flu like symptoms, and injection site reactions. As beta interferons and glatiramer acetate are all taken relatively frequently (ranging from every other day, to every two weeks), the side effects are unsurmountable for some. For some, the storage and planning involved around these treatments is also difficult to fit around their life. Many people with MS have been in touch to comment on why they would like to take cladribine over the first line injectables they are currently taking or have been offered: *"I'd be delighted to take this new drug if available. I am currently on, or meant to be on, Copaxone injections. I find it really sore, my injections sites flame up and swell for days at a time, I've actually stopped taking it now"* *"As much as the copaxone injections has helped me (for which I am truly grateful) I would definitely like to try something more simpler";" I would be interested in Cladribine if it became available as I was not ready to start on injections which would intrude in my life."* It is not just those who are struggling with the side effects of the first line injectable treatments who find cladribine's unique mode of administration appealing. People who are currently taking the available oral treatments for MS, dimethyl fumarate and fingolimod have spoken about why they would be interested in taking a less frequent tablet: "I am currently on tecfidera and have very little side effects but my only problem is memory. I am sometimes forgetful so having to take two tablets a day sometimes I miss them"; "Currently struggling to remember to take one tecfidera a day let alone the two I should be having!!" **Impact on quality of life compared with second line treatments** The other DMTs available include daclizumab, alemtuzumab and natalizumab. The latter two are the most effective licensed treatments for MS but they also carry a higher risk of side effects which for many is off putting. Natalizumab and daclizumab also consist of monthly infusions and injections respectively. Studies have found that the treatments which have the highest adherence rates are those which come in pill form

	and require less frequent administration, with pills preferred to injections by 93% of respondents in one study.[22] These also play a strong role in influencing a person's choice to start a treatment. For many people with more severe relapsing MS, alemtuzumab is seen as undesirable due to the common side effect of developing thyroid problems. This affects as many as 40% of people and in turn requires lifelong medication to treat.[23] Understandably, this puts off many despite alemtuzumab's proven effectiveness at treating relapsing MS: *"Lemtrada is another DMD I'm considering and although it is a more effective treatment the potential side effects (thyroid problems, IPT) may perhaps rule it out as an option for me, therefore Cladribine would again be preferable."* Cladribine's 6 month wash out period also means that someone taking it would be able to safely get pregnant 6 months after taking the final course. Currently the only other treatment which is recommended as safe to take while pregnant is glatiramer acetate, as well as alemtuzumab, which have a four month wash out period, so another more effective option which can be taken over a two year period would mean more women would be able to plan for a family without risking coming off treatment. Natalizumab also comes with a higher risk of serious side effects including PML (progressive multifocal leukoencephalopathy), which one in four can die from. People who have JC virus are at a higher risk of getting PML and are therefore less suitable candidates for taking natalizumab. Cladribine comes with relatively few serious side effects. In 2011 there were concerns that cladribine might be linked to an increased cancer risk, but long term studies have shown that cladribine does not increase the risk of cancer compared with other DMTs.

22 Utz et al, Patient preferences for disease-modifying drugs in multiple sclerosis therapy: a choice-based conjoint analysis, 2014, *Therapeutic Advances in Neurological Disorders* , Vol 7, Issue 6, pp. 263 – 275.

23 Udiawar, M, & Bolusani, H. Alemtuzumab and thyroid dysfunction in patients with multiple sclerosis: experience in a university hospital, Society for Endocrinology BES 2014

	Helping people with MS to remain in work In an MS Society survey we found that, at some point, a relapse had prevented 82% of people with MS from carrying out their work duties (paid employment) and that a further 89% were unable to fulfil their usual roles and responsibilities during a relapse. Over half of the respondents reported that a relapse often or always has an impact on their ability to carry out their work duties.[24] A positive appraisal of cladribine would increase the number of treatments available for people with MS and therefore increase the likelihood that more people identify DMTs which best suit their MS. This would result in more people effectively slowing the progression of disability and enjoying a fulfilling work life for longer. **Positive impact on lifestyle and carers** People with MS often need support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. At times of relapses and as disability progresses the need for this support increases and the impact on carers can be greater. Recent research by the MS Society on the needs of people with MS who received care, support or assistance from a friend or family member had increased from 71% to 85% from 2013 to 2016.[25] The effect MS has, not only on the person's life that has the condition, but also on those close to them is significant. As cladribine could potentially represent a new highly effective treatment it would increase the chance of people finding a DMT which works for them and lead to a reduction on the reliance on carers as more people are treated.

[24] MS Society's 'Perspectives of people with MS on relapses and disease modifying drugs', 2010.
[25] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	While cladribine has an appealing mode of administration for many people with MS, it has to be tailored to each individual based on their weight and could potentially be confusing to follow instructions. The importance of sticking to the correct treatment regimen including the follow up blood tests needs to be adhered to. It is important that the pharmaceutical company effectively manage these potential issues. More general side effects recorded in the clinical trials included headaches and symptoms of the common cold. Opportunistic infections, particularly herpes virus infections, were more common in people taking cladribine.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	People who are more at risk of the more serious side effects associated with alemtuzumab or natalizumab could benefit more from taking cladribine. People who have needle phobia and have continued to have disease activity while taking the other available oral treatments.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and	

the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Cladribine has shown to be highly effective at reducing relapses, brain atrophy and disability progression in clinical trials and follow up studies.
- The mode of administration which consists of two courses of pills offers an innovative new way to take treatment for MS. Studies have highlighted the importance of oral treatments and less frequent administration in deciding treatment preferences.
- 44% of people who could potentially benefit from a DMT are not taking one currently, so more DMT options mean it is more likely that people are able to find a treatment that works for them, improving adherence and efficacy overall. This has been witnessed with the uptake of DMTs increasing in recent years with the increase of available options.
- Evidence shows the importance of treating early with a DMT in reducing relapses and slowing disability progression.

- DMTs enable people with MS to take control of their lives and maintain their independence, thereby reducing productivity and societal costs associated with living with MS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

[ID64] Cladribine tablets for treating relapsing-remitting multiple sclerosis

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	Information Management Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding and rely on donations, fundraising and gifts in wills to fund our services.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, concern about switching to a new disease modifying drug (DMD), dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses.

carers to include in your submission?	This gives us a valuable insight into the wide range of issues that are important to people with relapsing remitting MS. We have also discussed cladribine treatment with people currently receiving injections as an off-licence treatment.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations. MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will have relapsing remitting MS (RRMS). MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms. Many of these invisible symptoms are sensitive

	areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends. In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. For example, a caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS. Research evidence supports the treatment of people with relapsing remitting MS with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	MS care involves a mix of clinical management of symptoms, responsive services to manage relapses and other acute deteriorations, therapies including physiotherapy and occupational therapy, tailored, evidence based information, support for effective self-management and, for those with RRMS, access to the range of DMDs and support to make the choice that is right for their condition, their lifestyle and their treatment goals. The majority of people with RRMS are eager to start treatment with one of the DMDs and aware of the importance of starting treatment soon after diagnosis. A number of DMDs are available for relapsing remitting MS: • beta interferons • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • daclizumab • natalizumab • alemtuzumab It is not possible to say which of these treatments are preferred; the widening range of DMDs gives greater scope for personalised treatments. If MS remains active despite taking one of the DMDs there is more potential to switch to a treatment with a different mechanism of action. Different responses to DMDs from one person to another are not easily captured in clinical trial data but are important to address in clinical practice. Through different aspects of our work with people affected by MS, we are aware that a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of

	the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. People with MS rely heavily on their MS specialist team to provide information and guidance to help with treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.
8. Is there an unmet need for patients with this condition?	Clearly, the most significant unmet need for people with MS is a cure. In the absence of a cure, people with MS want to live a life free from the impact of their disease. For many people, the ultimate goal of taking one of the DMDs is to reduce their risk of disease progression and future disability. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress that relapses cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to DMDs. For those people with very active relapsing MS - either rapidly evolving severe or highly active despite treatment - the side effects associated with the current, more effective DMDs is a cause for concern, for example the risk of PML with natalizumab and secondary autoimmune conditions with alemtuzumab. For people with very active relapsing MS, the option to switch to a more effective DMD with minimal or reversible side effects would be a major benefit. Remaining in employment is of critical importance to people with MS. Within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and psychological consequences. Cost effectiveness calculations do not take account of the burden of loss of work on the individual, their family and society.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	People with MS have highlighted the following as advantages of cladribine treatment: **Reducing the risk of relapses** In CLARITY, a large phase III study, cladribine reduced relapse rates by 58% more than placebo. Although it is difficult to make direct comparisons, this efficacy appears to be equivalent to or greater than other oral DMDs. **Reducing invisible MS activity** In the CLARITY study, cladribine reduced lesion count by 74% compared to placebo. **Reducing disability progression** The risk of 3 month sustained disability progression was reduced by 33% compared to placebo. **No evidence of disease activity** In a post-hoc analysis of CLARITY, a significantly greater proportion of patients treated with cladribine remained disease activity-free (no relapses, no 3 month sustained disability increase, no active MRI lesions); at 96 weeks 44.2% were free of disease activity compared to 15.8% in the placebo group. **Novel treatment schedule** Cladribine is taken orally, which has been shown to be a route of administration preferred by the majority of people with RRMS. The recommended dosing schedule has not been confirmed but it is expected to be two short courses, requiring 10 days of treatment in year 1 and year 2. This will result in decreased overall service usage and greatly reduce the risk of forgetting to take medication as occurs with more frequent, for example daily, dosing required with other DMDs. Taking cladribine as pills will avoid the need to travel to a hospital clinic for treatment. **Benefit and risk balance**

	So far, few side effects have been reported from clinical trials. There have been no reports of progressive multifocal leukoencephalopathy or opportunistic infections and cladribine has not been reported to cause secondary autoimmune side effects. The combination of relatively high efficacy and low side effects offers significant benefits over other more effective DMDs, such as natalizumab and alemtuzumab. **Innovative mechanism of action** Several aspects of cladribine's mechanism of action make it a valuable additional treatment choice for people with relapsing MS. Cladribine works by interfering with DNA synthesis and repair resulting in a selective and gradual reduction in the numbers of T and B lymphocytes. This avoids the infusion reaction caused by cell lysis experienced during alemtuzumab treatment. The components of the immune system involved with fighting infections are largely spared, reducing the risk of infections after treatment. The experience of one particular person illustrates the advantages of cladribine treatment: Shortly after diagnosis, this young man started treatment with a beta interferon, Rebif. Because of continued MS activity he was switched to Gilenya but had had to stop treatment because of serious and persistent liver problems. Natalizumab was considered but rejected on advice from his consultant because he was at high risk of developing PML. As a result, he did not take any DMDs for several years and experienced relapses approximately every three months. This had a particularly significant emotional impact for himself, his wife and young family and he was unable to continue working. He switched neurologist and was offered off-licence cladribine given by injections. He had his first course of treatments in 2014 and the second in 2015 with nothing since. Because cladribine was given as injections, he had to attend a hospital clinic, but found the injections very straight forward and had minimal reactions to the treatment. He recognised that when cladribine is available as tablets, these will be taken at home which will be much more convenient. The fact that tablets, like the injections, will be taken as two short courses in year 1 and 2 is also attractive as it leaves him free to get on with life without a daily reminder of MS. Since starting cladribine, his MS has been much more stable, with just one relapse, keeping him on an "even keel", his emotional well-being, family and social life have greatly improved. He will be seeing his

	neurologist in the autumn to review his MS activity and decide whether a further course of cladribine injections is necessary. Overall, he is very grateful to have been offered cladribine treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines. Overall, the potential risk of side effects from individual drugs tends to be the biggest barrier to starting a treatment. The previous refusal of a marketing authorisation for cladribine on grounds of safety is likely to be a cause for concern. While some people will be reluctant to take cladribine because of this, we anticipate that people who are suitable for cladribine will be reassured by an explanation of how the original refusal has been reversed.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We are submitting this response in advance of publication of full prescribing information from the EMA. However, at the time that cladribine was refused marketing authorisation it was being considered for people with high disease activity or people with active MS despite treatment with other DMDs. Post-hoc analysis of the CLARITY study show that cladribine was equally effective in all sub-groups.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None
Other issues	
13. Are there any other issues that you would like the committee to consider?	Cladribine has a different mechanism of action to other DMDs. Given the heterogeneous nature of MS, both in disease course and in response to treatments, a broadening range of drugs which work in different ways increases the potential for personalisation of treatment. Two short courses of tablets taken in year 1 and year 2 offers an alternative dosing schedule to other DMDs, increasing scope to tailor treatment to individual needs.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • MS is a complex and unpredictable condition which has an impact on all aspects of life; early, proactive treatment is essential to prevent future disability • combination of high efficacy and low level of serious side effects make cladribine an attractive alternative to other more effective DMDs • cladribine offers a novel treatment schedule, aiding adherence and minimising service usage	

- as with other DMDs an individual and their MS team will need to consider the risks and benefits of cladribine
- adding cladribine to the range of DMDs gives greater scope for personalisation of treatments

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Cladribine tablets for treating relapsing-remitting multiple sclerosis

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Neurologists (ABN)**

3. Job title or position	**Consultant Neurologist and member of the ABN Neuroinflammatory Advisory Group**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The ABN is an organisation to which neurologists and neurologists in training may join and whose remit is to develop neurological services in the UK, support neurological training and development and education. It is funded by its members through subscription and has developed national guidelines for the use of disease modifying therapies in MS and advises the NHS/Department of Health on neurological issues and provision in the UK.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	The therapy has shown in clinical trial that it is capable of reducing relapses and slowing disability progression in relapsing-remitting (RR) multiple sclerosis. The treatment aim for clinicians in RR MS is to stop relapses, stop formation of new MRI activity on T2 and post Gadolinium contrast T1 scans and stabilise disability in patients.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	As a clinician treating RR MS a significant treatment response may be considered to be: (1) a significant reduction/stop in relapses; (2) No evidence of new MRI activity and (3) disability stabilisation with no progression.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Although other therapies do exist for RR MS there is unmet need. Firstly, no current therapies can completely prevent disease 'breakthrough' either by new relapse, MRI activity or clinical deterioration. Secondly, significant medium term and long-term risk exists for patients with a number of the currently available therapies. Thirdly, people with RR MS may not be able to take some or all current therapies either because they may be at greater risk of a significant safety concern or they have already been exposed to a therapy and had disease breakthrough. Finally, from a patient perspective a number of current therapies for some may be too 'intensive' either in their administration (e.g. requiring regular hospital infusions) or monitoring (requiring frequent – for example monthly – blood testing) which although may offer the patient a possibility of disease control does so at an unacceptable level of intrusion into lifestyle and quality of life.
What is the expected place of the technology in current practice?	
9. How is the condition	Widely accepted strategy is the use of disease modifying therapies (DMT)s preferably early in the course of RR MS (but there is still value treating at other stages of RR MS) where there is evidence of inflammatory

currently treated in the NHS?	disease activity usually as evidenced by the presence of clinical relapses and/or new MRI activity.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, Giovannoni G, Miller D, Rashid W, Schmierer K, Shehu A, Silber E, Young C, Zajicek J. Pract Neurol. 2015 Aug;15(4):273-9.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Broadly there is a defined pathway of care in which some DMTs are specific to 'first-line' use usually in patients of lower/moderate disease activity and other agents reserved for 'second-line' either for treatment 'failure' from one of the first line agents or used as a first therapy in patients who are specifically felt by defined criteria to have high disease 'activity'. There is some degree of uncertainty or difference as several agents exist in each space so there is variance between patients as to which agents are used but broadly a consensus has emerged based on the clinical guidelines that are in existence as detailed above in this section.
• What impact would the technology have on the current pathway of care?	This therapy would be a potentially effective therapy for treating inflammatory active RR MS. Although other drugs do exist in this space it is likely this therapy will make an impact as its safety profile in comparison to its efficacy in trial data looks extremely favourable and also its administration (intermittent short courses of tablets every six months) and proposed intensity of monitoring would appear to be favourable in comparison to a number of existing DMTs.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This therapy would fit in with other current NHS available therapies for inflammatory active RR MS.

• How does healthcare resource use differ between the technology and current care?	There is some potential with this technology for a lower degree of monitoring and administration intensity in comparison to other therapies that exist in this space – for example alemtuzumab and natalizumab. Potentially this could mean a reduced number of visits for day case administration of therapy and monitoring visits either to a specialist nurse or clinician.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care from designated neuroscience centres which have the expertise and MS-specialist capacity to build up an acceptable level of therapy specific knowledge, correctly identify suitable potential patients and safely monitor risk associated with the therapy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This potentially may be subject to local variance. A potential advantage of this technology is that it is an oral medication and hence would not impact on current secondary care infusion capacity. Sufficient monitoring capacity will need to be in place and additionally as the technology is an infrequent oral medication there will need to be a mechanism in place for delivery of the medication to the patient and clear determination that the therapy has been administered.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	It is possible that the clinical results may be no better than currently available higher efficacy/second line therapies such as alemtuzumab and natalizumab. However, there are potentially clear benefits to some patients and clinicians in terms of its infrequent oral method of delivery and likely intensity of monitoring and level of side effects/safety as determined by currently available trial data.
• Do you expect the technology to increase length of life more than current care?	Unlikely – MS as a chronic condition is relatively insensitive in showing impact of DMTs on length of life.
• Do you expect the	Yes, the mode of administration, intensity of monitoring and apparent level of safety in comparison to

technology to increase health-related quality of life more than current care?	certain equivalent therapies in terms of efficacy has the potential to favourably impact on quality of life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As a technology that reduces immune mediated inflammatory response in MS which drives clinical relapses and disability this therapy should only be used in patients who demonstrate evidence of current inflammatory activity.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Potentially easier than some other equivalent (in efficacy) DMTs for patients and healthcare professionals as an infrequent oral therapy that may not require monthly blood monitoring. Pre-screening for infections such as TB may be required.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Start rules in line with other equivalent therapies will be needed. Stopping criteria already exist for DMTs and this technology should be subject to these. No definite additional testing is required although it is increasingly common practice for clinicians to assess treatment effect for all DMTs with MRI initially at yearly intervals.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The potential favourable quality of life impact for the patient for having a therapy that needs just tablet medication at six-monthly intervals as opposed to a regular therapy may be missed
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	No other currently available oral DMT requires such infrequent administration in MS making this genuinely innovative for people with MS. Some people with MS may be either on a therapy which is impacting negatively on their quality of life because of the intensity of administration or monitoring or safety concerns or may be on no therapy altogether because of the inability to commit to current DMT administration or

benefits and how might it improve the way that current need is met?	monitoring schedules or concern due to an unacceptable level of perceived risk.
• Is the technology a 'step-change' in the management of the condition?	Yes, for reasons above
• Does the use of the technology address any particular unmet need of the patient population?	Other therapies do exist in this space – the potential unmet need this therapy may address is in respect to its infrequent oral administration.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The therapy is generally well tolerated but pre-treatment advice and surveillance will be required regarding infections such as TB and herpes group of viruses. Careful and clear counselling will be needed with regards to safety in pregnancy especially as the therapies remains active for up to six months. There was initial concern at time of initial license application with regards to a potential link with neoplasms. This appears not to be a significant issue on further re-analysis of longer term data with the number of neoplasms experienced by patients on Cladribine not being significantly different to expected background frequency.
Sources of evidence	
18. Do the clinical trials on the	The main trial (Giovannoni et al, NEJM 2010) was a placebo controlled Phase III study in RR MS. Hence

technology reflect current UK clinical practice?	there is some uncertainty as to how much more effective this technology is in comparison with a standard first line comparator.
• If not, how could the results be extrapolated to the UK setting?	Yes – the outcome data (relapse, MRI and disability) appear to be in line with other second line, higher efficacy therapies. In addition, post hoc analysis and longer-term data would appear to show efficacy in higher disease activity patients.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Composite of relapses, MRI activity and disability – yes this was measured in trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	MRI was the main surrogate outcome – drawbacks are recognised such as incomplete correlation to clinical outcomes – but MRI is widely accepted in clinical community as a relevant surrogate outcome measure. There is evidence that early MRI may predict long-term clinical outcome and this is often used as a justification for early treatment in this patient group.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA32, TA127, TA254, TA303, TA312, TA320?	No
21. How do data on real-world experience compare with the trial data?	Such data for this technology is too limited to give an accurate answer.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23a How are the following groups defined in clinical practice in the NHS: *Please state clinical symptoms (such as the number of relapses), imaging outcomes and previous treatments if relevant for definition of subgroup.* • People with active relapsing-remitting multiple sclerosis • People with highly active relapsing-	RR MS is a clinical phenotype described in a consensus paper published in 1996 (Lublin and Reingold, Neurology 1996). It describes a patient group who from presentation manifest symptoms which can wax and wane over weeks or even months/years with relative stability between events (relapses). Disease activity (defined by frequency of relapses and increasingly presence of new MRI lesions) can vary between patients and as a therapy which appears to primarily modify the immune mediated inflammatory response in MS it is likely patients who exhibit such pathology e.g. evidence of relapse and/or new MRI activity for instance in the last 12 months will most benefit from the technology. Trial evidence would suggest the RR MS group deemed to be highly active either second line or first line will most benefit. The rapidly evolving severe RR MS group are also likely to most significantly benefit.

remitting multiple sclerosis • People with rapidly evolving severe relapsing-remitting multiple sclerosis 23b Are there any overlaps between the groups list in 23a? If so, please specify. 23c Are there any other groups of people with relapsing-remitting multiple sclerosis not listed in 23a? If so, please specify.	
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Good efficacy
- Infrequent administration
- Oral therapy
- Low intensity monitoring
- Acceptable medium-term safety profile

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Cladribine tablets for treating relapsing-remitting multiple sclerosis [ID64]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Malcolm Qualie**
2. Name of organisation	**NHS England**

3. Job title or position	**Pharmacy Lead, Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England has published a policy on the use of medicines in MS and a service specification for neuroscience centres (which in part includes MS services) which can be found here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-d/d04/ In addition, NHS England plan to publish an algorithm this year to cover all funded directly acting MS therapies.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	The pathway of care is not yet well defined since the introduction of the new directly acting medicines over the last 3 to 4 years. Cladribine is considered in the more effective group of therapies for multiple sclerosis (alongside alemtuzumab, natalizumab and fingolimod). Opinion is divided between those who advocate the use of cladrabine first-line in regular multiple sclerosis (similar to alemtuzumab's indication) versus restricting its use for more aggressive suptypes of disease (similar to the "rapidly evolving" and "highly active" indications for natalizumab and fingolimod respectively).

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	Cladribine would offer an alternative option to patients with highly active disease. It may suit those patients who would rather not be on long term oral medication or for those who find it difficult to travel for intravenous medication or who would prefer not to receive such medication.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	It is currently not being used outside any Pharma sponsored clinical trials.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If it is deemed cost effective by NICE it will be made available to suitable patients.

• How does healthcare resource use differ between the technology and current care?	Cladribine is administered in two short bursts of treatment in the first and second years. It is anticipated that no further therapy will be required in the following two years. This is similar to alemtuzumab which is delivered over two cycles in the first two years but the third cycle may be required in either year 3 or 4 and it is IV vs oral. Natalizumab is a monthly intravenous medication and fingolimod, whilst oral, is a daily treatment. Therefore healthcare resource is likely to significantly reduce. In addition, the number of blood tests required are lower cf the other 3 options.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Cladribine can be administered (taken) in the patients home.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No, all testing required to highlight reduced effect is already in place. The main indicator of reduced effect is relapse ie acute attacks.
10. What is the outcome of any evaluations or audits of the use	No audits have taken place.

of the technology?	
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that I'm aware of.
11b. Consider whether these issues are different from issues with current care and why.	n/a

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Cladribine tablets for treating relapsing-remitting multiple sclerosis ID64

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	
2. Are you (please tick all that apply):	**x**☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	MS SOCIETY
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't **x**☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **x**☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	x☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Uncertain you never know what tomorrow will be like, complex – hard to understand and manage frustrating, few people understand the many hidden symptoms. All depends on the individual Mser and their consultant and hio successful that relationship is.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and	Depends where you live and your attitude to MS. Widely different everywhere, and different between consultants, get the right hospital and trust and consultant then it's a manageable disease. Get left out and linked to a conservative trust, or consultant even in the London teaching hospital circuit and life can

care available on the NHS?	be pretty bad.
10. Is there an unmet need for patients with this condition?	Drugs for Advanced MS and Primary Progressive MS and CIS pending more relapses A treatment style and integrate management which understands that that better management slowing progression and even remylination will probably come from a combination of drugs not just one on its own.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The tablet delivery, reduction in hospital visits, the good safety profile especially from a patient point of view no more site reactions. It works in a different way And seems to be more inline with new approaches to MS as an immune disease.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Loss of contact with consultant. Might be expensive for some struggling Trusts,
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and	women wanting to have a family who wikll kniow this type of drug will have left their system after treatment, people who have had site reactions, anyone who works, people with CIS

explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Cost which will determine if we can get another MS drug MS type restrictions, if it's just for highly active RRMS why not CIS and Advanced MS where age becimes a factor. Older people probably wont have been included in trials as per the current culture, yet more people with ms are living better lives so age should not be a barrier.
Other issues	
15. Are there any other issues that you would like the committee to consider?	Not sure that any patient who knows, or finds out, that cladribine was initially rejected on safety grounds will be happy with the change of regulator's minds. How do you want to reassure people as cancer scares stick/ I have only had the injections not tablet but still find it no fuss.
Key messages	
17. In up to 5 bullet points, please summarise the key messages of your statement: • Good, easy drug to help people self manage their MS - if it's cost effective in tablet form • safe drug great for nervous patients, keeping on with treatment and could be used to promote combination therapy • meets current new thinking into the immune drivers of MS • shouldn't it be restricted to RRMS when it has promise as a combination drug, urgent trials in other types needed.	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Multiple sclerosis - cladribine [ID64]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	**Amy Mackelden**
2. Are you (please tick all that apply):	**x** a patient with the condition? a carer of a patient with the condition? a patient organisation employee or volunteer? other (please specify):
3. Name of your nominating organisation	MS Trust
4. Did your nominating organisation submit a submission?	**x** yes, they did no, they didn't I don't know

5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it no, I disagree with it I agree with some of it, but disagree with some of it other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	**x** I have personal experience of the condition I have personal experience of the technology being appraised I have other relevant personal experience. Please specify what other experience: I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As relapsing remitting MS is a a degenerative condition, living with it can be challenging. There's a lot of stress in knowing that the disease could, at any moment, worsen, and that the trajectory of MS is so unpredictable. There are other day to day symptoms, that vary in severity, including tingling and numbness all over my body, limited mobility, immense fatigue that affects my ability to work in a regular job, emotional issues, anxiety and depression, and unpredictable, stabbing nerve pain. As the DMT (Tysabri) I am currently on has been working for three years, my condition has not worsened in that time, and I am currently able to live a fairly “normal” life.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I have been very lucky, and was prescribed Tysabri very quickly after diagnosis. Not everyone is as lucky, and the available drugs offered often vary. I attend a clinic every four weeks at Southampton General, and am administered the drug routinely, and my condition is monitoring. The care available to me, and the constant monitoring (MRI once a year) has been great.
10. Is there an unmet need for patients with this condition?	Having a wider selection of DMTs to choose from, particularly as they carry such different risks, is a good thing.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Ease - pill form. No need to visit a hospital. Ability to manage own condition day to day.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Having to take regular pills, as opposed to one hospital trip a month, and then several weeks without needing treatment.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If	Patients who live far away from hospitals that administer certain DMTs would benefit from being able to manage their drugs remotely.

so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	

Topic-specific questions	

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: □ MS is an unpredictable illness. □ Having access to a range of treatments greatly improves a patient's life. □ Being able to administer the drug orally, at home, rather than via hospital or clinic visits, is positive. □ □

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

ID64 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/10

Completed 21st August 2017

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Rui Duarte, Health Technology Assessment Lead, LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LRiG, University of Liverpool

Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analyst), LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Jeremy Hobart, Consultant Neurologist, Plymouth Hospitals NHS Trust

Ian Pomeroy, Consultant Neurologist, The Walton Centre NHS Foundation Trust

Correspondence to: Rui Duarte, Health Technology Assessment Lead, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 21st August 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/194/10

Declared competing interests of the authors: Dr Hobart has received consultancy fees and speaking fees from Genzyme, Biogen and Roche; reimbursement fees from Genzyme, Biogen and Novartis to attend conferences; hospitality fees and research funds from Genzyme, Biogen and Acorda; funding for a member of staff from Acorda and Biogen; and funds for the running of a departmental unit from Genzyme, Merck and Biogen. Dr Pomeroy has received reimbursement fees from Biogen and Novartis to attend conferences.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Duarte R, Mahon J, Nevitt S, Greenhalgh J, Boland A, Beale S, Kotas E, McEntee J, Hobart J and Pomeroy I. Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]: A Single Technology Appraisal. LRiG, University of Liverpool, 2017

Contributions of authors:

Rui Duarte	Critical appraisal and summary of the clinical evidence
James Mahon	Critical appraisal of the economic evidence
Sarah Nevitt	Critical appraisal of the statistical evidence
Janette Greenhalgh	Critical appraisal of the clinical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence
Sophie Beale	Critical appraisal of the economic evidence
Eleanor Kotas	Critical appraisal of the company's search strategies
Joanne McEntee	Critical appraisal of the company submission
Jeremy Hobart	Clinical advice and critical appraisal of the clinical sections of the company submission
Ian Pomeroy	Clinical advice and critical appraisal of the report

All authors read and commented on draft versions of this report.

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
AC	Appraisal Committee
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARR	annualised relapse rate
AST	aspartate aminotransferase
BCMS	British Columbia Multiple Sclerosis
BNF	British National Formulary
BSC	best supportive care
CDP	confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CS	company submission
CSR	clinical study report
DIC	deviance information criterion
DMF	dimethyl fumarate
DMT	disease-modifying therapy
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimension
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FDA	Food and Drug Administration
FE	fixed-effects
GA	glatiramer acetate
Gd+	gadolinium enhancing
H	high-dose cladribine tablets over 48 weeks
HBV	hepatitis B virus
HCV	hepatitis C virus
HDA	high disease activity
HR	hazard ratio
HRQoL	health-related quality of life
HSU	health state utility
ICER	incremental cost effectiveness ratio
IFN-β1a	interferon-β1a
IPE	iterative parameter estimation
ITT	intention-to-treat
JC virus	John Cunningham virus
K-M	Kaplan-Meier
KFS	Kurtzke Functional systems
L	low-dose cladribine tablets over 48 weeks
LCI	lower bound of 95% confidence interval
LOCF	last observation carried forward
LYs	life years
MCMC	Markov Chain Monte Carlo
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSQOL-54	multiple sclerosis quality of life-54
NEDA-3	no evidence of disease activity
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ONS	Office for National Statistics
P	placebo

PAS	patient access scheme
PH	proportional hazards
PML	progressive multifocal leukoencephalopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
RCT	randomised controlled trial
RE	random-effects
RES	rapidly-evolving severe
RF	relapse-free
RPDFTM	rank preserving structural failure time model
RR	rate ratio
RRMS	relapsing-remitting multiple sclerosis
SD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-Item Short Form Survey
SLR	systematic literature review
SmPC	summary of product characteristics
SOT	sub-optimally treated
SPMS	secondary progressive multiple sclerosis
STA	single technology appraisal
TA	technology appraisal
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse events
TSAP	trial statistical analysis plan
UCI	upper bound of 95% confidence interval
VAS	visual analogue scale
vs	versus

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck in support of the use of cladribine tablets (mavenclad®) for two subgroups of people with relapsing-remitting multiple sclerosis (RRMS), namely, rapidly-evolving severe (RES) and sub-optimally treated (SOT) patients.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is adults with RRMS. The company has provided clinical evidence for people with RRMS, people with high disease activity (HDA-RRMS) and people with RES-RRMS and SOT-RRMS; the latter three subgroups were post-hoc classifications of people in the CLARITY trial.

Intervention

In June 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features; people with RES-RRMS and SOT-RRMS are included in the population with highly active relapsing MS.

Cladribine tablets are administered orally. The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.

Comparators

The final scope issued by NICE sets out different comparators for (i) people with RRMS who have not had previous treatment, (ii) people with RRMS who have received previous treatment, (iii) people with RES-RRMS and (iv) people with highly active RRMS despite previous treatment (i.e., people with SOT-RRMS).

No evidence was provided in the company submission (CS) for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

The company carried out network meta-analyses (NMAs) using data from four populations: people with RRMS, people with HDA-RRMS, RES-RRMS and SOT-RRMS. The company compared cladribine tablets with a range of disease-modifying treatments (DMTs) including alemtuzumab, natalizumab, fingolimod and daclizumab.

Outcomes

Direct evidence is available from the CLARITY trial for the outcomes of qualifying annualised relapse rate (ARR), severity of relapse, disability, adverse events (AEs) and health-related quality of life (HRQoL). Freedom from disease activity using the 'no evidence of disease activity' (NEDA-3) composite clinical outcome, time to 6-month confirmed disability progression (CDP) and proportion of people with 6-month CDP were evaluated retrospectively.

Other considerations

- No evidence has been provided in the CS for the people described in the subgroup section of the final scope issued by NICE
- A patient access scheme (PAS) application for cladribine tablets is not included in the CS
- The company has not presented a case for cladribine tablets to be assessed against the NICE End of Life criteria
- The company has not identified any equity or equality issues.

1.3 Summary of the clinical evidence submitted by the company

The company presents evidence for the clinical effectiveness of cladribine tablets from the CLARITY trial. The CLARITY trial was a randomised, double-blind, placebo-controlled, multicentre, phase III trial designed to investigate the use of cladribine tablets in people with RRMS.

Direct evidence

The results from the CLARITY trial show that treatment with cladribine tablets is associated with a statistically significant improvement in qualifying ARR compared to placebo in the intention-to-treat (ITT) population, HDA-RRMS and RES-RRMS subgroups but not in the SOT-RRMS subgroup.

For secondary outcomes relating to relapse, cladribine tablets are shown to have a numerical advantage over placebo; these advantages are statistically significant within the ITT population, HDA-RRMS and RES-RRMS subgroups but not in the SOT-RRMS subgroup.

For secondary outcomes relating to disability progression, cladribine tablets are shown to have a numerical advantage over placebo; these numerical advantages are statistically significant

within the ITT population and HDA-RRMS subgroup but not for the RES-RRMS and SOT-RRMS subgroups.

Results of the composite, post-hoc, efficacy outcome NEDA-3, defined as 'no evidence of disease activity', showed numerically and statistically significant advantages for cladribine tablets compared to placebo in the ITT population and in all three subgroups.

In the overall population of the CLARITY trial, the proportions of treatment-emergent AEs (TEAEs) were similar in the cladribine tablets arm and in the placebo arm (80.7% and 73.3% respectively). Consistent with the mechanism of action of cladribine tablets, substantially more patients in the cladribine tablets arm compared with patients in the placebo arm experienced lymphopenia (21.6% versus 1.8% respectively) and leukopenia (5.6% versus 0.7% respectively).

Indirect evidence

The results of the NMAs that were undertaken for the efficacy outcomes of interest (qualifying ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) generally show numerical and/or statistically significant advantages for cladribine tablets compared to most comparators, except for alemtuzumab and natalizumab. For alemtuzumab and natalizumab, the NMA results generally show a numerical disadvantage for cladribine tablets. However, there were very limited data available for the key efficacy outcomes for the RES-RRMS and SOT-RRMS subgroups.

Results of an additional meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS subgroups, predict that all comparators are less effective in the SOT-RRMS subgroup than in the RES-RRMS subgroup. Furthermore, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy in either subgroup.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The CLARITY trial was of good quality and was well conducted; participant characteristics were balanced across the two trial arms and the pre-planned statistical methods used were generally appropriate.

The clinical effectiveness evidence presented within the CS is mainly based upon three subgroups that were defined post-hoc as they were not considered to be relevant at the time of the original analysis of the CLARITY trial data. In addition, three post-hoc outcomes (NEDA-

3, time to 6-month CDP and proportion of people with 6-month CDP) were presented within the CS which were not included in the original analyses of the CLARITY trial data. The ERG understands why the company defined subgroups and outcomes retrospectively, i.e., to allow comparisons with the comparators/populations specified in the final scope issued by NICE. However, the ERG notes that the sizes of the RES-RRMS (cladribine, n=50; placebo, n=41) and SOT-RRMS (cladribine, n=19; placebo n=32)) subgroups are small and it is therefore difficult to detect statistically significant differences in outcomes.

Indirect evidence

The ERG considers that the company's general approach to undertaking NMAs and meta-regression) were appropriate in terms of the trials and comparators included, the statistical methodology employed, the model selection criteria, the choice of most appropriate model, and the interpretation of results.

The results of the NMAs carried out by the company should be viewed with caution due to the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab in the RES-RRMS and SOT-RRMS populations.

The company also performed a meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS. However, in light of the company's stated objectives, the ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo model in Microsoft Excel to generate cost effectiveness evidence for the comparison of cladribine tablets versus other DMTs. Evidence has been generated for the RES-RRMS and SOT-RRMS subgroups and the choice of comparator DMT depends on whether patients are able to receive alemtuzumab. The comparators for patients with RES-RRMS who are able to receive alemtuzumab are alemtuzumab and natalizumab, otherwise the comparators are natalizumab and daclizumab. The comparators for patients with SOT-RRMS who are able to receive alemtuzumab are alemtuzumab and fingolimod, otherwise the comparators are fingolimod and daclizumab.

The company model is a simplified version of models used to inform previous NICE multiple sclerosis technology appraisals. The basic structure comprises 11 health states: 10 Expanded Disability Status Scale (EDSS) states and a single state for death from all causes. In each cycle period (1 year) the cohort is at risk of moving to a higher EDSS state, moving to a lower

EDSS state, remaining in the current EDSS state, or dying. This is referred to as the natural history model. Adjustments to this model are made to reflect the effect of treatment on patient experience (for example, relapse rates, effect of treatment on rate of progression between health states, waning of drug efficacy over time, discontinuation of treatment and HRQoL). The model time horizon is set at 50 years and the perspective is that of the UK NHS and Personal Social Services. Model outcomes have been measured in quality adjusted life years (QALYs), and both costs and QALYs have been discounted at an annual rate of 3.5%, as recommended by NICE.

Within the company model, patient experience is reflected using published data, data from the CLARITY and CLARITY-EXT trials, clinical advice, and results from the company's NMAs and meta-regression. Resource use and costs have been estimated using information from the CLARITY trial, published sources and advice from clinical experts. Full list prices have been used to represent the cost of all DMTs. The company is unaware of the patient access prices for daclizumab and fingolimod.

Using list prices, the company base case incremental cost effectiveness ratios (ICERs) for the comparisons of treatment with cladribine tablets versus all the comparator DMTs, for both the RES-RRMS and SOT-RRMS subgroups, show that treatment with cladribine tablets is dominant.

The company carried out a wide range of deterministic sensitivity analyses. Results show that incremental net health effects are most sensitive to variation in the effect of DMT on 6-month CDP. Other key drivers include the rate at which costs and outcomes are discounted, baseline risk, the adjustment factor applied to the natural history model to account for the faster EDSS progression of patients with RES-RRMS and treatment discontinuation.

The company undertook probabilistic sensitivity analyses to assess the uncertainty surrounding the parameter values used in the model. Results from these analyses support the company's base case results as, for each analysis, treatment with cladribine dominates all other DMTs.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that model outputs are of limited use to decision makers. The ERG's two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets (versus placebo, and versus all other DMTs considered by the company), and (ii) the inclusion of costs and benefits that are outwith the NICE reference case. Whilst changes to the model can

address the second of these issues, no data are available to address the uncertainty around clinical benefit.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence on cladribine tablets from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 19 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model).
- Confidence/credible intervals from the NMAs and meta-regression for cladribine tables and the other DMTs are wide. Even if the ERG had no concerns about the NMA and meta-regression, assessment of comparative effectiveness of cladribine tablets versus other DMTs would be speculative.
- After 2 years, the modelling of waning of treatment effectiveness, treatment discontinuation rates and efficacy of re-exposure to cladribine tablets or alemtuzumab, all of which have significant impact on overall effectiveness of each DMT, are almost entirely based on assumptions.
- The model submitted by the company only considers a single line of treatment. However, the ERG recognises that data to populate a more realistic lifetime model that includes multiple lines of treatment are not currently available.

The NICE reference case

- The NICE reference case stipulates that outcomes should reflect all direct health effects, whether for patients or for other people. However, costs (in the form of lost income) and health benefits (in the form of disutility associated with EDSS states and progression) to carers are included in the company model. The ERG considers that carers' lost income is not a direct cost and that health benefits to carers cannot be considered to be direct health benefits from treatment with cladribine tablets and that, therefore, neither should have been included in the company model.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical evidence

- The CLARITY trial was of good quality and was well conducted
- Participant characteristics were balanced across the two trial arms and the pre-planned statistical methods used were generally appropriate
- The methodological approach to the NMAs was generally appropriate.

Cost effectiveness evidence

- The company economic model, whilst difficult to check fully, appeared to be well constructed and fit for purpose
- Substantial effort had been taken to identify parameter values for the model.

1.7.2 Weaknesses and areas of uncertainty

Clinical evidence

- The HDA-RRMS, RES-RRMS and SOT-RRMS subgroups and three outcomes (NEDA-3, time to 6-month CDP and people with 6-month CDP) presented within the CS were not included in the original statistical analysis plan for the CLARITY trial
- The subgroup analyses were based on a small number of people
- The results from the NMAs are limited by the paucity of data available for the key efficacy outcomes
- The ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

Cost effectiveness evidence

- There is no statistically significant evidence of effectiveness of cladribine tablets compared to placebo for the SOT-RRMS subgroup to incorporate into the economic model
- For the RES-RRMS subgroup, no statistically significant evidence was presented that cladribine tablets affect 6-month CDP more than placebo. This is important as slowing disease progression is the single biggest driver of cost effectiveness for any DMT
- There is no robust statistically significant evidence that cladribine tablets are more effective at reducing qualifying ARR than any other DMT in the RES-RRMS subgroup
- Long-term efficacy for DMTs, their waning of effect, levels of treatment discontinuation, re-exposure rates and efficacy after re-exposure are essentially unknown
- Disutility values and the costs of informal carer were included in the model. The ERG considers that both of these are outside of the NICE reference case.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG considers that given the inherent uncertainty of the effectiveness evidence for cladribine tablets versus placebo and other DMTs, no changes could be made to the company

model that would generate robust cost effectiveness results. However, the ERG considers that some modifications can be made to the model to address some of the concerns raised in the ERG critique. For RES-RRMS these changes are:

- Modifications to qualifying ARR and 6-month CDP parameter values for cladribine tablets, alemtuzumab and daclizumab
- Setting the waning of treatment effect for cladribine equal to other DMTs
- Removing carers disutility
- Using alternative costs for EDSS states used in previous submissions
- Stopping treatment discontinuation for natalizumab and daclizumab after 2 years except if a patient reaches EDSS state 7.

Applying these changes over a 50-year time horizon results in:

- Treatment with cladribine tablets becoming dominated by alemtuzumab
- Treatment with cladribine tablets no longer dominating natalizumab, costing less (-£133,754) than natalizumab but generating fewer QALYs (-1.650) with an ICER per QALY **lost** of £81,050
- Treatment with cladribine tablets no longer dominating daclizumab, costing less (-£87,566) than daclizumab but generating fewer QALYs (-1.362) with an ICER per QALY **lost** of £64,269.

For interventions that are less costly and less effective (in terms of QALYs gained) than a comparator, the ICERs relate to the amount of money saved for every QALY that is lost by using the intervention rather than the comparator. When this is the case, an intervention will be considered cost effective if the ICER generated is **above** the willingness to pay threshold rather than below it.

In the absence of statistically significant trial evidence to show that treatment with cladribine is more effective than placebo for patients with SOT-RRMS for either 6-month CDP or qualifying ARR, there is no robust basis for any cost effectiveness results produced by an economic model.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Sections B.1.3.1 and B.1.3.2 of the company submission (CS)[1] include an overview of multiple sclerosis (MS) and a brief description of the effects of the disease on people with MS. Key points from these sections of the CS are included as bulleted items in Box 1. The Evidence Review Group (ERG) considers that these points are accurate but that they lack detail on the burden of MS to people, carers and society.

Box 1 Company overview of multiple sclerosis

- MS is the most common debilitating neurological disease among young adults.[2]
- Approximately 85% of people with MS initially present with relapsing-remitting multiple sclerosis (RRMS), which is characterised by periodic acute exacerbations of disease activity (relapses) followed by periods of remission.[3]
- Relapses in people with RRMS are unpredictable and are associated with inflammation and development of new focal lesions, followed by periods of remission, leading to partial or complete recovery.[3]
- Over time (typically 15-20 years following disease onset), most people with RRMS will enter a phase of progressive neurodegeneration, with or without periodic relapses, associated with the accumulation of permanent disability, termed secondary progressive MS (SPMS).[3-6] In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course.
- Some people with RRMS experience a more aggressive disease course. These people can be categorised as having high disease activity RRMS (HDA-RRMS); the definition of HDA-RRMS is evolving. HDA-RRMS can be associated with a constellation of clinical and imaging activities, including those defined by the European Medicines Agency (EMA) specifically for two other treatments for MS, natalizumab [7] and fingolimod:[8]
  - failure to respond to an adequate course of at least one disease-modifying therapy (DMT), presenting with at least one relapse in the previous year while on therapy and at least nine T2-hyperintense lesions or at least one gadolinium-enhancing lesion, or
  - treatment naïve with at least two disabling relapses in the last 1 year and at least one gadolinium-enhancing lesion or significant increase in T2-lesion load
- The time course for disease progression in RRMS is variable. The time it takes to reach an Expanded Disability Status Scale (EDSS) score of 6, noted as disability requiring assistance to walk, is reported to range between 15 years and 32 years from disease onset although there are multiple factors that can impact the time course of disease progression in RRMS including the age of the individual at disease onset, the initial disease course, and frequency of relapses.[6]
- In addition to clinical symptoms, people with RRMS may present with subclinical disease activity, in particular plaque lesions in the brain detected by magnetic resonance imaging (MRI), which often occur during remission. These lesions are indicative of active inflammatory disease activity and may predict disability and MS prognosis.[9]

Source: CS, Section B.1.3.1, Section B.1.3.2

The ERG notes that the final scope issued by NICE[10] describes the symptoms experienced by people with MS. The symptoms experienced by people with MS vary and might include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

The final scope issued by NICE[10] describes the relapsing-remitting form of multiple sclerosis (RRMS). It is stated in the scope that RRMS is characterised by periods of remission (when

symptoms are mild or disappear altogether) followed by relapses (which may or may not result in residual disability). Some people with RRMS can progress to develop secondary progressive multiple sclerosis (SPMS).

2.2 Critique of company's overview of current service provision

The company presents a brief overview of the clinical care pathway in Sections B.1.3.2 and B.1.3.3 of the CS and provides details of the McDonald diagnostic criteria for MS in Table 5 of the CS.[11] The ERG considers that the overview of the clinical care pathway in the CS is largely accurate.

The ERG notes that there is no current cure for MS and that RRMS is managed using disease-modifying therapies (DMTs). The aim of treatment with DMTs is to reduce the frequency and severity of relapses.

The company reports that the Association of British Neurologists (ABN)[12] classifies DMTs into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles). The DMTs in each category are listed in the CS (CS, Figure 6), and reproduced here in Figure 1. The company does not know whether the ABN will designate cladribine tablets as a Category 1 or Category 2 DMT. The company suggests that a new category might be needed (CS, p24). Clinical advice to the ERG is that cladribine tablets are likely to be considered as a Category 2 drug.

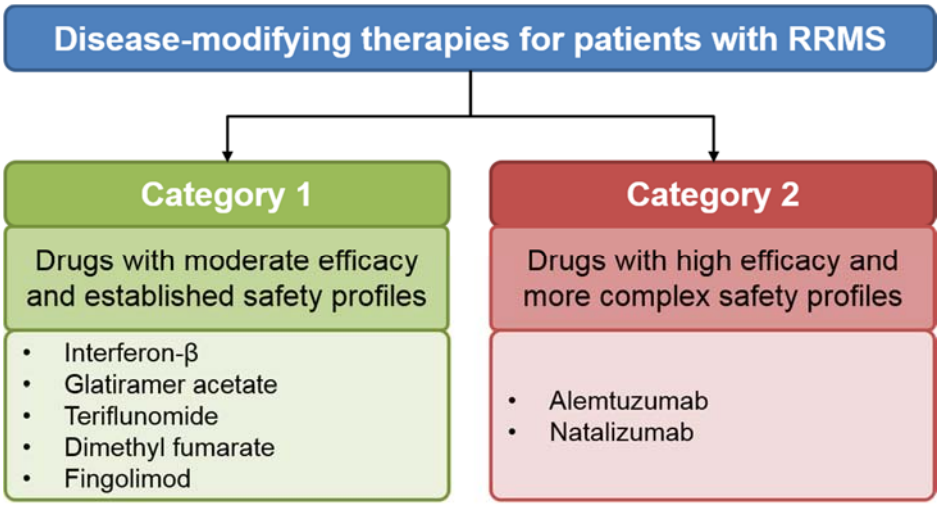


Figure 1 Categorisation of disease-modifying therapies according to the ABN guidelines

Source: CS, Figure 6

2.3 Indication / market authorisation

The company received a negative opinion in response to its 2009 marketing authorisation application to the European Medicines Agency (EMA)[13] for the treatment of people with RRMS

and to a subsequent application for conditional approval for the treatment of people with high disease activity RRMS (HDA-RRMS) in 2010 (CS, pp18-20). The company states that the Committee for Medicinal Products for Human Use (CHMP) acknowledged the efficacy benefits of treatment with cladribine tablets, but raised concerns about the safety profile (CS, p19). The company reports that the Food and Drug Administration (FDA) issued a complete response letter following the company's request in 2010 for conditional approval of the use of cladribine tablets to treat people with MS in the USA with HDA-RRMS.

A new marketing authorisation application was submitted to the EMA in June 2016 following the availability of new data (i.e. from the integrated safety analysis performed on combined data from the CLARITY, CLARITY-EXT and ORACLE trials, and the PREMIERE registry), which the company states 'has substantiated the positive clinical efficacy of cladribine tablets while also mitigating safety concerns previously identified by the CHMP' (CS, p20).

At the time the CS was submitted to NICE (26th June 2017), cladribine tablets did not have a marketing authorisation in Europe. The company had anticipated that the marketing authorisation for cladribine tablets would be for adults with HDA-RRMS (CS, p11). However, on the 22nd June 2017, the CHMP of the EMA[14] issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features. The company states throughout the CS that they were assuming that the marketing authorisation granted by the EMA would be for the HDA-RRMS population, which includes people with rapidly-evolving severe RRMS (RES-RRMS) and people with RRMS sub-optimal therapy (SOT-RRMS). The HDA-RRMS is a narrower population than the highly active relapsing MS population.

2.4 Summary of relevant clinical guidance and guidelines

The CS does not include details of relevant published guidance and treatment guidelines for MS. A summary of the available NICE guidance for technologies included as comparators in the final scope issued by NICE is provided in Table 1.

The ERG notes that although beta interferon and glatiramer acetate are not currently recommended by NICE for the treatment of people with MS, these therapies are available in the NHS through a risk sharing scheme arranged by the Department of Health.[10] Beta interferon and glatiramer acetate are being assessed as part of an ongoing multiple technology appraisal (TA32).[15]

Table 1 Summary of NICE guidance for comparators inlcuded in the final scope issued by NICE

NICE guidance	Title	Recommendation
TA32[16] (2002) Update in progress	Beta interferon and glatiramer acetate for the treatment of multiple sclerosis	Neither beta interferon nor glatiramer acetate are recommended for the treatment of MS in the NHS in England and Wales.
TA127[17] (2007)	Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis	Natalizumab is recommended as an option for the treatment of RES MS. RES MS is defined as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.
TA254[17] (2012)	Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis	Fingolimod is recommended as an option for the treatment of highly active RRMS in adults, only if: • patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and • the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.
TA303[17] (2013)	Teriflunomide for treating relapsing–remitting multiple sclerosis	Teriflunomide is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if: • patients do not have highly active or RES-RRMS and • the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
TA320[18] (2014)	Dimethyl fumarate for treating relapsing‑remitting multiple sclerosis	Dimethyl fumarate is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if: • patients do not have highly active RES-RRMS and • the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
TA312[19] (2014)	Alemtuzumab for treating relapsing‑remitting multiple sclerosis	Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active RRMS.
TA441[20] (2017)	Daclizumab for treating relapsing–remitting multiple sclerosis	Daclizumab is recommended as an option for treating multiple sclerosis in adults, only if: • the person has active RRMS previously treated with disease-modifying therapy, or RES-RRMS (that is, at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI) and • alemtuzumab is contraindicated or otherwise unsuitable and • the company provides the drug with the discount agreed in the patient access scheme.
ID809[15] (in development)	Multiple sclerosis - interferon beta, glatiramer acetate (review TA32)	Publication date to be advised

MRI=magnetic resonance imaging; MS=multiple sclerosis; RES=rapidly-evolving severe; RRMS=relapsing–remitting multiple sclerosis; TA=technology appraisal

2.5 Innovation

The company puts forward the case that treatment with cladribine tablets is an innovative treatment (CS, section B.2.12). The company's case is set out in Box 2.

Box 2 Company's case for cladribine tablets as an innovative treatment

The key innovations for people with MS relate to the drug's posology:

- Short course, oral treatment: cladribine tablets require two short courses of oral treatment over 2 years, which could be self-administered at home, providing efficacy over a total of 4 years with no additional treatment required in years 3 and 4. This allows people with MS to be treated with minimal disturbance to their lives, with fewer medications to take and fewer hospital appointments compared with other DMTs.
- Monitoring burden: The contrast in monitoring requirements between cladribine tablets and other DMTs is significant and the impact on peoples' daily life is likely to be considerable. Six blood tests will be recommended for cladribine tablets during the first 2 years of treatment. Alemtuzumab, another annual treatment (for 2 years) for example, requires monthly blood monitoring.
- Fewer restrictions on family planning: MS typically affects young adults between the age of 20 and 40 years and twice as many women than men. People with MS receiving DMTs are recommended to stop treatment when they become pregnant, thereby increasing the risk of a relapse. Treatment with cladribine tablets allows people with MS to be treated in Year 1 and Year 2 with no further treatment in Year 3 and Year 4 and means that family planning can be considered from 6 months following the last dose of cladribine tablets in Year 2.
- Patient preference: The short course, oral nature of cladribine treatment was considered by the ABN as a potential motivator to some people with MS, preferred over the frequent monitoring burden and AEs associated with infusions, a comment that was reflected in the responses from the MS Society and MS Trust in the NICE scope consultations.
- In a Discrete Choice Experiment in the UK, people with MS considered that the attributes of cladribine tablets would provide [redacted] treatment options (overall) [redacted] treatment option in a future treatment landscape.

The key benefits for the healthcare system are financial, associated with the considerably lower administration and monitoring burden compared with other DMTs:

- Administration: Over the 4 years of cladribine tablets treatment, 20 days of oral dosing is required compared with 8 days of infusion for alemtuzumab, monthly infusions of natalizumab (approximately 48 over 4 years) and over 1,400 oral tablets where people with MS take one tablet per day.
- Monitoring: During their 2 years of treatment, people with MS receiving cladribine tablets will only require a total of six blood tests over 2 years (people with severe lymphopenia may require more tests) and monitoring for PML, which is a common opportunistic infection that can be fatal in people with weakened immune systems (although no case of PML has been reported to date with cladribine tablets). However, a baseline MRI should be performed before initiating cladribine tablets (usually within 3 months). In comparison, people with MS receiving natalizumab, fingolimod or alemtuzumab require multiple blood tests and additional analyses such as urinalysis, ophthalmological analyses, MRI and cardiovascular monitoring. The lower monitoring burden of people with MS treated with cladribine tablets compared with other DMTs results in lower monitoring costs over 4 years and increases the potential cost savings to NHS England.

ABN=Association of British Neurologists; AE=adverse event; DMT=disease-modifying therapy; MRI=magnetic resonance imaging; MS=multiple sclerosis; PML=progressive multifocal leukoencephalopathy
Source: CS, p78

Clinical advice to the ERG is that an oral MS treatment only given in two cycles that are 12 months apart, with no treatment in between or after, and with no unique monitoring above the standard, represents a step change and innovative treatment for people with MS.

2.6 Number of people with MS eligible for treatment with cladribine tablets

The company estimates that in England, the maximum number of people with MS who will be eligible for treatment with cladribine tablets ranges from 3983 people in 2017 to 4094 people with MS in 2021 (Table 2). The company claims that there are no data on the prevalence of HDA-RRMS in current UK clinical practice and has therefore estimated the proportion of people with HDA-RRMS eligible for treatment with cladribine tablets from the prevalence of HDA-RRMS in the population of the CLARITY trial (CS Budget Impact Analysis Section 3). The ERG considers this method to be appropriate since clinical advice to the ERG is that the incidence and prevalence of HDA-RRMS is unknown and participants included in the CLARITY trial are representative of people with MS likely to be treated in UK clinical practice. The company did not estimate the number of people in England with RES-RRMS and SOT-RRMS, i.e. the target populations for which cost effectiveness evidence was submitted by the company.

Table 2 Company's estimated incidence and prevalence of MS in England from 2017 to 2021

Epidemiology input	2017	2018	2019	2020	2021
Size of adult population in England[21]	42,523,609	42,857,169	43,170,266	43,456,282	43,717,703
Incidence rate of MS[22]	0.009%	0.009%	0.009%	0.009%	0.009%
Proportion of patients with RRMS - incidence[23]	77.0%	77.0%	77.0%	77.0%	77.0%
Prevalence rate of MS[22]	0.20%	0.20%	0.20%	0.20%	0.20%
Proportion of patients with RRMS - prevalence[24]	42.0%	42.0%	42.0%	42.0%	42.0%
Proportion eligible for treatment[25]	31.0%	31.0%	31.0%	31.0%	31.0%
Proportion with HDA-RRMS[26]	33.2%	33.2%	33.2%	33.2%	33.2%
Incidence of HDA-RRMS patients	306	309	311	313	315
Prevalence of HDA-RRMS patients	3676	3705	3732	3757	3780
Total population size	3983	4014	4043	4070	4094

HDA=high disease activity; MS=multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis
Source: Adapted from the company's budget impact analysis submission, Table 7

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[10] and that addressed within the CS is presented in

Table 3. Each parameter in

Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**
Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**
Population Adults with RRMS	Adults with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for cladribine tablets
Intervention Cladribine tablets	Cladribine tablets
Comparators For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab • dimethyl fumarate • teriflunomide For people with rapidly evolving severe RRMS • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab • fingolimod	Intervention Cladribine tablets Comparators For people who have not had previous treatment Cladribine tablets vs placebo For people who have received previous treatment Cladribine tablets vs placebo For people with rapidly evolving severe RRMS Cladribine tablets vs placebo For people with highly active RRMS despite previous treatment Cladribine tablets vs placebo
	Direct evidence The CLARITY trial was designed to compare the clinical effectiveness of cladribine tablets vs placebo in people with RRMS. The company presented clinical data for the following populations: *For people with RRMS* Cladribine tablets vs placebo *For people with HDA-RRMS* Cladribine tablets vs placebo *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs placebo *For people with highly active RRMS despite previous treatment (also known as the sub-optimal therapy group) (SOT-RRMS)* Cladribine tablets vs placebo **Indirect evidence** The company used network meta-analysis and meta-regression to compare cladribine with relevant comparators as follows:

Table 3 is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**

Population Adults with RRMS	Adults with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for cladribine tablets
Intervention Cladribine tablets	Cladribine tablets
Comparators For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab • dimethyl fumarate • teriflunomide For people with rapidly evolving severe RRMS • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab • fingolimod	**Direct evidence** The CLARITY trial was designed to compare the clinical effectiveness of cladribine tablets vs placebo in people with RRMS. The company presented clinical data for the following populations: *For people with RRMS* Cladribine tablets vs placebo *For people with HDA-RRMS* Cladribine tablets vs placebo *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs placebo *For people with highly active RRMS despite previous treatment (also known as the sub-optimal therapy group) (SOT-RRMS)* Cladribine tablets vs placebo **Indirect evidence** The company used network meta-analysis and meta-regression to compare cladribine with relevant comparators as follows:

Table 3 Comparison between NICE scope and company decision problem

	For people with RRMS Cladribine tablets vs alemtuzumab Cladribine tablets vs beta-interferon Cladribine tablets vs daclizumab Cladribine tablets vs dimethyl fumarate Cladribine tablets vs glatiramer acetate Cladribine tablets vs teriflunomide Cladribine tablets vs fingolimod Cladribine tablets vs natalizumab *For people with HDA-RRMS* Cladribine tablets vs alemtuzumab Cladribine tablets vs beta-interferon Cladribine tablets vs dimethyl fumarate Cladribine tablets vs glatiramer acetate Cladribine tablets vs teriflunomide Cladribine tablets vs fingolimod Cladribine tablets vs natalizumab *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs alemtuzumab Cladribine tablets vs daclizumab Cladribine tablets vs natalizumab *For people with highly active RRMS despite previous* treatment (SOT-RRMS) Cladribine tablets vs alemtuzumab Cladribine tablets vs daclizumab Cladribine tablets vs fingolimod **No evidence** No evidence is presented in the CS for: For people with RRMS who have not had previous treatment For people with RRMS who have received previous treatment
Outcomes • relapse rate • severity of relapse • disability (for example EDSS) • symptoms of MS (such as fatigue, cognition and visual disturbance) • freedom from disease activity • mortality • AEs • HRQoL	The company presented results for the following outcomes: • qualifying annualised relapse rate • severity of relapse • disability (EDSS) • AEs • HRQoL • MRI lesions

Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness was assessed using ICERs per QALY gained for the RES-RRMS and SOT-RRMS subpopulations
The reference case stipulates that 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	The model time horizon is 50 years
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS and Personal Social Services perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies should be taken into account.	A PAS for cladribine tablets is not included in the CS
Other considerations If the evidence allows, the following subgroups of patients will be considered: • people with RRMS whose disease has inadequately responded to treatment with DMT • people with RRMS whose disease is intolerant to treatment with DMT • people with RRMS who are planning pregnancy	No evidence is presented in the CS for: • people with RRMS whose disease has inadequately responded to treatment with disease modifying therapy • people with RRMS whose disease is intolerant to treatment with disease modifying therapy • people with RRMS who are planning pregnancy
Special considerations None identified	None identified

AE=adverse event; CS=company submission; EDSS=Expanded Disability Status Scale; HDA=high disease activity; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; MRI=magnetic resonance imaging; N/A=not applicable; NEDA-3=no evidence of disease activity; NICE=National Institute for Health and Care Excellence; PAS=patient access scheme; QALY=quality adjusted life year; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated; vs=versus
Source: CS, pp15-17

3.1 Population

The population specified in the final scope issued by NICE is adults with RRMS.

The clinical effectiveness evidence presented in the CS is derived from the CLARITY[27] trial which compared cladribine tablets to placebo. People were recruited to the CLARITY trial if they had a diagnosis of RRMS. Clinical effectiveness results for the overall trial population, the HDA-RRMS population, and subgroups of the HDA-RRMS population (i.e. RES-RRMS and SOT-RRMS) are provided in the CS. Only the RES-RRMS and SOT-RRMS subgroups are considered in the company's economic analyses.

The ERG notes that 28 people were recruited from the UK to the CLARITY trial. Clinical advice to the ERG is that the population included in the CLARITY trial is representative of people with MS likely to be treated in UK clinical practice. The company estimates that, from 2017, approximately 4000 people with HDA-RRMS in England would be eligible for treatment with

cladribine tablets each year (as discussed in Section 2.6 of the ERG report). Estimates of the incidence and prevalence of people in England and Wales with RES-RRMS and SOT-RRMS have not been provided in the CS.

It is recommended within the draft Summary of Product Characteristics (SmPC)[28] for cladribine tablets that they should be used with caution in the elderly as clinical studies have not included people with MS over 65 years of age; compared to younger persons, this age group is likely to have decreased hepatic or renal function, more concomitant diseases and use other treatments. In addition, the use of cladribine tablets has not been established, and therefore is not advised, in people with MS with moderate or severe renal or hepatic impairment.[28]

3.2 Intervention

The intervention described in the CS and in the final scope issued by NICE is cladribine tablets. The mechanism of action, method of administration and dosage of cladribine tablets is set out in Table 4.

Table 4 Mechanism of action, method of administration and dosage of cladribine tablets

Item	Description
Mechanism of action	Cladribine is a deaminase-resistant nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells. The mechanism by which cladribine tablets exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to multiple sclerosis.[29] A distinguishing feature of cladribine tablets is discontinuous immunosuppression. Periods of lymphocyte depletion around treatment are followed by repopulation resulting in durable efficacy well beyond the period of treatment
Method of administration and dosage	Cladribine tablets are administered orally. The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a person receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. No further treatment is required in years 3 and 4

Source: CS, Table 3

The CS (p21) and the SmPC[28] include the caution that, due to the effect of treatment with cladribine tablets on lymphocytes, 'lymphocyte counts must be normal before cladribine tablets initiation in Year 1, and patients should have at least 800 cells/mm^3 before initiation of cladribine tablets in Year 2. In the absence of this, a treatment course could be delayed for up to 6 months to allow lymphocyte counts to recover.'

The effect of treatment with cladribine tablets on the immune system may result in an increase in the likelihood of infections. Screening for latent infections should be performed before initiation of therapy in year 1 and year 2 and patients should be monitored for signs and symptoms suggestive of any infection, with particular attention to herpes zoster.[28] The advice

in the SmPC[28] is that the initiation of cladribine tablets should be delayed until infections have been fully controlled.

The company claims that following completion of the two courses of treatment, no further treatment with cladribine tablets is required in years 3 and 4 (CS, p21). However, in the company's Budget Impact Analysis, the company estimates that 13.5% of patients would require a repeat course of cladribine tablets within the first 4 years of treatment initiation (CS Budget Impact Analysis, Table 1). The company's estimate was based on the proportion of participants who relapsed in the CLARITY-EXT trial.[30] The company states that re-initiation of cladribine tablets after year 4 has not been assessed (CS, p21).

3.3 Comparators

The final scope issued by NICE does not explicitly specify comparators for the whole adult population with RRMS. Instead, the final scope sets out different comparators for (i) people who have not had previous treatment, (ii) people who have received previous treatment, (iii) people with RES-RRMS and (iv) people with highly active RRMS despite previous treatment, which the company termed as SOT-RRMS.

No evidence was provided for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

The CS includes network meta-analyses (NMAs) that include data from the RRMS population (i.e., CLARITY trial intention-to-treat [ITT] population) and data from the HDA-RRMS subpopulation; neither of these populations was part of the final scope issued by NICE.

Only the NMAs that included data from the RES-RRMS and SOT-RRMS populations match the populations and comparators set out in the final scope issued by NICE (Table 5). However, the RES-RRMS and SOT-RRMS subgroups and efficacy and safety analyses were not pre-specified in the CLARITY trial statistical analysis plan (SAP). All of the efficacy analyses are based on data from a small number of people.

Table 5 Comparators listed in the final scope for which the company presented indirect clinical evidence

Population	Definition	Comparators
RES-RRMS	People with 2 or more relapses in prior year whether on treatment or not, and at least 1 T1Gd+ lesion	Natalizumab Alemtuzumab Daclizumab
SOT-RRMS	People with 1 or more relapse in the prior year while on DMT and at least 1 T1Gd+ lesion or 9 T2 lesions	Fingolimod Alemtuzumab Daclizumab

DMT=disease modifying therapy; Gd+=gadolinium enhancing; RES=rapidly-evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated

Source: adapted from CS, Table 62

3.4 Outcomes

The outcomes specified in the final scope issued by NICE and considered in the CS are qualifying annualised relapse rate [ARR]), severity of relapse, disability, AEs and health-related quality of life (HRQoL). In addition, the company included magnetic resonance imaging (MRI) lesions, explaining that clinicians commonly use MRI results to assist in the diagnosis and prognosis of RRMS. Freedom from disease activity was evaluated post-hoc using the 'no evidence of disease activity' (NEDA-3) composite clinical outcome defined as no relapses, no 3-month confirmed EDSS progression, no new or enhancing T1 gadolinium enhancing (Gd+) lesions and no new or enlarging T2 lesions. Time to 6-month confirmed disability progression (CDP) and people with 6-month CDP were also evaluated retrospectively. Clinical advice to the ERG is that NEDA-3 and CDP scores have not been validated as predictors of long term outcome. Symptoms of MS (such as fatigue, cognition and visual disturbance) was a specified outcome in the final scope issued by NICE but was not addressed in the CS. Clinical advice to the ERG is that symptoms of MS as specified in the final scope issued by NICE were not commonly reported at the time when the CLARITY trial was designed.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained for the RES-RRMS and SOT-RRMS subgroups. Outcomes were assessed over a 50-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services (PSS) perspective. The company subdivided the RES-RRMS and SOT-RRMS subgroups as described in Table 6.

Table 6 Summary of populations and comparators considered in the CS for the economic analysis

Population	Definition	Comparators within scope
RES-RRMSa	RES-RRMS and able to receive alemtuzumab	Natalizumab Alemtuzumab
RES-RRMSb	RES-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Natalizumab Daclizumab
SOT-RRMSa	SOT-RRMS and able to receive alemtuzumab	Fingolimod Alemtuzumab
SOT-RRMSb	SOT-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Fingolimod Daclizumab

RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated
Source: adapted from CS, Table 62

The company states that these subdivisions were necessary to align the results of the current appraisal with the recommendation set out in the Final Appraisal Determination (FAD) for daclizumab (TA441).[20] Daclizumab is recommended as a treatment for people with RES-RRMS and SOT-RRMS and for whom alemtuzumab is contraindicated or unsuitable. Daclizumab is therefore a relevant comparator to cladribine tablets in people with RES-RRMS and SOT-RRMS who are unable to receive alemtuzumab. The ERG agrees that the approach employed by the company is appropriate. However, the subgroup analyses were not pre-specified and the analyses are based on small number of participants.

3.6 Other considerations

No evidence has been provided in the CS for the subgroups specified in the NICE scope, specifically, for people with RRMS whose disease has inadequately responded to treatment with a DMT, for people with RRMS for whom treatment with a DMT is not suitable because of intolerance or contraindication, and patients with RRMS who are planning pregnancy.

The company did not identify any equity or equality issues.

The company states that a patient access scheme (PAS) application for cladribine tablets is not included in the CS (CS, Table 3). The ERG notes that fingolimod and daclizumab are both available to the NHS at discounted PAS prices. PAS prices are confidential and therefore not known to the company. The ERG has re-run the company's base case analyses using the discounted PAS prices (see Confidential Appendix to this ERG report for results).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the review methods

4.1.1 Searches

The company carried out a systematic search of the literature in January 2017 to identify randomised controlled trials (RCTs) investigating the efficacy and safety of cladribine tablets for the treatment of people with RRMS. Separate searches were conducted for the retrieval of cost effectiveness studies, HRQoL studies and 'health state unit cost and resources' studies. The searches were conducted in February 2016 and updated in January 2017.

Full details of the searches and the strategies used to locate clinical evidence are reported in Section B.2.1 and Appendix D of the CS. There are some syntax errors with regards to the translation of the search strategies between databases, for example, the PubMed interface does not use NEAR, therefore any search lines using NEAR do not execute correctly in the PubMed Interface. The company has not translated the searches consistently between databases; the search terms for the disease that was used for the Medline and Embase searches are not the same as the search terms used in The Cochrane Library and PubMed searches. However, the ERG considers that these errors are unlikely to have resulted in any papers being missed due to the search terms still being relevant and comprehensive. No clinical trial registries were searched by the company, which could have resulted in some relevant ongoing trials being missed. The ERG updated the company searches for the period between January and July 2017 and is satisfied that no relevant studies have been missed.

The ERG considers that the company's searches were carried out to an adequate standard, however, they could have been executed more consistently. The searches accurately reflected the population and indication described in the final scope issued by NICE.

The data sources searched and the time spans for the searches are provided in Table 7. A summary of, and ERG comments on, the review methods used by the company are presented in Table 8.

Table 7 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	Not specified, possibly from database inception	February 2016, updated January 2017
	MEDLINE		
	MEDLINE In-Process		
	Cochrane Central Library of Controlled Trials (CENTRAL)		
Congress proceedings	Academy of Managed Care Pharmacy (AMCP) (Biannual meeting) American Academy of Neurology (AAN) (Annual meeting) American Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) (Annual meeting) American Neurological Association (ANA) (Annual meeting) Consortium of Multiple Sclerosis Centers (CMSC) (Annual meeting) European Academy of Neurology (EAN) (Annual meeting)* European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (Annual meeting) European Federation of Neurological Societies (EFNS) International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	2012	February 2016, updated January 2017
Clinical trial registries	ClinicalTrials.gov	Not searched	
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry		

Source: CS, Appendix D, Table 5 and Table 6

Table 8 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	10,825 unique studies	• The last update was carried out in January 2017 meaning that there is a risk that some relevant studies may not have been included in the search results • There are some syntax errors with regards to the translation of the search strategies between databases meaning that some searches would not execute correctly • Clinical trial registries were not searched. Ongoing clinical trials were therefore not identified in the CS
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 7 of Appendix D of the CS (pp15-16)	49 unique trials based on 779 publications and 2 CSRs	• Use of two independent assessors improves the quality of the review
Additional eligibility criteria		
Search limits		It is unclear if the searches were restricted to studies published in English language. However, the legend in PRISMA flow diagram indicates that non-English studies were excluded. Relevant non-English language studies may not have been included
Quality assessment		
The company assessed the risk of bias of the CLARITY trial using the minimum criteria recommended by NICE.[31] The results of the company assessment of the CLARITY trial are presented in the CS The company assessed the risk of bias of the RCTs included in company's NMA using the Jadad score[32] and the minimum criteria recommended by NICE.[31] The results of the company's assessment of risk of bias of the RCTs included in the company's NMA are presented in an embedded file in Appendix D of the CS		

CS=company submission; CSR=clinical study report; ERG=Evidence Review Group; NMA=network meta-analysis; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT=randomised controlled trial
Source: CS, Appendix D Table 7

4.1.2 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of cladribine tablets from one RCT (the CLARITY trial). The CS includes a narrative description of this trial.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trial: the CLARITY trial

The company presents evidence for the clinical effectiveness of cladribine tablets from the CLARITY trial. The CLARITY trial was a randomised, double-blind, placebo-controlled, multicentre, phase III trial designed to investigate the use of cladribine tablets in people with RRMS.

Other trials

Neither the company nor the ERG identified any trials that directly compare cladribine tablets with any of the comparators listed in the final scope issued by NICE.

Data from the CLARITY-EXT trial were included in the CS to provide supportive evidence for the assumptions about the waning of the effect of cladribine tablets that are used in the company's economic model and safety. Waning assumptions used in the company model are further discussed in Section 5.3.6 of this report.

Safety data extracted from the PREMIERE registry[33] and ORACLE trial[34] were used, in addition to safety data from the CLARITY and CLARITY-EXT trials, as part of an integrated safety analysis. The PREMIERE registry[33] collects safety data on patients that received a 3.5 mg/kg dose of cladribine tablets as part of any RCT. The ORACLE trial[34] assessed the effect of cladribine tablets at a cumulative dose of 3.5 mg/kg or 5.25 mg/kg over 96 weeks versus placebo in patients who experienced a single, first clinical event suggestive of MS. The patient population in the ORACLE trial[34] does not match the patient population(s) specified in the final scope issued by NICE.

4.2.2 Key characteristics of the CLARITY trial

The key characteristics of the CLARITY trial are provided in the CS (Section B.2.3) and are summarised in Table 9.

The trial was conducted internationally, with six treatment centres located in the UK. Patients were randomised 1:1:1 to receive either low-dose cladribine tablets 3.5 mg/kg cumulative (n=433), high-dose cladribine tablets 5.25 mg/kg cumulative (n=456) or placebo (n=437) over a period of 96 weeks. The CLARITY trial was divided into two 48-week treatment periods (year 1 and year 2) with four 28-day treatment cycles in year 1 (week 1, week 5, week 9, week 12) and two 28-day treatment cycles in year 2 (week 48 and week 52). Cladribine tablets were given as 0.875 mg/kg/cycle with the number of tablets administered being standardised based on weight. People allocated to receive cladribine tablets 3.5 mg/kg cumulative, were given cladribine tablets in week 1, week 5, week 48 and week 52 and placebo in week 9 and week 12. People allocated to receive cladribine tablets 5.25 mg/kg cumulative were given cladribine tablets in all treatment cycles and people allocated to placebo were given placebo in all cycles.

The company states that results from the CLARITY trial demonstrated 'no considerable differences' in the efficacy and safety of 3.5 mg/kg cladribine tablets compared to 5.25 mg/kg cladribine tablets[27] and so the 5.25 mg/kg cladribine tablets dose was omitted from the CLARITY-EXT trial.[35] Furthermore, 3.5 mg/kg is the anticipated EMA licensed dose for

cladribine tablets. Therefore, only results for the 3.5 mg/kg cladribine tablets treatment arm (compared to the placebo treatment arm) are presented within the CS and only the 3.5 mg/kg cladribine tablets and placebo arm data contribute to the NMA and to the economic evaluation. For these reasons, all subsequent mentions of treatment with cladribine tablets in this ERG report refer to a 3.5 mg/kg dose.

The CLARITY trial had pre-planned subgroup analysis of active RRMS patients grouped into treatment-naïve RRMS and treatment-experienced RRMS. The company states that the results of these subgroups were not included in the CS as they did not expect that cladribine tablets would obtain marketing authorisation for these populations.

Table 9 Key characteristics of the CLARITY trial

Trial	**CLARITY**
Trial design	Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week
Eligibility criteria for participants	Diagnosis of MS according to the McDonald criteria RRMS with ≥1 relapses within 12 months before study Clinically stable and not had a relapse within 28 days prior to day 1 of study MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria EDSS score between 0 to 5.5, inclusive
Settings and locations where the data were collected	155 investigative sites in 32 countries (28 patients in 6 sites across the UK)
Trial drugs - Interventions and comparators	Patients (N=1326) were randomised (1:1:1) to receive: LL: cladribine tablets 3.5 mg/kg cumulative over 96 weeks (n=433) HL: cladribine tablets 5.25 mg/kg cumulative over 96 weeks (n=456) PP: placebo (n=437)
Trial drugs - permitted and disallowed concomitant medication	• Corticosteroids were permitted to treat acute relapses, however, long-term use (>14 days) necessitated patient withdrawal from the trial • IFN-β1a (Rebif) was permitted as rescue medication after 24 weeks from the start of the trial – to qualify for Rebif rescue medication, patients had to meet the following criteria: o Patients who experience >1 qualifying relapse, and/or o Patients who have a sustained increase in their EDSS of ≥1 point (or ≥1.5 points if baseline EDSS was 0) over a period of 3 months or greater)
Primary outcomes (including scoring methods and timings of assessments)	Qualifying ARR – defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement
Other outcomes used in the economic model/specified in the scope	Disability progression Mortality Adverse effects of treatment HRQoL NEDA-3 (post-hoc) 6-month CDP (post-hoc)

Pre-planned subgroups	Prior treatment Treatment-naïve Treatment-experienced
Post-hoc subgroups	HDA-RRMS (licensed population) RES-RRMS SOT-RRMS

ARR=annualised relapse rate; CDP=confirmed disease progression; EDSS=expanded disability status scale; H=high-dose cladribine tablets over 48 weeks; HDA=high disease activity; HRQoL=health-related quality of life; IFN-β1a=interferon-β1a; KFS=Kurtzke Functional systems; L=low-dose cladribine tablets over 48 weeks; MRI=magnetic resonance imaging; MS=multiple sclerosis; NEDA-3=no evidence of disease activity; P=placebo; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated
Source: CS, Table 8

4.2.3 Characteristics of patients enrolled in the CLARITY trial

The key baseline characteristics of patients included in the CLARITY trial are presented in Table 10. The company considers that the patients' baseline characteristics are generally well-balanced, and that although there is a higher proportion of patients (≈5%) who had received previous DMT in the placebo group than in the cladribine tablets group, the difference is not statistically significant (CS, Section B.2.3.4). Disease duration from first onset was statistically significantly lower in the cladribine tablets 3.5 mg/kg group than in the placebo and cladribine tablets 5.25 mg/kg groups in the published paper. Mean disease duration reported in the CS for the placebo and cladribine groups is shorter than reported in the paper. In response to the ERG clarification letter, the company acknowledged these differences and explained that the differences were due to the different definitions used for disease duration. In the published paper,[27] the duration was defined as "the time (in years) from the first attack until randomisation", whereas for the results of the re-analyses presented in the CS, the duration was adapted to a more commonly used definition, "the time (in years) from the MS diagnosis date until randomisation".

Table 10 Baseline characteristics of patients in the CLARITY trial

Characteristic	CLARITY	
	Placebo (n=437)	Cladribine tablets 3.5 mg/kg (n=433)
Mean (SD) age, years	38.7 (9.9)	37.9 (10.3)
Female, %	65.9	68.8
Previous DMT use, %	30.2	25.4
Mean disease duration, years	5.2	4.7
Mean (SD) EDSS	2.9 (1.3)	2.8 (1.2)
Mean (SD) T1 Gd+ lesions	0.8 (2.1)	1.0 (2.7)
Mean (SD) T2 lesions	27.4 (17.7)	25.3 (16.3)

DMT=disease-modifying therapy; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; SD=standard deviation
Source: CS, Table 13

The CS also includes the baseline characteristics of the subgroups defined by the company (i.e., HDA-RRMS, RES-RRMS and SOT-RRMS). The baseline characteristics of these subgroups are presented in Table 11. The ERG notes that small numbers of people were

included in the RES-RRMS and the SOT-RRMS subgroups (see Table 11 for details). The ERG notes that some patients could be classified as RES-RRMS and/or SOT-RRMS and, according to the company during the clarification teleconference that was held with NICE and the ERG, some patients may have been included in both of these subgroups resulting in double counting.

The ERG notes that the HDA-RRMS subgroup is larger than the sum of the numbers of patients in the RES-RRMS and SOT-RRMS subgroups.

Table 11 Patients baseline characteristics in the CLARITY trial by subgroup

Characteristic	Placebo subgroups			Cladribine tablets 3.5 mg/kg subgroups		
	HDA-RRMS (n=149)	RES-RRMS (n=41)	SOT-RRMS (n=32)	HDA-RRMS (n=140)	RES-RRMS (n=50)	SOT-RRMS (n=19)
Mean (SD) age, years	37.1 (10.2)	33.3 (8.2)	38.0 (8.8)	36.3 (9.5)	33.4 (7.9)	34.7 (8.0)
Female, %	63.1	58.5	68.8	72.9	72.0	73.7
Previous DMT use, %	37.6	24.4	100.0	32.9	34.0	100.0
Mean disease duration, years	4.8	3.9	7.6	3.9	2.9	5.8
Mean (SD) EDSS	3.0 (1.4)	2.9 (1.4)	3.6 (1.6)	2.9 (1.3)	2.8 (1.4)	3.2 (1.5)
Mean (SD) T1 Gd+ lesions	1.0 (2.8)	3.5 (4.6)	1.2 (2.1)	1.3 (3.5)	3.6 (5.6)	0.5 (0.8)
Mean (SD) T2 lesions	29.9 (19.8)	36.8 (24.4)	35.7 (21.1)	25.2 (17.2)	31.6 (16.8)	26.6 (18.1)

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; HDA=high disease activity; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SD=standard deviation; SOT=sub-optimally treated
Source: CS, Table 14

4.2.4 Statistical approach adopted

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the CLARITY trial that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[36] the trial protocol,[37] the trial statistical analysis plan (TSAP)[38] and the CS, which included post-hoc subgroup analyses of the CLARITY trial.

The objective of the CLARITY-EXT trial was to evaluate safety of extended treatment with cladribine tablets and to provide supportive evidence for assumptions on waning used in the economic analysis rather than to evaluate efficacy. With the exception of waning assumptions, data from the CLARITY-EXT trial were not used to populate the submitted economic model. Waning assumptions are further discussed in Section 5.3.6 of this ERG report. Therefore, the methodology and the statistical approach of the CLARITY-EXT trial are not discussed within this ERG report but can be found in Section B.2.3 and Section B.2.4 of the CS respectively.

Analysis populations

The populations used for analyses of different outcomes of the CLARITY trial are summarised in Table 12. Data from the ITT population were analysed for all pre-planned primary and important secondary efficacy outcomes and data from the safety population were used in all safety analyses. The ERG notes that data from additional trials were combined with data from the CLARITY trial in an integrated safety analysis in the CS (Section B 2.10.3); further details of the safety population and analyses presented within the CS are described in Section 4.5 of this ERG report.

The ERG is satisfied that the populations for pre-planned outcomes were pre-defined in the TSAP (p85) and that all relevant results are reported within the CSR (p102-106).

The ERG notes that analyses of HRQoL are defined in the CLARITY protocol (pp 69-70) but the analysis population for these analyses is not defined in either the CLARITY trial protocol or in the TSAP. Information in the CSR for the CLARITY trial (requested by the ERG via the clarification process) indicates that assessment of HRQoL 'is provided as a separate report in appendix 16.1.13'. The company did not provide this appendix at the time of submission or during the clarification process.

In addition to the pre-planned ITT population, three additional subgroups were defined post-hoc and analysed within the CS: HDA-RRMS, RES-RRMS and SOT-RRMS subgroups (see Section 3.3 of this ERG report for further details of the subgroups). The ERG acknowledges that the post-hoc definition of subgroups, not originally included in the CLARITY trial, was necessary to address two of the subpopulations described in the NICE decision problem, but emphasises the decreased statistical power within these smaller subgroups which must be taken into account when interpreting the results of the post-hoc analyses of the CLARITY trial.

Table 12 CLARITY trial analysis populations

Analysis	Population
Efficacy (pre-planned)	Primary and secondary efficacy outcomes which were pre-planned and were analysed in the ITT population which was defined as all participants who underwent randomisation
Efficacy (post-hoc)	Primary and secondary efficacy outcomes, including outcomes defined post-hoc and were analysed in the following populations: • ITT population which was defined as all participants who underwent randomisation • RES-RRMS subgroup defined as participants with ≥2 relapses in the prior year whether on treatment or not and participants with ≥1 T1Gd+ lesion • SOT-RRMS subgroup defined as participants with ≥1 relapse in the previous year while on treatment and participants with ≥1 T1 Gd+ lesion or ≥9 T2 lesions • HDA-RRMS subgroup defined as participants with one relapse in the previous year while on disease modifying therapy and ≥1 T1 Gd+ lesion or ≥9 T2 lesions or participants with ≥2 relapses in the prior year whether on treatment or not
Safety (pre-planned)	The safety population was defined as all participants who received at least one dose of a study drug and for whom follow-up safety data were available

Gd+=gadolinium enhancing; HDA=high disease activity; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy;
Source: CS, Table 28, CLARITY TSAP (p85)

Outcomes and analysis approach in the CLARITY trial

The primary objective of the CLARITY trial was to evaluate the efficacy of cladribine tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in participants with RRMS.

Definitions and methods of statistical analysis for the primary efficacy outcome and important secondary efficacy outcomes of the CLARITY trial used within the economic model or relevant to the final NICE scope are provided in Table 13.

Table 13 Description and method of analysis for key efficacy outcomes in the CLARITY trial

Outcome	Outcome definition	Statistical analysis[a]
Primary efficacy outcome (pre-planned)		
Qualifying ARR	Qualifying annualised relapse rate at 96 weeks A relapse was defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement	The ARR endpoint was analysed using a Poisson regression model with a fixed-effect for treatment group with log of time on trial as an offset variable The ratio of qualifying annualised relapsed rates in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing) confidence intervals (CI) were estimated An approximate Chi-square test based on Wald statistics was used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error

Other efficacy outcomes used in the economic model / specified in the scope (pre-planned)		
RF	Proportion of (qualifying) relapse-free participants at 96 weeks A relapse was defined as for primary outcome 'Qualifying ARR'	Analysed using a logistic-regression model with a fixed-effect for treatment group The odds ratio of being (qualifying) relapse-free in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing, see 'Qualifying ARR') confidence intervals (CI) were estimated
3 month CDP	Time to 3-month CDP at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed with the use of a Cox proportional-hazards model with a fixed-effect for treatment group The time to 3-month CDP was measured as: date associated with the first 3-month CDP – start date of treatment + 1 Subjects that discontinued before week 96 without 3-month CDP, as well as subjects without 3-month CDP were censored and their time on study was used in the time to event analysis The hazard ratio of time to 3-month CDP at 96 weeks in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing, see 'Qualifying ARR) confidence intervals (CI) were estimated Kaplan-Meier plots by treatment group were also generated
	Proportion of participants with 3-month CDP at 48 weeks and at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Proportion of (qualifying) relapse-free participants at 96 weeks'
Time to first qualifying relapse	Time to first qualifying relapse A relapse was defined as for primary outcome 'Qualifying ARR'	Analysed using equivalent methodology as 'Time to 3-month CDP at 96 weeks'

Other efficacy outcomes used in the economic model / specified in the scope (post-hoc)		
NEDA-3	NEDA-3 was defined as the absence of disease activity (all three conditions must be met): • No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions Complete definitions of each condition are provided in the company response to the ERG clarification letter	The primary measurement for assessment of absence of disease activity (NEDA-3) was be the Kaplan-Meier estimated cumulative probability of the disease-free state by 48 and 96 weeks for the CLARITY trial The outcome was also analysed with the use of a Cox proportional hazards model where time to disease activity (days) was calculated as the: date of first occurrence of disease activity – randomisation date + 1 Participants were censored if there was a disease event, defined as any of the following • Qualifying relapse • 3 month CDP • new or enhancing Gd+ T1 lesion • new or enlarging T2 lesion Or if absence of disease activity was unknown Participants were censored on their last date in the study or at the date of their last complete MRI assessment if their status was unknown All analyses were stratified by treatment naïve and previously treated participants Further definitions of the assessments at 48 weeks and 96 weeks are provided in the company response to the ERG clarification letter
6 month CDP	Time to 6-month CDP at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Time to 3-month CDP at 96 weeks'
	Proportion of participants with 6-month CDP at 48 weeks and at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Proportion of (qualifying) relapse-free participants at 96 weeks' Further definitions of the assessments at 48 weeks and 96 weeks are provided in the company response to the ERG clarification letter

ARR=annualised relapse rate; CDP=confirmed disability progression; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; KFS=kurtzke functional systems; NEDA-3=absence of disease activity; RF=relapse-free
Source: CS, Section B.2.3.3; TSAP (p94-96)

The ERG is satisfied that, for the pre-planned outcomes, the outcome definition and the analysis method for each of the efficacy outcomes were pre-specified in the TSAP, and that all results are reported fully in the CSR. The company notes that the original pre-planned analyses were conducted with region as a fixed-effect within statistical models, however, this fixed-effect was omitted from the re-analyses conducted for the CS, due to concerns regarding statistical model convergence within the smaller post-hoc subgroups. The definition of a relapse during the trial was pre-defined in the TSAP (p9) and an independent evaluating physician who was unaware of treatment allocations within the trial performed neurologic

examinations and determined whether a clinical event fulfilled criteria consistent with a relapse.[27]

The ERG notes that several terms are used interchangeably in the CS and related documents (TSAP, protocol, CLARITY trial publication, CSR) referring to endpoints related to disability; such as confirmed disease progression, confirmed disability progression, sustained progression of disability and sustained change in EDSS score. For consistency of terminology, this ERG report uses the term CDP to refer to endpoints related to disability as this terminology is closest to the outcomes specified in the NICE scope. The definition of CDP used within the CLARITY trial was pre-defined in the TSAP (p95).

Comparison of the three treatment groups of the CLARITY trial (3.5 mg/kg cladribine tablets, 5.25 mg/kg cladribine tablets and placebo) for all pre-planned primary and secondary efficacy outcomes was performed via an approximate Chi-square test based on Wald Statistics and Hochberg's step-up method for multiple comparisons to protect the type I error. Treatment effect estimates with 95% confidence intervals (CI) were presented if cladribine doses were significantly different from placebo, and 97.5% CIs were to be presented if only one cladribine dose was significantly different from placebo.

Three outcomes were defined by the company post-hoc and presented in the CS: NEDA-3, time to 6-month CDP and proportion of participants with 6-month CDP. The company states that NEDA-3 was captured post-hoc for the CLARITY trial due to the publication of literature after the completion of the CLARITY trial in 2010 suggesting that that freedom from disease activity was becoming an increasingly important endpoint in MS and that this outcome could be used to measure treatment effect beyond the duration of a trial.[39-41] Since the completion of the CLARITY trial, the EMA has released guidance[42] recommending the use of 6-month CDP to define sustained accumulation of disability, in line with this, the company has also reported time to 6-month CDP and proportion of participants with 6-month CDP post-hoc for the CLARITY trial in the CS. Clinical advice to the ERG is that NEDA-3 and CDP scores have not been validated as predictors of long-term outcome.

The ERG notes that the Cox regression methodology employed for the analysis of pre-planned outcomes (i.e., time to 3-month CDP and time to first qualifying relapse) and post-hoc outcomes (i.e., time to 6-month CDP and time to achieve NEDA-3 status) require the assumption of proportional hazards (PH) for the interpretation of estimated hazard ratios (HRs). The PH assumption was not originally tested for any of the pre-planned outcomes of the CLARITY trial or the post-hoc outcomes presented in the CS. In response to the ERG clarification letter, the company provided plots of the log (-log [Estimated Survival Distribution

Function]) against log (Time since Study Entry) for each outcome analysed by Cox regression methodology for the ITT population and for each of the three post-hoc subgroups. The company concludes that the lines on the plots are close to parallel in the entire ITT population and within the subgroups and therefore the PH assumption holds. The ERG agrees with this assessment for the ITT population and the HDA-RRMS subgroup, but considers the plots for the RES-RRMS and SOT-RRMS subgroups for each outcome difficult to interpret, due to the small numbers of participants within these subgroups.

Additional efficacy endpoints were also used for the CLARITY trial such as the endpoint associated with MRI lesions, severity of relapses, worsening of disease and rescue therapy use. These additional endpoints did not contribute to the economic model so are not discussed further within this ERG report. Further information regarding these outcomes is available in Section B.2.3.3 of the CS and numerical results for severity of relapses and worsening of disease were provided in the company response to the ERG clarification letter.

Patient reported endpoints (i.e. HRQoL) and safety endpoints (i.e. AEs) were also measured in the CLARITY and CLARITY-EXT trials. Further details of these outcomes are described in Section 4.4 and Section 4.5 of this ERG report respectively.

ERG assessment of the statistical approach of the CLARITY trial

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the CLARITY trials is provided in Table 14. Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company but notes that information regarding the pre-planned methodology relating to HRQoL is limited.

The ERG acknowledges that three subgroups (Table 12) and three outcomes (Table 13) were defined post-hoc following the completion of the CLARITY trial. From the information provided in the CS and additional information provided by the company in response to the ERG clarification letter, the ERG is satisfied that the statistical approach of the post-hoc analyses employed by the company was appropriate. The ERG notes the inherent limitation of reduced statistical power when conducting post-hoc analyses, particularly within smaller subgroups than originally defined, as is the case within the CLARITY trial.

Table 14 ERG assessment of statistical approach used to analyse data from the CLARITY trials

Component	Statistical approach with ERG comments
Sample size calculation	The sample size calculation is presented in Table 16 of the CS: A sample size of 1290 participants (430 participants in each treatment arm) provided 90% power to detect a clinically meaningful 25% relative reduction in ARR at 96 weeks when comparing each of the cladribine tablets arms to the placebo arm. The target sample was calculated using a 2-sided t-test assuming 1) the mean number of qualifying relapses during 96 weeks was 2.1 for the placebo treatment arm, 2) a relative 25% reduction in mean number of qualifying relapses and 3) a common standard deviation of 2.02 for the number of qualifying relapses, a 10% non-evaluable rate and a type I error rate for each cladribine tablets group versus the placebo group at 2.5%. Assumptions regarding the number of relapses were based on 2-year data from the placebo group of the PRISMS trial.[43] The ERG is satisfied that this sample size calculation was provided in the TSAP (p84).
Protocol amendments	Protocol amendments were provided by the company, in addition to an original protocol and the final protocol with all amendments incorporated. Nine amendments were made between March 2005 and September 2008. All amendments and rationale for amendments are outlined in detail. Four amendments were made to adapt the trial procedures to country specific regulations and five amendments were made to trial procedures such as eligibility criteria, baseline assessment, definitions and measurement times of endpoints, adverse event recording, trial visit times and statistical analysis methodology. The ERG is satisfied with the rationale for the amendments and that all amendments were made before the trial completion date (date of last subject last visit was 12 November 2008, CSR, p1) and before the post-hoc analyses undertaken within the CS so amendments were unlikely to have been driven by the results of the trial.
Imputation of missing data	The approach to handling missing data for the re-analysis of the CLARITY trial presented within the CS was amended to an approach the company considers more appropriate to the original approach specified within the TSAP (outlined on p130-133 for efficacy outcomes and MRI outcomes). Details of the differences in the analysis approaches to missing data are outlined in Appendix 11.1 of this ERG report. The principal differences between the approaches were that data were not excluded or imputed for participants receiving rescue medication and, rather than imputing event times, participants with missing data were considered as 'unknown' in time-to-event analyses. The ERG agrees with the company that the approach in the re-analysis was more appropriate than the approach in the original analysis.

Component	Statistical approach with ERG comments
Pre-planned subgroup analyses	Pre-planned subgroup analyses of key efficacy endpoints in the CLARITY trial are available in the TSAP (p138). If a statistically significant and clinically relevant treatment by region interaction was found, summaries of treatment by region were performed. If at least 10% of the subjects received any disease modifying drug as rescue medication, a parameter for intake the rescue medication and an interaction term between treatment and intake of rescue medication would be added into the models for the continuous efficacy parameters. If the interaction is significant and clinically relevant, separate analyses would have been will be conducted for those who took combination therapy and those who did not take any rescue medication. The ERG is satisfied that results of pre-planned subgroup analyses by region are presented within the CSR (p357-365) for all efficacy outcomes. The ERG notes that these subgroup analyses were not presented in the CS. The ERG is satisfied that no subgroup analysis of rescue medication was performed, as only 3.5% of participants received rescue medication (CSR, p167). The ERG notes that subgroup analyses presented within the CS were defined post-hoc so were not included in the CLARITY protocol, TSAP or CSR.
Pre-planned sensitivity analyses	Pre-planned sensitivity analyses of key efficacy endpoints in the CLARITY trial are available in the TSAP (p138-139). Sensitivity analyses to examine the robustness of results were planned with modified treatment groups to take account of combination therapy if at least 10% of the subjects received any disease modifying drug as rescue medication. Sensitivity analysis was also planned to take account of any baseline imbalance, defined as a statistically significant difference between the treatment groups in any baseline parameter. The ERG assumes that these sensitivity analyses were not carried out as less than 10% of subjects received rescue medication (CSR, p167) and as there were no statistically significant imbalances in any baseline parameter (CSR, p95), although this is not explicitly stated within the CSR.
Analysis of AEs	Many different summaries of AEs are provided in the CSR. All AEs, TEAEs, SAEs, deaths, AEs leading to treatment and study discontinuation are summarised by treatment group, by study time period (Week 0 to 48, Week 48 to 96), by region and by system organ class. Pre-specified TEAEs are presented separately. Numbers of events and number of events per subject, in addition to the incidence rates of events (number of occurrences of a specific event divided by the total number of all events) are presented. The ERG is satisfied that the methodology used to analyse the AEs is appropriate and was pre-specified in the TSAP (p106-114) and that all summary tables of AEs are presented within the CSR (p445-1045).

Component	Statistical approach with ERG comments
Analysis of PROs	HRQoL was assessed by the change from baseline to 96 weeks in MSQOL-54 (physical function, role limitations-physical, role limitations-emotional, health perceptions, mental health and change in health) and the SF-36 Health Survey (physical functioning, role, general health and mental health). Additional subscales of the HRQoL tools were also considered. Treatment effect comparisons were based on the change from baseline to 96 weeks in the mean score of the respective scales using an two-way ANOVA model with effects for treatment, region and their interaction (included if significant or removed if non-significant). A p-value of <=0.05 in the treatment effect will be considered statistically significant. Where applicable, last observation carried forward (LOCF) method would be used to substitute for missing post-baseline data. The ERG notes that the statistical methodology for analysing HRQoL is presented in the protocol (p69-70) but is not presented in the TSAP. The ERG is mostly satisfied that the methodology used to analyses HRQoL was appropriate but is concerned about the use of LOCF method for imputing missing post-baseline data due to the biases associated with this method.[44] The ERG acknowledges that imputed and non-imputed results are provided in the CS (p44) and there are no changes in conclusions.

AE=adverse event; AESI=adverse events of special interest; ANOVA=analysis of variance; CI=confidence interval; CS=company submission; CSR=clinical trial report; ERG=Evidence Review Group; HRQoL=health-related quality of life; K-M=Kaplan-Meier; LOCF=last observation carried forward; MRI=magnetic resonance imaging; MSQOL-54=multiple sclerosis quality of life-54; PRO=patient-reported outcome; SAE=serious adverse events SD=standard deviation; SF-36=36 item short form; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan
Source: adapted from the CS, CLARITY CSR, CLARITY protocol, CLARITY TSAP, the company's response to the ERG clarification letter, and ERG comment

4.2.5 Risk of bias assessment for the CLARITY trial

The company assessed the risk of bias in the CLARITY trial using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[31] The company's risk of bias assessment, and ERG comments, are presented in Table 15.

The ERG considers that the risk of bias in the CLARITY trial was low for four of the seven criteria, and unclear for the remaining criteria. The ERG agrees with the company that there was a lower proportion (≈5%) of patients who had received previous therapy with any DMT in the cladribine 3.5 mg/kg group than in the placebo or cladribine 5.25 mg/kg groups. Disease duration from time of onset was statistically significantly lower in the cladribine tablets 3.5 mg/kg group (7.9±7.2 years) than in the placebo (8.9±7.4 years) or cladribine tablets 5.25 mg/kg (9.3±7.6 years) groups. Although the trial is described as being double-blinded, the treating physician was not blinded to treatment allocation. The company states that the methods used to account for missing data in the post-hoc analyses presented in the CS were more appropriate than the methods used for this purpose in the CSR. The ERG agrees with this conclusion (further discussed in Section 4.2.4).

Table 15 Risk of bias assessment of the CLARITY trial

Study question	Company assessment		ERG comment
	Addressed in the trial	Risk of bias	
Was randomisation carried out appropriately?	Yes	Low	Agree - computer-generated randomisation schedule
Was the concealment of treatment allocation adequate?	Yes	Low	Agree - treatment allocation concealed from evaluating physician
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Low	Unclear - differences in previous treatment with DMTs and disease duration from time of onset
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Low	Unclear - treating physician and study coordinators were aware of treatment allocation. Participants and physicians performing neurologic examinations were blinded to treatment allocation
Were there any unexpected imbalances in drop-outs between groups?	No	Low	Agree - similar proportions of drop-outs across the three groups
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low	Unclear - SF-36 data were collected but the company was unable to analyse the results due to a lack of availability of baseline measures
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Appropriate methods were used to account for missing data	Low	Agree - analyses were performed according to the ITT principle and appropriate methods used to account for missing data

DMT=disease-modifying therapy; ITT=intention-to-treat; SF-36=36-Item Short Form Survey
Source: CS, Table 17, document embedded to Appendix D

4.3 Results from the CLARITY trial

All results from the CLARITY trial presented in this section come from post-hoc analyses which were performed between 18th July 2016 and 10th August 2016.[26]

There are minor discrepancies between the results presented within the CS (and within this ERG report) and the results presented within the CSR for the CLARITY trial and the primary publication,[27] which were both prepared in 2010. Detailed reasons for the differences in the numerical results due to the differences in statistical modelling are presented in Appendix 10.1 of this ERG report.

4.3.1 Participant flow in the CLARITY trial

A total of 1326 participants were randomised in the CLARITY trial; 437 to the placebo treatment arm, 433 to the 3.5 mg/kg cladribine tablets treatment arm and 456 to the 5.25 mg/kg cladribine tablets treatment arm.

Table 16 summarises the participant flow in the cladribine tablets and placebo treatment arms; 398 (91.9%) participants in the cladribine tablets arm completed the 96-week study (of which 395 [91.2%] completed treatment) and 380 (87.0%) participants in the placebo arm completed the 96-week study (of which 377 [86.3] completed treatment).

The mean time of participation in the CLARITY trial was 91.0 weeks in the cladribine tablets arm and 87.8 weeks in the placebo arm.[27]

Table 16 Participant disposition in the CLARITY trial

Number of participants	Cladribine tablets	Placebo
Randomised	433	437
Completed 96 week study: n (% of randomised)	398 (91.9)	380 (87.0)
Completed Treatment: n (% of randomised)	395 (91.2)	377 (86.3)
Withdrew: n (% of randomised)	35 (8.1)	57 (13.0)
• Lost to follow-up	• 8 (1.8)	• 4 (0.9)
• Adverse event	• 5 (1.2)	• 5 (1.1)
• Protocol violation	• 4 (0.9)	• 10 (2.3)
• Insufficient efficacy	• 5 (1.2)	• 21 (4.8)
• Death	• 1 (0.2)	• 2 (0.5)
• Other[a]	• 12 (2.6)	• 15 (3.4)

[a] Other reasons for discontinuation were consent withdrawal for administrative, convenience and personal reasons.
Source: CS, adapted from Appendix D 1.2.1; Giovannini et al 2010, adapted from Supplemental Figure 2

As introduced in earlier sections of this ERG report, in addition to the ITT population (i.e. all randomised participants), three post-hoc subgroups were defined for analysis; HDA-RRMS, RES-RRMS and SOT-RRMS. The number of participants within each of the analysis subgroups from the CLARITY trial is presented in Table 11.

4.3.2 Primary efficacy outcome: qualifying annualised relapse rate

The primary efficacy outcome of the CLARITY trial was qualifying ARR, measured at 96 weeks; results for the ITT population of the CLARITY trials and the three post-hoc subgroups are presented in Table 17.

Cladribine tablets were associated with a statistically significant relative reduction in qualifying ARR compared with placebo within the ITT population, HDA-RRMS subgroup and RES-RRMS-subgroup. There was also a numerical advantage for cladribine tablets over placebo in the SOT-RRMS subgroup, but this reduction was not statistically significant. The ERG notes that due to the small numbers of participants within the SOT-RRMS subgroup (19 and 32 for cladribine tablets and placebo respectively), it is unlikely that this post-hoc analysis, or any of the post-hoc analyses within this subgroup, has the statistical power to detect a difference between the treatments.

Table 17 Qualifying ARR results at 96 weeks in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
Qualifying ARR (95% CI)	0.14 (0.12 to 0.17)	0.34 (0.30 to 0.38)
Relative reduction in ARR (%)	58.22	
Rate ratio (95% CI, p-value)	0.42 (0.33 to 0.53; p<0.001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
Qualifying ARR (95% CI)	0.16 (0.12 to 0.22)	0.46 (0.38 to 0.55)
Relative reduction in ARR (%)	65.29	
Rate ratio (95% CI, p-value)	0.35 (0.24 to 0.50; p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed		
Qualifying ARR (95% CI)		
Relative reduction in ARR (%)		
Rate ratio (95% CI, p-value)		
SOT-RRMS subgroup		
Number of participants analysed		
Qualifying ARR (95% CI)		
Relative reduction in ARR (%)		
Rate ratio (95% CI, p-value)		

ARR=annualised relapse rate; CI=confidence interval, HDA=high disease activity; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 18 and Table 30

4.3.3 Secondary efficacy outcomes: pre-planned outcomes

A pre-planned secondary outcome of the CLARITY trial was time to first qualifying relapse; results for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 18.

Cladribine tablets were associated with a statistically significant delay in time to first qualifying relapse compared with placebo within the ITT population, HDA-RRMS subgroup and RES-RRMS-subgroup. There was also a numerical advantage for cladribine tablets over placebo in the SOT-RRMS subgroup, but this delay was not statistically significant.

Table 18 Time to first qualifying relapse in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of relapse-free participants, % (95% CI)	80.3 (76.1 to 83.8)	61.1 (56.2 to 65.6)
HR (95% CI, p-value)	0.45 (0.34 to 0.58; p<0.0001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of relapse-free participants, % (95% CI)	77.1 (68.8 to 83.5)	53.3 (44.7 to 61.2)
HR (95% CI, p-value)	0.40 (0.26 to 0.61; p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of relapse-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of relapse-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 18 and Table 31

Another pre-planned secondary outcome of the CLARITY trial was the proportion of qualifying relapse-free participants at 48 weeks and at 96 weeks; results for the ITT population of the CLARITY trials and the three post-hoc subgroups are presented in Table 19. A higher proportion of participants were qualifying relapse-free at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 19 Proportion of qualifying relapse-free participants in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Relapse, n (%)	60 (13.9)	82 (18.9)	110 (25.2)	161 (36.8)
Relapse-free, n (%)	353 (81.5)	327 (75.5)	300 (68.6)	237 (54.2)
Unknown,[a] n (%)	20 (4.6)	24 (5.5)	27 (6.2)	39 (8.9)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Relapse, n (%)	21 (15.0)	30 (21.4)	50 (33.6)	66 (44.3)
Relapse-free, n (%)	112 (80.0)	101 (72.1)	89 (59.7)	69 (46.3)
Unknown,[a] n (%)	7 (5.0)	9 (6.4)	10 (6.7)	14 (9.4)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Relapse, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Relapse-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Relapse, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Relapse-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with no relapse are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 19 and Table 32; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

Two secondary outcomes associated with disability were pre-planned in the CLARITY trial. Results of time to 3-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 20.

Cladribine tablets were associated with a statistically significant delay in time to 3-month CDP compared with placebo within the ITT population and HDA-RRMS subgroup. There was also a numerical advantage for cladribine tablets over placebo in the RES-RRMS-subgroup, but this delay was not statistically significant. The comparative risk of disability progression at 96 weeks in the treatment groups could not be evaluated in the SOT-RRMS subgroup as no participants in the cladribine tablets group had confirmed 3-month CDP at 96 weeks within this subgroup (Table 20).

Table 20 Time to 3-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of progression-free participants, % (95% CI)	85.1 (81.3 to 88.2)	76.3 (71.9 to 80.2)
HR (95% CI, p-value)	0.59 (0.43 to 0.81; p=0.0011)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of progression-free participants, % (95% CI)	91.0 (84.7 to 94.8)	71.7 (63.4 to 78.5)
HR (95% CI, p-value)	0.28 (0.15 to 0.54; p=0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of progression-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of progression-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NE=not estimable; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source; CS, adapted from Table 20 and Table 33

Results of the proportion of participants with 3-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 21. A lower proportion of participants had 3-month CDP at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 21 Proportion of participants with 3-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Progression, n (%)	36 (8.3)	62 (14.3)	65 (14.9)	97 (22.2)
Progression-free, n (%)	377 (87.1)	344 (79.4)	340 (77.8)	292 (66.8)
Unknown,[a] n (%)	20 (4.6)	27 (6.2)	32 (7.3)	48 (11.0)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Progression, n (%)	6 (4.3)	12 (8.6)	27 (18.1)	39 (26.2)
Progression-free, n (%)	126 (90.0)	116 (82.9)	109 (73.2)	89 (59.7)
Unknown,[a] n (%)	8 (5.7)	12 (8.6)	13 (8.7)	21 (14.1)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with 3 month-CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 21 and Table 34; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

As noted in Section 4.3.2 of the ERG report, the ERG re-iterates that due to the small numbers of participants within the SOT-RRMS subgroup (19 and 32 for 3.5 mg/kg cladribine tablets and placebo, respectively), it is unlikely that any of the post-hoc analyses of the secondary efficacy outcomes has the statistical power to detect a difference between the treatments.

4.3.4 Secondary efficacy outcomes: post-hoc analyses

Two additional secondary outcomes associated with disability were defined in a post-hoc analysis to demonstrate prolonged efficacy in the reduction of disability progression following 3.5 mg/kg cladribine tablets. Results of time to 6-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 22.

Cladribine tablets were associated with a statistically significant delay in time to 3-month CDP compared with placebo within the ITT population and HDA-RRMS subgroup. There was also a numerical advantage for cladribine tablets over placebo in the RES-RRMS-subgroup, but this delay was not statistically significant. The comparative risk of disability progression at 96

weeks in the treatment groups could not be evaluated in the SOT-RRMS subgroup as no participants in the cladribine tablets group had confirmed 3-month CDP at 96 weeks within this subgroup (Table 22).

Table 22 Time to 6-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of progression-free participants, % (95% CI)	90.6 (87.4 to 93.1)	83.3 (79.3 to 86.6)
HR (95% CI, p-value)	0.53 (0.36 to 0.78; p=0.0014)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of progression-free participants, % (95% CI)	95.5 (90.2 to 97.9)	77.7 (69.8 to 83.8)
HR (95% CI, p-value)	0.18 (0.08 to 0.44; p=0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of progression-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of progression-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	

CDP=confirmed disability progression; CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NE=not evaluable; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 22 and Table 35

Results of the proportion of participants with 6-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 23. A lower proportion of participants had 6-month CDP at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 23 Proportion of participants with 6-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Progression, n (%)	25 (5.8)	39 (9.0)	53 (12.1)	69 (15.8)
Progression-free, n (%)	386 (89.1)	363 (83.8)	348 (79.6)	315 (72.1)
Unknown,[a] n (%)	22 (5.1)	31 (7.2)	36 (8.2)	53 (12.1)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Progression, n (%)	2 (1.4)	6 (4.3)	23 (15.4)	31 (20.8)
Progression-free, n (%)	129 (92.1)	121 (86.4)	112 (75.2)	96 (64.4)
Unknown,[a] n (%)	9 (6.4)	13 (9.3)	14 (9.4)	22 (14.8)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with 6-month CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 22 and Table 36; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

An additional post-hoc composite efficacy outcome, NEDA-3, was defined as no relapses, no 3-month confirmed EDSS progression, no new or enhancing T1 Gd+ lesions and no new or enlarging T2 lesions. Results of time to NEDA-3 for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 24.

Cladribine tablets had no evidence of disease activity over the entire duration of the CLARITY trial compared to placebo within the ITT population and within all three post-hoc subgroups.

The ERG encourages caution when interpreting the results of these post-hoc analyses due to the inherent limitation of reduced statistical power, particularly within smaller subgroups than originally defined. In particular, the ERG notes caution when interpreting the result of 'time to achieve NEDA-3 status' in the SOT-RRMS subgroup; this is the only outcome for which a significant advantage to 3.5 mg/kg cladribine tablets over placebo is observed for this small subgroup.

Table 24 Time to achieve NEDA-3 status in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of NEDA-3 status, % of participants, (95% CI)	40.1 (34.5 to 45.6)	12.6 (8.8 to 17.0)
HR (95% CI, p-value)	2.21 (1.88 to 2.61, p<0.0001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of NEDA-3 status, % of participants, (95% CI)	43.7 (35.0 to 52.0)	6.9 (2.8 to 13.6)
HR (95% CI, p value)	2.86 (2.14 to 3.81, p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of NEDA-3 status, % of participants, (95% CI)	[redacted]	[redacted]
HR (95% CI, p value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of NEDA-3 status, % of participants, (95% CI)	[redacted]	[redacted]
HR (95% CI, p value)	[redacted]	

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NEDA-3=no evidence of disease activity; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 23 and Table 37

4.4 Health-related quality of life

Three different questionnaires were used in the CLARITY trial to collect data on the impact of treatment with cladribine tablets on patients' HRQoL, namely:

- disease specific multiple sclerosis quality of life questionnaire (MSQoL-54)[45]
- EQ-5D-3L questionnaire and EQ visual analogue scale (VAS)[46]
- short-form health survey (SF-36)[47]

No statistically significant differences in any of the domains of the MSQoL-54 (CS, section B.2.6.1.4) were observed when treatment with cladribine tablets was compared with placebo. Statistically significant improvements in the EQ-5D VAS (p=0.001) and EQ-5D-3L index scores (p<0.001) were observed when treatment with cladribine tablets was compared to placebo.

In the CS, and in the CSR, it is mentioned that the MSQoL-54 and SF-36 questionnaires were not initiated at the start of the CLARITY trial and, therefore, a limited number of responses were obtained (CS, section B.2.6.1.4). The company claims (CSR, p50) that, as the MSQoL-54 questionnaire was not widely translated into non-English languages at the time when the

trial was conducted, the MSQoL-54 questionnaire was only applied to sites in the UK, US, Australia, Canada and Italy.

Analyses of HRQoL data to compare the effect of treatment with cladribine tablets versus the comparators included in the final scope issued by NICE are only presented for the ITT population, i.e. for the RRMS population (CS, Section B.2.6.1.4). Utility values obtained from the CLARITY trial for the RES-RRMS and SOT-RRMS subgroups based on the EQ-5D-3L questionnaire are provided in the CS (appendix H.1.4, pp107-108). Comparisons of cladribine tablets versus placebo using data only from the RES-RRMS and SOT-RRMS subgroups are not presented in the CS.

Given the limited information provided by the company in the CS, the ERG is unable to comment further on the HRQoL data from the CLARITY trial. Information in the CSR for the CLARITY trial (requested by the ERG via the clarification process) indicates that assessment of HRQoL 'is provided as a separate report in appendix 16.1.13'. The company did not provide this appendix at the time of submission or during the clarification process.

4.5 Adverse events

The AEs experienced by patients during the CLARITY trial are reported in the CS (Section B.2.10.1). The company has also provided supportive evidence for the safety of cladribine tablets from the CLARITY-EXT trial (CS, Section B.2.10.2) as well as results from an integrated safety analysis that includes data from four sources: the CLARITY trial, the CLARITY-EXT trial, the ORACLE MS trial[34] and the PREMIERE prospective registry study[33] (CS, Section B2.10.3). In this report, the ERG discusses only the AE data from the CLARITY trial as these are the data used to populate the company's economic model.

4.5.1 Adverse events reported in the CLARITY trial

The AEs reported in the CS are derived from the overall population of patients in the CLARITY trial who were randomised to receive cladribine tablets at a dose of 3.5 mg/kg (n=430) or placebo (n=435) and who received at least one study treatment. No AE data are provided for the RES-RRMS (n=91) and SOT-RRMS (n=51) subgroups of patients from the CLARITY trial. Clinical advice to the ERG is that the AEs recorded for the overall population of the CLARITY trial are relevant to the patients in the RES-RRMS and the SOT-RRMS subgroups.

Number of treatment cycles and treatment compliance

The ERG notes from the CSR for the CLARITY trial that [redacted] of patients treated with cladribine tablets completed all six cycles of treatment compared with [redacted] of patients in the placebo arm. The ERG also notes that treatment compliance was high at [redacted] and [redacted] in

the cladribine and placebo arms. The company measured treatment compliance as the number of tablets taken divided by the expected number of tablets that would be required by the protocol's defined body weight categories.

Treatment discontinuation due to AEs

The company reports that the proportions of patients who discontinued treatment due to AEs was low; 3.5% (n=15) of patients in the cladribine tablets arm and 2.1% (n=9) of patients in the placebo arm. The company provides a summary of the AEs that led to treatment discontinuation in Table 44 of the CS. The AEs in the cladribine arm included: lymphopenia, decreased lymphocyte count, abnormal lymphocyte count, toxic hepatitis, fibroadenoma of the breast, ovarian cancer, uterine leiomyoma, dermatitis, allergic dermatitis, erythematous rash, myocardial infarction, ulcerative colitis, nausea and breast mass. The AEs leading to treatment discontinuation in the placebo arm included: appendicitis, varicella, pregnancy, liver disorder, suicide, intentional self-injury, cough, pulmonary oedema, cardiac hypertrophy, anorexia, haemorrhagic stroke and nephrosclerosis. In most cases, AEs leading to treatment discontinuation were experienced by a single patient.

Treatment emergent adverse events

Overall treatment emergent adverse events

The company reports that the proportions of treatment-emergent AEs (TEAEs) were similar in the cladribine tablets arm and the placebo arm of the CLARITY trial (80.7% and 73.3%). The company has summarised the TEAEs reported in ≥5% of patients.

The ERG notes that most of the TEAEs listed in Table 25 were reported by more patients in the cladribine tablets arm compared to patients in the placebo arm; however, the differences in frequency were generally small. Larger differences in frequency are apparent between patients in the cladribine tablets arm compared to patients in the placebo arm for leukopenia (5.6% versus 0.7%) and lymphopenia (21.6% versus 1.8%). The company has discussed the relationship between lymphopenia and cladribine tablets in the TEAEs of special interest section of the CS. The company also states that the higher rate of leukopenia is linked to the higher rate of lymphopenia (CS, Section B.2.10.3.1).

The ERG notes that three TEAEs occurred in more patients in the placebo arm than in the cladribine tablets arm: urinary tract infection (9% versus 5.3%), fatigue (6% versus 4.7%) and pharyngolaryngeal pain (5.7% versus 4.4%).

Table 25 Summary of TEAEs reported in ≥5% of patients in the CLARITY trial

Adverse event	Cladribine tablets (3.5mg/kg) n=430		Placebo n=435	
	Patients (%)	Events (%)	Patients (%)	Events (%)
Headache	104 (24.2)	264 (10.5)	75 (17.2)	189 (9.7)
Lymphopenia	93 (21.6)	123 (4.9)	8 (1.8)	11 (0.6)
Nasopharyngitis	62 (14.4)	107 (4.3)	56 (12.9)	95 (4.9)
Upper respiratory tract infection	54 (12.6)	118 (4.7)	42 (9.7)	80 (4.1)
Nausea	43 (10.0)	74 (2.9)	39 (9.0)	49 (2.5)
Back pain	34 (7.9)	39 (1.6)	28 (6.4)	42 (2.1)
Urinary tract infection	23 (5.3)	39 (1.6)	39 (9.0)	51 (2.6)
Influenza-like illness	34 (7.9)	48 (1.9)	31 (7.1)	40 (2.0)
Diarrhoea	30 (7.0)	45 (1.8)	29 (6.7)	37 (1.9)
Influenza	28 (6.5)	34 (1.4)	27 (6.2)	43 (2.2)
Fatigue	20 (4.7)	27 (1.1)	26 (6.0)	29 (1.5)
Arthralgia	27 (6.30)	44 (1.8)	21 (4.8)	23 (1.2)
Pharyngolaryngeal pain	19 (4.4)	32 (1.3)	25 (5.7)	29 (1.5)
Leukopenia	24 (5.6)	26 (1.0)	3 (0.7)	6 (0.3)

TEAE=treatment emergent adverse event
Source: CS Table 45

Serious treatment emergent adverse events

The company reports that more patients in the cladribine tablets arm experienced serious TEAEs than in the placebo arm (8.4% versus 6.4%). The company summarises the serious TEAEs by category of system organ class and states that the system organ classes with the largest proportion of serious TEAEs are those listed in rows 1 to 3 of Table 26. The ERG has added the data in row 4 onwards (CSR, pp1002-3).

Table 26 Serious TEAEs in the CLARITY trial (largest proportions)

System organ class	Cladribine tablets (3.5mg/kg) n=430	Placebo n=435
Infections and infestations	2.3%	1.6%
Hepatobiliary disorders	0.7%	0.7%
Gastrointestinal disorders	0.9%	0.5%
Injury, poisoning and procedural complications	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]

Source: CS Section B.2.10.1.2 and CLARITY CSR (p1002 and 1003)

Two patients in the cladribine tablets arm and two patients in the placebo arm died. The company did not consider that the deaths were related to the treatment administered during the trial.

Treatment emergent adverse events of special interest

The company has selected lymphopenia, infections and infestations, and malignancies as being TEAEs of special interest in the CLARITY trial and discusses these in Section B.2.10.1.3 of the CS.

Lymphopenia

The company claims that the higher rate of lymphopenia recorded in the cladribine tablets arm compared to the rate in the placebo arm (21.6% versus 1.8% is consistent with the mechanism of action of cladribine tablets. The company states that only four (0.5%) patients in the cladribine tablets arm discontinued treatment due to lymphopenia and, that at the end of the trial, eight (0.9%) patients in the cladribine tablets arm had Grade ≥3 lymphopenia. However, at further follow-up, the lymphocyte count for these eight patients had improved to Grade 0 or Grade 1.

Infections and infestations

The company briefly discusses the incidence of infections and infestations in the cladribine tablets arm and in the placebo arm (47.7% versus 42.5%); the company states that most of these infections occurred in the upper respiratory tract. The company reports that infection with herpes was 'common' in the cladribine tablets arm of the trial and that most cases were moderate to severe. Except for one case of herpes oticus, the herpes infections were successfully treated.

Malignancies

Three patients in the cladribine tablets arm of the CLARITY trial developed isolated malignancies: malignant melanoma, ovarian carcinoma and metastatic pancreatic carcinoma. The ERG notes from the EMA report[14] provided by the company that the EMA has concluded that there is no conclusive evidence of an increased risk of malignancies in people with MS who are treated with cladribine tablets. The EMA opinion is based on the results of the integrated safety analysis conducted by the company and presented in the CS.

ERG summary of adverse events in the CLARITY trial

Clinical advice to the ERG is that in NHS clinical practice, lymphopenia is associated with treatment with DMTs. Lymphopenia is an issue if it leads to infection; however, the risk of

infection in the CLARITY trial appears to be similar to the risks associated with other DMTs used in the NHS.

4.6 ERG critique of the indirect evidence

The company performed a series of NMAs to establish the comparative effectiveness of cladribine tablets versus relevant comparator treatments across the subpopulations relevant to the NICE scope.

4.6.1 Trials identified for inclusion in the network meta-analysis

The company conducted a systematic literature review (SLR) to identify RCTs which assessed the efficacy, HRQoL, safety and tolerability outcomes associated with key interventions in the treatment of RRMS. Further details of the SLR including inclusion and exclusion criteria and study selection can be found in Appendix D.1.1.1 and Appendix D.1.1.2 of the CS and Section 4.1 of this report.

As per the SLR inclusion criteria, the included RCTs recruited adult participants (≥18 years) with a confirmed diagnosis of RRMS. Some of the studies included within the SLR also included a small number of participants with progressive disease. The company excluded trials with more than 20% of progressive participants from the SLR and so included only studies with a minimum of 80% of participants with RRMS. Five trials,[48-52] with up to 12.3% of participants included in each trial, had progressive disease and none of these trials reported results separately for the RRMS only population. Therefore, a small proportion of the patients included within the NMAs had progressive MS rather than RRMS and this should be taken into consideration when interpreting results from networks that include one or more of these five trials.[48-52]

Table 27 provides a summary of the number of trials, participants, participant years and events (where applicable) contributing to the NMA for the key efficacy outcomes for the ITT population and for the three post-hoc subgroups.

Trial specific summary results and treatment networks for key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are provided in Appendix 10.2 of this ERG report. Trial-specific summary results for other efficacy outcomes, HRQoL outcomes and AEs can be found in Appendix A of the company response to the ERG clarification letter.

Table 27 Summary of trials and participants contributing to NMAs

Outcome	Analysis population	Number of trials	Number of participants / person years	Number of events
Efficacy outcomes				
ARR	ITT	39	36,863 person years	14,051
ARR hospital treated	ITT	10	15,005 person years	1552
ARR requiring steroid treatment	ITT	14	18,718 person years	4876
3-month CDP at 24 months	ITT	16	12,496 participants	2588
6-month CDP at 24 months	ITT	18	13,440 participants	1902
Relapse-free at 12 months	ITT	29	21,556 participants	14,676
Relapse-free at 24 months	ITT	24	15,191 participants	8813
NEDA-3 at 24 months	ITT	5	3874 participants	1924
ARR	HDA-RRMS	11	Not provided	Not provided
3-month CDP at 24 months	HDA-RRMS	6	Not provided	Not provided
6-month CDP at 24 months	HDA-RRMS	3	Not provided	Not provided
6-month CDP at 24 months at any time point	HDA-RRMS	4	Not provided	Not provided
Relapse-free at 24 months	HDA-RRMS	4	1169 participants	654
ARR	RES-RRMS	10	Not provided	Not provided
3-month CDP at 24 months	RES-RRMS	4	Not provided	Not provided
6-month CDP at 24 months	RES-RRMS	4	476 participants	80
ARR	SOT-RRMS	3	Not provided	Not provided

HRQoL and adverse event outcomes				
EQ-5D at 12 months	ITT	3	1285 participants	NA
EQ-5D at 24 months	ITT	5	5047 participants	NA
EQ-5D VAS at 12 months	ITT	4	3608 participants	NA
EQ-5D VAS at 24 months	ITT	4	3222 participants	NA
Study withdrawals (all cause)	ITT	39	22,617 participants	3633
Treatment withdrawals (all cause)	ITT	26	17,094 participants	3277
Study withdrawals (due to AEs)	ITT	28	19,967 participants	890
Treatment withdrawals (due to AEs)	ITT	31	20,596 participants	1294
Any AE	ITT	23	16,880 participants	14,484
Any SAE	ITT	28	19.917 participants	2639
Any TRAE	ITT	4	2886 participants	1582
Any grade 3/4 AE	ITT	3	2681 participants	235
Any cardiovascular events	ITT	4	3242 participants	138
Any infection	ITT	18	12,279 participants	5959
Any serious infection	ITT	7	5808 participants	144
Depression	ITT	19	12,001 participants	1234
ALT increased	ITT	20	13,291 participants	1538

AE=adverse event; ALT=alanine aminotransferase; ARR=annualised relapse rate; AST=aspartate aminotransferase; CDP=confirmed disability progression; EQ-5D=EuroQol 5 dimension questionnaire; HDA=high disease activity; HRQoL=health-related quality of life; ITT=intention-to-treat; RES=rapid evolving severe; RRMS=relapsing remitting multiple sclerosis; SAE=serious adverse event; SOT=sub-optimal therapy TRAE=treatment-related adverse events; VAS=visual analogue scale
Source: Appendix A, company response to ERG clarification letter

The ERG has produced weighted networks from the summary information for each NMA provided by the company to allow for assessment of the relative amount of information available for treatment comparisons in the network. The ERG notes that the networks displayed in Figure 5, Figure 6, Figure 11, Figure 12 and Figure 13 in Appendix 10.2 of this ERG report include previously unpublished data from the PRISMS trial,[43] this trial was also sponsored by the company, to allow the connection of cladribine tablets to alemtuzumab (via INF-β-1a Rebif 44 µg) for the ITT population, HDA-RRMS and RES-RRMS subgroups. The company notes that even when making use of unpublished data, it was not possible to connect cladribine tablets to alemtuzumab in the SOT-RRMS subgroup (see Figure 7 in Appendix 10.2 of this ERG report).

The company used funnel plots and contour-enhanced funnel plots to assess the possibility of publication bias for the following outcomes: qualifying ARR, 3-month CDP at 24 months and 6-month CDP at 24 months (CS, Appendix D, Figure 3, Figure 4 and Figure 5). The company concludes that the possibility of publication bias is unlikely. The ERG agrees with this interpretation and did not identify any additional trials that met the company's eligibility criteria (i.e., adults with RRMS) for inclusion in the network.

The ERG notes that the company did not provide information about the number of participants (or participant years) contributing to the NMAs of the key efficacy outcomes for the post-hoc subgroups, except for 6-month CDP at 24 months in the RES-RRMS subgroups. Furthermore, the ERG is unable to extract the participant numbers or the definitions used in the trials for the RES-RRMS and SOT-RRMS subgroups from the published literature of all of the trials. It is difficult for the ERG to fully interpret NMA results from the subgroups without details of the subgroup definitions and number of participants contributing to them. Therefore, the ERG assessments of the NMA results are made based on the relative precision of the summary results provided for the subgroups (i.e. the standard errors of the summary rate ratios or HRs, see network plots presented in Appendix 11.2 of this ERG report).

4.6.2 Methodological approach to the indirect comparison and/or multiple treatment comparison

The company intended to perform an NMA on all populations of interest where data were available (ITT, HDA-RRMS, RES-RRMS and SOT-RRMS) for several efficacy, safety tolerability and HRQoL outcomes. See Table 27 of this ERG report for a full list of outcomes considered by the company.

Data sources used within the NMAs were obtained from the published clinical literature, and from unpublished study reports for the CLARITY and PRISMS[43] trials. The company performed NMAs using a hierarchical Bayesian approach with Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS.

A summary of the methodological and statistical approach of taken by the company for the NMAs is provided in Table 28.

The company presents NMA results from a random-effects (RE) model for all efficacy outcomes analysed in the ITT population, except for NEDA-3, where results are presented from a fixed-effects (FE) model. NMA results were presented from a FE model for efficacy outcomes from the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups due to the limited number of studies contributing to the evidence networks. NMA results were presented from a mixture of FE or RE models depending on the number of studies contributing to NMA for HRQoL and AEs (see Appendix E of company response to ERG clarification letter for further details).

The ERG acknowledges that fitting RE models within small networks is difficult and agrees that the use of FE models may have been appropriate for the subgroups. However, as baseline characteristics, inconsistency and heterogeneity measures within the post-hoc subgroups are not available, the ERG notes that it is difficult to judge whether important statistical

inconsistency or heterogeneity is present within the results for the subgroups; hence, it is difficult to interpret the numerical NMA results within the subgroups.

Table 28 summarises the ERG's assessment of the methodological and statistical approaches used for the NMAs conducted by the company.

Table 28 ERG assessment of methodological and statistical approaches used for the NMAs

Component	Statistical approach with ERG comments
NMA model choice	ARR was analysed as a Poisson outcome with the total number of relapses observed within a treatment group and the total number of person-years of follow-up for that treatment group as the input data. CDP outcomes (3-month CDP and 6-month CDP at 24 months) were analysed as time-to-event outcomes, assuming an exponential distribution with participants having CDP sustained for 3 months defined as event within a treatment group and the total number of participants randomised for that treatment group defined as input data adjusted for study duration. Further details of the methodological approach and the approach for other efficacy outcomes, safety tolerability and health-related quality of life outcomes can be found in Appendix D 1.1.4.4 of the CS and in the company response to the ERG clarification letter. The ERG considers that the modelling of each outcome in NMA was appropriate
Arm-based or contrast-based NMA model	The company stated that an arm-based model was used rather than a contrast-based model was used to estimate the HRs and relative ARR to increase the amount of evidence contribution in the NMA and that these analyses were validated by comparing HRs and relative ARR reported across the studies contributing to the analysis versus posterior estimates from the NMA. The ERG acknowledges the rationale of the company for employing an arm-based approach but notes the potentially serious limitations of this approach, such as biases in the resulting relative treatment effects due to over-inflated posterior variances and difficulties in translating relative effects from such approaches to predictions of new absolute or relative effects.[53]
NMA model validation	In order to further validate the output of the NMA, anchor based indirect treatment comparisons based on the methods of Bucher et al[54] and a Frequentist approach to NMA was also performed via a generalised linear mixed model (GLMM) approach. The company states that the findings from these two validation analyses were in line with the Bayesian NMA. The ERG agrees that validation of results via a range of methodological approaches is advisable, results of validation were not provided to the ERG so the ERG cannot comment on the robustness of results

Component	Statistical approach with ERG comments
Investigation of heterogeneity	In response to the ERG clarification letter, the company provided results of meta-regression analyses that had been conducted to investigate the impact of baseline characteristics on heterogeneity; the ERG assumes the results provided were from analyses conducted in the ITT population. No significant associations between baseline characteristics and the outcome were found for most of the efficacy outcomes (i.e., 3-month or 6 month CDP or proportion of participants remaining relapse-free) but for ARR, significant associations with EDSS score and percentage of females were found. The company states that as effect size and credible intervals for EDSS and percentage female were close to 0, it is unlikely that this difference would translate into any clinical relevance. The ERG agrees that this statement is a reasonable judgement. The company states that both fixed-effects (FE) and random-effects (RE) models were considered for NMAs and that the choice of FE versus RE model was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC). The model with lowest DIC and/or the closest total residual deviance to the number of data points in the model was considered the best fitting model. The ERG considers that the DIC is a measure of model fit rather than of statistical heterogeneity and that choices between FE and RE models within an NMA should be made taking into account consistency of trial designs, populations and evidence sources, rather than solely on model fit. In response to the ERG clarification letter, the company provided between-study standard deviation values from RE NMA models in the ITT population as a measure of heterogeneity.
Investigation of inconsistency	Inconsistency within closed loops of the network was investigated via inconsistency factors to test the consistency between direct and indirect results that contributed to the NMA analysis.[55] In response to the ERG clarification letter, the company provided results of all tests of inconsistency for efficacy outcomes for the ITT population and found no significant evidence of inconsistency within results for the key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months). Potential inconsistency was found for one loop for the proportion of participants relapse-free at 12 months, therefore the ERG suggests that results of this NMA should be interpreted with caution. The ERG considers this approach to investigating inconsistency to be appropriate but notes that it was unclear whether any inconsistency was present in results for the NMAs of the post-hoc subgroups (where closed loops were present).

ARR=annualised relapse rate; CDP=confirmed disability progression; DIC=deviance information criterion; EDSS=expanded disability status scale; ERG=evidence review group; FE=fixed-effects; HR=hazard ratio; ITT=intention-to-treat; NMA=network meta-analysis; RE=random-effects
Source: CS, Appendix D, company response to ERG clarification letter and ERG comment

4.6.3 Characteristics of trials included in the network meta-analysis

Trial design and participant characteristics of the CLARITY trial are presented in Section 4.2.2 and Section 4.2.3 respectively of this ERG report. General trial design characteristics are presented in Appendix D.1.1.4.1 of the CS, inclusion and exclusion criteria of the trials are presented in Appendix D.1.1.4.2 of the CS and participant characteristics are presented in Appendix D.1.1.4.3 of the CS.

The ERG notes that all participant characteristics presented within the CS relate to the ITT populations of the trials and that demographic information within the post-hoc subgroups (HDA-RRMS, RES-RRMS, SOT-RRMS) is not presented. Therefore, considerations of variability of participant characteristics and the additional analyses conducted to investigate the impact of baseline characteristics on the outcomes of the NMAs apply to the ITT population only and do not necessarily translate to the post-hoc subgroups.

Participant populations were generally quite similar across the trials included in the NMAs, however demographic information was frequently omitted from published trial reports, particularly regarding ethnicity. The mean age by treatment arm across trials ranged from 27.4 to 40.7 years. All trials (except for one treatment arm in one trial[56]) recruited more females than males, with the proportion of females ranging from 33.3 to 78.95% across treatment arms across trials.

The most variability was observed in the mean disease duration at baseline, ranging from 1 to 10.3 years across treatment arms across trials and EDSS score which was reported in a variety of ways across studies (mean and standard deviation, median and range etc.) and makes comparing this characteristic across arms across trials difficult. Overall, the mean or median EDSS score was between 2 and 3 for the majority of treatment arms across trials.

The company acknowledges the uncertainty around disease duration and EDSS score and conducted meta-regression analyses considering these characteristics and other baseline characteristics as sources of heterogeneity in the analysis (see Section 4.6.2 of this ERG report for further discussion).

The company also conducted sensitivity analyses to evaluate the impact of study characteristics on the results of the NMA based on blinding, diagnostic criteria, year of publication and study phase. Further details of these sensitivity analyses for the key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are provided in Appendix 10.3 of this ERG report and sensitivity analysis results for other efficacy outcomes and tolerability outcomes are provided in Appendix B of the company response to the ERG clarification letter.

The company states that the definition of relapse was subject to slight variation but that '…it was commonly defined as new or worsening symptoms that last 24 hours and occurs in the absence of fever or infection' (CS, Appendix D, Table 7). The company also states that the definition of CDP varied between trials but that '…it was commonly defined as at least 1 point EDSS increase, or a 0.5 point increase if the baseline EDSS was ≥ 5.5, confirmed during two subsequent neurological examinations separated by an interval of at least three to six months free of relapses.' (CS, Appendix D, Table 7). The ERG notes that variation in outcome definitions should be taken into account when interpreting the results of the NMAs.

The ERG considers that the trial designs and participant characteristics are broadly similar and that the additional sensitivity analyses undertaken by the company to examine areas of uncertainty in trial design and baseline characteristics (particularly disease duration and EDSS

score) are appropriate. The ERG does not consider that the observed differences across the trials would violate the assumption of transitivity required for the inclusion of these trials in the same network. The ERG also considers that presenting results from a RE model for the ITT population which takes account of statistical heterogeneity arising from variation across trials was an appropriate approach taken by the company. However, the ERG is uncertain whether presenting results from a FE model (rather than from an RE model) for the post-hoc subgroups was the most appropriate approach (see Section 4.6.2 of this ERG report for further discussion).

4.6.4 Assessment of risk of bias of the trials included in the network meta-analysis

The company performed an assessment of study quality and risk of bias using the NICE checklist[31] for all trials included in the NMAs. Detailed information for each domain of quality can be found in Appendix D.1.1.3 and Appendix D.1.1.4 of the CS. A summary of the risk of bias domains is also provided in Appendix 10.4 of this ERG report.

Overall, the ERG agrees with the quality assessments made by the company and notes that the majority of trials included within at least one NMA were generally of good quality. However, important design information was omitted from some trial publications relating to methods of randomisation, allocation concealment and blinding and that the possibility of selective reporting bias could not be excluded from over a third of included trials.

4.6.5 Results from the indirect comparison and/or multiple treatment comparison

Summary results for key efficacy outcomes

A summary of NMA results for cladribine tablets versus the comparators of interest is presented in Table 29 for the key efficacy outcomes for the ITT population and for the three post-hoc subgroups.

The ERG notes that Table 29 clearly demonstrates the paucity of comparative data for cladribine tablets versus the comparators of interest within all three post-hoc subgroups, particularly for the outcomes of 3-month CDP at 24 months and 6-month CDP at 24 months for which no comparative data are available for the SOT-RRMS subgroup.

Summary NMA results for the proportion of participants remaining relapse-free at 12 months and 24 months and the proportion of participants with no evidence of disease activity (NEDA-3) at 24 months in the ITT population are presented in Table 11 of Appendix D of the CS. Summary NMA results for the proportion of participants remaining relapse-free at 24 months

in the HDA-RRMS subgroup are presented in Table 11 of Appendix D of the CS. No further efficacy outcomes could be evaluated in the NMAs for the RES-RRMS and SOT-RRMS subgroups.

Herein, this section of this ERG report focusses mainly on the RES-RRMS and SOT-RRMS subgroups as these subgroups contribute efficacy data to the economic analyses.

Table 29 Summary of efficacy NMA results between cladribine tablets 3.5 mg/kg and comparators for ITT population and post-hoc subgroups

Cladribine tablets 3.5 mg/kg versus	ARR				3-month CDP at 24 months				6-month CDP at 24 months			
	ITT	HDA	RES	SOT	ITT	HDA	RES	SOT	ITT	HDA	RES	SOT
Placebo	↑	↑	↑	↑	↑	↑	↑	-	↑	↑	↑	-
Alemtuzumab12 mg, qd	↓	↔	↓	-	↓	-	-	-	↓	↑	↑	-
Daclizumab HYP 150 mg, q4w	↔	-	↑	-	↔	-	-	-	↔	-	-	-
DMF, 240 mg, bid	↑	↑	-	-	↔	↑	-	-	↑	-	-	-
Fingolimod, 0.5mg, qd	↔	↔	↑	↔	↑	↑	↔	-	↑	-	-	-
GA, 20 mg, qd	↑	↑	-	-	↑	↑	-	-	↑	-	-	-
GA, 40 mg, tiw	↑	-	-	-	-	-	-	-	-	-	-	-
IFN-β-1a, 30 µg, q1w	↑	↑	↑	↑	↑	-	-	-	↑	-	-	-
PEG IFN beta-1a, 125 µg, q2w	↑	-	-	-	-	-	-	-	-	-	-	-
IFN-β-1a, 22 µg, tiw	↑	-	-	-	↔	-	-	-	-	-	↑	-
IFN-β-1a, 44 µg, tiw	↑	-	↑	-	↔	-	-	-	↑	↑	-	-
IFN-β-1b, 250 µg, eod	↑	-	-	-	↑	-	-	-	↓	-	-	-
Natalizumab, 300 mg, q4w	↓	↓	↓	-	↓	-	↓	-	↓	-	↓	-
Teriflunomide, 7 mg, od	↑	↑	↑	-	↑	-	↓	-	↑	-	-	-
Teriflunomide,14 mg, od	↑	↑	↑	-	↑	-	↓	-	↑	-	-	-

ARR=annualised relapse rate; bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; HDA=high disease activity; HYP=high yield process; IFN=Interferon; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once weekly; q4w=every 4 weeks; RES=rapidly evolving severe; SOT=sub-optimal therapy
Source: CS, Appendix D, adapted from Table 11, Table 12 and Table 13

↑ Indicates better efficacy for cladribine tablets 3.5 mg/kg; ↓ indicates lower efficacy for cladribine tablets 3.5 mg/kg; "↔" indicates equivalent efficacy of cladribine tablets 3.5 mg/kg and comparator; cells highlighted in green represent statistically significant results in favour of cladribine tablets 3.5 mg/kg; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies. Highlighted represent statistically significant results in favour of cladribine tablets

A random-effects model was applied to NMA for the ITT population and a fixed-effects model was applied to NMA for the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups

The ERG also notes one discrepancy between Table 12 and Table 15 (CS, Appendix D) for the results of 3-month CDP at 24 months in the HDA-RRMS subgroup. The former table of summary results indicates a statistical advantage to fingolimod 0.5 mg qd, while the latter table of narrative results indicates a statistical advantage to DMF 240 mg bid. The ERG assumes that Table 12 (CS, Appendix D) contains a typographical error and this error has been corrected in Table 16 of this ERG report

NMA results for qualifying annualised relapse rate

Table 30 presents the numerical NMA results for ARR for the ITT population and the three post-hoc subgroups. When interpreting results, the company defines a (non-statistically significant) 'numerical advantage' as a rate ratio or HR of less than 0.9 or greater than 1.1 and 'similar results' as a rate ratio or HR between 0.9 and 1.1. The ERG agrees that these interpretations are appropriate.

In the ITT population, cladribine tablets were associated with a statistically significantly greater reduction in ARR compared with placebo and many other comparators (see Table 30). A numerical advantage was observed for alemtuzumab and natalizumab over cladribine tablets although the advantage was not statistically significant. Where data were available, comparisons in the HDA-RRMS subgroup were generally consistent with comparisons in the ITT population, with the exception that alemtuzumab was numerically comparable to cladribine tablets in the HDA-RRMS subgroup.

In the RES-RRMS subgroup, cladribine tablets were statistically significantly better than placebo, IFN-β-1a 30 µg, and teriflunomide 14 mg. Cladribine tablets were also numerically better than daclizumab, fingolimod, INF-β-1a (Rebif 44 µg) and teriflunomide 7 mg while alemtuzumab and natalizumab were numerically better than cladribine tablets; however, none of these numerical advantages was statistically significant. In the SOT-RRMS subgroup, cladribine tablets were numerically better than placebo and IFN-β-1a 30 µg q1w, and comparable to fingolimod; none of these results were statistically significant.

The company argues that the results for cladribine tablets against alemtuzumab should be interpreted with caution due to heterogeneity between the studies assessing alemtuzumab; CARE-MS I (CAMMS323)[57], CARE-MS II (CAMMS423)[58] and CAMMS223.[59] The company notes key differences between these studies with respect to study phase, eligibility criteria (McDonald 2001[60] or McDonald 2005[61]), baseline EDSS, treatment history, and the onset of disease symptoms and notes the high risk of bias due to the open-label assessment in CARE-MS II trial.[58]

The ERG agrees that NMA results should be interpreted with caution where heterogeneity is considered to be present due to differences in designs and participant characteristics within the trials included in the network. The ERG also notes that any heterogeneity present in the network will impact on all comparisons made in the NMA, therefore all NMA results should be interpreted with caution rather than just the comparison of cladribine tablets against alemtuzumab.

Table 30 NMA results for ARR for cladribine tablets 3.5m g/kg versus comparators for ITT population and subgroups (random-effects model)

Cladribine tablets 3.5 mg/kg versus	ITT		HDA-RRMS		RES-RRMS		SOT-RRMS
	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)
Placebo	0.42 (0.32 to 0.54)	0.42 (0.05)	0.35 (0.24 to 0.51)	0.36 (0.07)	[redacted]	[redacted]	[redacted]
Alemtuzumab, 12 mg, qd	1.31 (0.95 to 1.82)	1.32 (0.22)	0.99 (0.59 to 1.66)	1.02 (0.27)	[redacted]	[redacted]	-
Daclizumab HYP, 150 mg, q4w	0.92 (0.67 to 1.26)	0.94 (0.15)	-	-	[redacted]	[redacted]	-
DMF, 240 mg, bid	0.79 (0.58 to 1.08)	0.8 (0.13)	0.66 (0.41 to 1.06)	0.68 (0.17)	-	-	-
Fingolimod, 0.5 mg, qd	0.91 (0.68 to 1.23)	0.92 (0.14)	0.95 (0.58 to 1.54)	0.98 (0.25)	[redacted]	[redacted]	[redacted]
GA, 20 mg, qd	0.64 (0.49 to 0.85)	0.65 (0.09)	0.44 (0.25 to 0.76)	0.46 (0.13)	-	-	-
GA, 40mg, tiw	0.62 (0.44 to 0.88)	0.63 (0.11)	-	-	-	-	-
IFN-β-1a, 22 µg, tiw	0.58 (0.43 to 0.81)	0.59 (0.10)	-	-	-	-	-
IFN-β-1a, 30 µg, q1w	0.52 (0.40 to 0.69)	0.53 (0.07)	0.49 (0.27 to 0.89)	0.52 (0.16)	[redacted]	[redacted]	[redacted]
IFN-β-1a, 44 µg, tiw	0.64 (0.48 to 0.84)	0.64 (0.09)	0.49 (0.31 to 0.78)	0.50 (0.12)	[redacted]	[redacted]	-
IFN-β-1b, 250 µg, eod	0.62 (0.47 to 0.84)	0.63 (0.09)	-	-	-	-	-
Natalizumab, 300 mg, q4w	1.24 (0.89 to 1.71)	1.25 (0.20)	1.14 (0.70 to 1.84)	1.17 (0.29)	[redacted]	[redacted]	-
PEG IFN beta-1a, 125 µg, q2w	0.63 (0.44 to 0.92)	0.65 (0.12)	-	-	-	-	-
Teriflunomide, 14 mg, od	0.63 (0.47 to 0.84)	0.63 (0.09)	0.63 (0.38 to 1.05)	0.65 (0.17)	[redacted]	[redacted]	-
Teriflunomide, 7 mg, od	0.55 (0.40 to 0.73)	0.55 (0.08)	0.51 (0.31 to 0.84)	0.53 (0.13)	[redacted]	[redacted]	-

bid=twice a day; CrI=credible interval; DMF=dimethyl fumarate; eod=every other day; GA=glatiramer acetate; HDA=high disease activity; HYP=high yield process; IFN=interferon; kg=kilogram; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; RES=rapidly evolving severe; RR=rate ratio; SD=standard deviation; SOT=suboptimal therapy; tiw=thrice a week
Source: CS, Appendix D, Table 14
Highlighted cells represent statistically significant results in favour of cladribine tablets 3.5 mg/kg
"-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies
A random-effects model was applied to NMA for the ITT population and a fixed-effects model was applied to NMA for the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups

NMA results for 3-month CDP sustained at 24 months

In both the ITT population and HDA-RRMS subgroup, at 24 months, cladribine tablets demonstrated a statistically significantly greater improvement compared with placebo in terms of 3-month CDP sustained for 3 months. In the HDA-RRMS subgroup, cladribine tablets were statistically significantly better than dimethyl fumarate (DMF) but there were no numerical or statistically significant differences between these treatments in the ITT population.

While numerically favourable results were observed with alemtuzumab and natalizumab compared with cladribine tablets in the ITT population, results in the HDA-RRMS subgroup numerically favoured cladribine tablets over natalizumab (comparisons versus alemtuzumab were not possible in the HDA-RRMS subgroup); although none of these results were statistically significant.

No comparative data were available to perform an NMA for 3-month CDP at 24 months in the RES-RRMS and SOT-RRMS subgroups.

As for the NMA of ARR, the company notes that the results for cladribine tablets against alemtuzumab should be interpreted with caution due to potential heterogeneity in the results of the alemtuzumab trials, due to the different phases, and because the comparison of cladribine tablets versus alemtuzumab was only feasible via bridging through two comparators i.e. INF-β-1a (Rebif 44µg) and INF-β-1a (Rebif 22µg). The ERG agrees with the company that these results should be interpreted cautiously, and notes that heterogeneity in the network will impact upon all comparisons therefore these results should also be interpreted with caution.

NMA results for 6-month CDP sustained at 24 months

Cladribine tablets were statistically significantly better than placebo and IFN beta-1a 44 µg in the HDA-RRMS subgroup. Cladribine tablets did not show a statistically significant advantage over any comparator.

Although, the NMA results in the ITT population numerically favoured alemtuzumab and natalizumab over cladribine tablets, in the HDA-RRMS group, cladribine tablets were numerically better than alemtuzumab (comparisons versus natalizumab were not possible in the HDA-RRMS subgroup).

In the RES-RRMS population, comparisons were only possible versus alemtuzumab, IFN-β-1a 44 µg, and natalizumab. Cladribine tablets were numerically better than placebo and IFN-β-1a 44 µg, and alemtuzumab and natalizumab were numerically better than cladribine tablets. None of these numerical advantages were statistically significant.

The company notes that the results for cladribine tablets against alemtuzumab should be interpreted with caution 'due to across trial differences between the studies assessing alemtuzumab 12 mg qd' (CS, Appendix D.1.1.1.6). In line with the NMA results for ARR and 3-month CDP at 24 months, the ERG notes that heterogeneity in the network will impact upon all comparisons, therefore all results should be interpreted with caution rather than just the cladribine tablets versus alemtuzumab results.

No comparative data were available to perform an NMA for this outcome in the SOT-RRMS subgroup.

NMA results for quality of life, tolerability and safety outcomes

NMAs were performed only within the ITT population for HRQoL, safety and tolerability; no comparative data for the three post-hoc subgroups were available for NMA.

Therefore this ERG report refers only briefly to these NMA results and further details can be found in Table 17 (CS, Appendix D) for HRQoL results including EQ-5D and ED-5D VAS at 12 months and 24 months, Table 18 (CS, Appendix D) for tolerability results including all cause or AE related study and treatment withdrawals, Table 19 and Table 20 (CS, Appendix D) for safety outcomes including adverse events (see Section 5.6.2 of this ERG report for a full list of safety outcomes reported). Clarification of which analyses were performed with an FE model and which were performed with an RE model are provided in Appendix E of the company response to the ERG clarification letter.

A limited number of HRQoL comparisons could be made using an NMA approach due to the available data (see Table 27). Few numerical or statistical differences were observed in HRQoL between cladribine tablets and available comparators.

Tolerability results were generally in favour of cladribine tablets except for alemtuzumab and IFN-β-1b 250 µg and a numerically lower proportion of treatment withdrawals due to AEs was observed with placebo compared with cladribine tablets.

No statistically significant difference was observed between cladribine tablets, placebo and comparators in terms of any AE, any SAE, and any Grade 3/4 AE. The risk of treatment-related AEs was significantly lower with cladribine tablets compared with INF-β-1a (Avonex) and INF-β-1a (Plegridy). However, the risk of any treatment-related AE was significantly higher in participants treated with cladribine tablets compared with placebo.

4.6.6 Additional assessment of indirect evidence

Uncertainties in the NMA

The company acknowledges that the paucity of data available to assess key efficacy outcomes in the subgroups listed in the NICE scope (particularly SOT-RRMS) is a limitation. In particular, it was challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations via a classic NMA due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network; see Section 4.6.1 of this ERG report and Appendix 10.1 of this ERG report for treatment networks.

Given the importance of the comparison with alemtuzumab in the UK, the company also conducted an additional meta-regression analysis for the outcome of 6-month CDP at 24 months with the aim of providing a more robust comparison between cladribine tablets and alemtuzumab, particularly in the SOT-RRMS population. The objective of the meta-regression was to estimate the efficacy of drug therapies in the RES-RRMS and SOT-RRMS subgroups, by relating efficacy to baseline risk, and centering baseline risk to the expected value in each group. Efficacy results estimated from this meta-regression for cladribine tablets compared to relevant comparators of interest for each subgroup are included in the company's economic analyses of 6-month CDP at 24 months.

The evidence network for the meta-regression is provided in Figure 2 and a summary of the trial data used in the meta-regression analysis is provided in Table 31

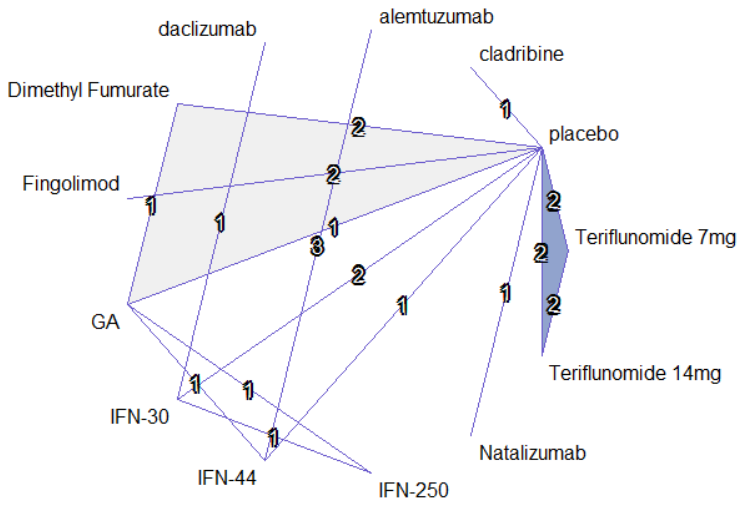


Figure 2 Evidence network for the meta-regression of 6-month CDP at 24 months

CDP=confirmed disability progression; IFN=interferon; GA=Glatiramer acetate
Source; CS, Appendix L, Figure 15

Table 31 Summary of the trials used in the meta-regression of 6 month CDP at 24 months

Study	Treatment 1	Event 1	Total 1	Treatment 2	Event 2	Total 2	Treatment 3	Event 3	Total 3	Number of arms
AFFIRM trial	Placebo	72	315	Natalizumab	69	627	NA	NA	NA	2
BECOME trial	Glatiramer acetate	6	39	IFN-β1a 250 mcg	4	36	NA	NA	NA	2
BRAVO trial	Placebo	46	450	IFN -β1a 44 mcg	35	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab 12mg	4	113	IFN -β1a 44 mcg	19	111	NA	NA	NA	2
CARE-MS I trial	Alemtuzumab 12mg	30	386	IFN -β1a 44 mcg	21	195	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab 12mg	54	436	IFN -β1a 44 mcg	43	231	NA	NA	NA	2
CONFIRM trial	Placebo	45	363	Dimethyl fumurate	28	362	Glatiramer acetate	38	360	3
Decide Trial	Daclizumab	83	919	IFN -β1a 30mcg	111	922	NA	NA	NA	2
DEFINE	Placebo	69	410	Dimethyl fumurate	52	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	63	355	Fingolimod	49	358	NA	NA	NA	2
FREEDOMS trial	Placebo	79	418	Fingolimod	53	425	NA	NA	NA	2
INCOMIN trial	IFN -β1a 30mcg	28	92	IFN -β1a 250 mcg	13	96	NA	NA	NA	2
MSCRG trial	Placebo	50	143	IFN -β1a 30 mcg	35	158	NA	NA	NA	2
REGARD trial	Glatiramer acetate	33	378	IFN -β1a 44 mcg	45	386	NA	NA	NA	2
TEMSO trial	Placebo	68	363	Teriflunomide 14 mg	49	359	Teriflunomide 7 mg	51	366	3
TOWER trial	Placebo	46	389	Teriflunomide 14 mg	43	372	Teriflunomide 7 mg	61	408	3
CLARITY trial	Placebo	[redacted]	[redacted]	Cladribine tablets	[redacted]	[redacted]	NA	NA	NA	2
PRISMS trial (unpublished data)	Placebo	[redacted]	[redacted]	IFN -β1a 44 mcg	[redacted]	[redacted]	NA	NA	NA	2

CDP=confirmed disability progression; IFN–β=interferon beta; NA=not applicable
Source: CS, Appendix L, Table 60

Methods of the meta-regression analysis

The company conducted the meta-regression using guidance from the NICE DSU document TSD3,[62] using a similar methodological approach to the analysis of 6-month CDP at 24 months in the NMA (see Section 4.6.2 of this ERG report).

The ERG considers that the meta-regression methodology employed by the company was appropriate with regards to modelling of the interaction term (independent, exchangeable or common effects) and choice of fixed or random-effects meta-regression model

The ERG notes that the meta-regression approach outlined in the TSD3[62] document is used to explore treatment-covariate interactions, such as an interaction between treatment effect and baseline risk, as a source of heterogeneity. The company has used the approach outlined in TSD3[62] to model treatment-covariate interactions to allow baseline risk estimates to predict treatment effect estimates for specific subgroups. The ERG is uncertain whether the approach outlined in TSD3[62] is valid for the company's objectives.

Eleven of the trials included in the meta-regression (see Table 31) were placebo-controlled trials and informed the baseline risk adjustment. The baseline risk 6-month CDP in the placebo RES-RRMS group of CLARITY was [redacted].

The treatment effects obtained from the meta-regression model are the log-hazard ratios (drug versus placebo) at the mean baseline risk value. Analyses performed centred on the baseline risk of the SOT-RRMS subgroup of the CLARITY trial yielded similar estimates of the relationship between effect and baseline risk as the RES-RRMS analysis, therefore only the baseline risk for the RES-RRMS analysis was used to predict outcomes.

Results of the meta-regression analysis on baseline risk

The company presents numerical results from four meta-regression models (FE or RE, common or exchangeable covariates) in Table 61 of Appendix K of the CS.

The company notes that, in terms of model fit, i.e. the DIC and posterior means of the residual deviances, there is not one model that is clearly favoured (model DICs ranging from [redacted]) and that all four models generated equally plausible effect estimates based on these model fit statistics.

Therefore the company concludes that the simpler common covariate model was preferred to an exchangeable model and that while fixed and random effects models generate equally plausible fits top the data, as heterogeneity is expected across the studies included in the network, the random-effect with common covariate model was preferred.

The ERG agrees with the assessment of the company that this model is the most appropriate of the four regression models for the data and the context of the decision problem. Results of this model are presented within Table 32 of this ERG report.

The interpretation of the log HRs within Table 32 of this ERG report correspond to the effect of the comparator (cladribine tablets, alemtuzumab, daclizumab, fingolimod or natalizumab) versus placebo for participants with a baseline probability of progression that is equal to the mean progression probability in the RES-RRMS population of the CLARITY trial (and un-centred and transformed to produce treatment effect estimates for comparator versus placebo consistent with the baseline risk in the SOT-RRMS subgroup). As all comparisons within the meta-regression are made versus placebo, the comparator interventions are compared in terms of the numerical results and overlap of credible intervals.

Table 32 Log and normalised hazard ratios on 6-month CDP after centering on baseline risk of the RES-RRMS subgroup of the CLARITY trial

Treatment versus placebo	Log HR from the random-effect model with common covariate for baseline risk				Normalised HR (derived from log-HR and baseline risk) and 95% credible intervals	
	Mean	SD	L95%	U95%	Centred on RES-RRMS	Centred on SOT-RRMS
Cladribine tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	Not applicable	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not applicable
Between-study SD	[redacted]	[redacted]	[redacted]	[redacted]	Risk in RES-RRMS population of [redacted]	Risk in SOT-RRMS population of [redacted]
Baseline risk covariate	[redacted]	[redacted]	[redacted]	[redacted]		
Residual deviance	[redacted]					
pD	[redacted]					
DIC	[redacted]					

CDP=confirmed disability progression; DIC=deviance information criterion; HR=hazard ratio; L95%=lower bound of 95% credible interval; pD=effective number of parameters; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SD=standard deviation; SOT=sub-optimal therapy; U95%=upper bound of 95% credible interval
Source: CS, Table 70; company response to ERG clarification letter

Meta-regression results show that cladribine tablets were predicted to be more efficacious than fingolimod (log hazard ratio relative to placebo of [redacted] for cladribine tablets versus [redacted] for fingolimod) and alemtuzumab ([redacted] versus [redacted]), but marginally less efficacious than natalizumab ([redacted] versus [redacted]) and daclizumab ([redacted] versus [redacted]).

Within the company decision problem (CS, Table 2), fingolimod was not specified as a comparator to cladribine tablets within the RES-RRMS subgroup and natalizumab was not

specified as a comparator to cladribine tablets within the SOT-RRMS subgroup. Therefore normalised HRs are not calculated for these comparisons.

Within the RES-RRMS subgroup, the corresponding normalised HRs were [redacted] for treatment effect of cladribine tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, in the RES-RRMS and [redacted] for natalizumab versus placebo. Within the SOT-RRMS subgroup the corresponding normalised HR in this population were [redacted] for cladribine tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, and [redacted] for fingolimod versus placebo.

The company concludes that the meta-regression predicted that all comparators are less effective in the SOT-RRMS subgroup than in RES-RRMS subgroup and, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy.

Validation of the meta-regression analysis

The company notes that the meta-regression model has two assumptions; firstly that baseline risk is predictive of effect size (on a linear scale, given that the meta-regression model is expressed on a complimentary log-log scale) and that the relationship between baseline risk and effect size explains the effects observed in the different subgroups (i.e. that any differences across subgroups are not due to other known or unknown factors).

The company validates the first assumption by plotting the log HR of each comparator compared to placebo versus baseline risk complimentary log-log scale and concludes that there is evidence of a consistent linear relationship between baseline risk and effect size for fingolimod, natalizumab and cladribine tablets (CS, Appendix K, Figure 16) and that the comparable slopes of these trend lines indicate that the relationship between effect size and baseline risk may also be consistent across drugs. The ERG agrees in principle with this interpretation but notes that evidence of a linear relationship is not consistent for all comparators within the meta-regression.

The company validates the second assumption by considering whether results produced by the meta-regression are sufficiently predictive of the subgroup effect sizes observed in individual studies (the CLARITY, AFFIRM[63], and PRISMS[43] trials), when un-centred and transformed to the corresponding baseline risks. Table 33 shows the predicted compared to the observed mean HR for the RES-RRMS subgroup for the relevant comparison of each trial. The company concludes that for the CLARITY and PRISMS[43] trials, the observed effect size has been accurately predicted by the meta-regression but for the natalizumab versus placebo

comparison from the AFFIRM[63] trial that the effect size has been under-estimated, with a predicted hazard ratio of [redacted] (observed).

Table 33 Predicted versus observed mean HR for RES-RRMS subgroup in the CLARITY, AFFIRM, and PRISMS trials

Therapy (vs placebo)	Study	Baseline risk in placebo group	Predicted effect size (mean hazard ratio)	Observed effect size (mean hazard ratio)
Cladribine tablets	CLARITY	[redacted]	[redacted]	[redacted]
Natalizumab	AFFIRM	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg	PRISMS	[redacted]	[redacted]	[redacted]

Source: adapted from CS, Appendix K, Table 64

The ERG suggests that the results presented within Table 33 of this ERG report may indicate that the relationship between baseline risk and effect size does not explain the differences observed across subgroups, hence the meta-regression approach may be invalid.

The company suggests that under-estimation may be due to the relationship between baseline risk and effect size estimate in the AFFIRM[63] trial differing between the relationship between baseline risk and effect size in other studies, including the CLARITY and PRISMS[43] trials. This suggestion contradicts the company's interpretation of their first validation (i.e., that the similar slope trend lines of natalizumab and cladribine tablets indicate that the relationship between effect size and baseline risk may also be consistent across drugs).

Due to the ERG's previously outlined concerns regarding the validation results presented by the company and uncertainty regarding whether the meta-regression approach is applicable to the objective of the company in this analysis, the ERG encourages caution when interpreting the results of this meta-regression.

4.7 Conclusions of the clinical effectiveness section

Direct clinical evidence

The direct clinical effectiveness evidence for cladribine tablets versus placebo was derived from the CLARITY trial. The ERG highlights the following points:

- The CLARITY trial was of good quality and was well conducted; participant characteristics were balanced across the treatment groups and the pre-planned statistical methods were generally appropriate.
- The clinical effectiveness evidence presented within the CS is mainly based upon three subgroups of participants that were defined post-hoc. In addition, three post-hoc outcomes were presented within the CS that were not included in the original analysis of the CLARITY trial. The ERG acknowledges the company rationale was necessary for defining subgroups and outcomes to address the NICE Decision Problem, but notes

the inherent limitation of reduced statistical power when conducting post-hoc analyses, particularly within smaller subgroups than originally defined within the CLARITY trial.

- The company amended their statistical approach with regards to missing data from the original analysis of the CLARITY trial for the re-analysis presented within the CS; the ERG agrees that the statistical approach used within the re-analysis is more appropriate than the original approach.
- Results of the pre-planned primary outcome show relative numerical reductions in qualifying ARR for cladribine tablets compared to placebo in the ITT population and in the three post-hoc subgroups. These results were statistically significant for the ITT population, HDA-RRMS and RES-RRMS subgroups but not for the SOT-RRMS subgroup.
- Results of pre-planned and post-hoc efficacy outcomes relating to relapse and disability progression generally show numerical advantages to cladribine tablets compared to placebo and the advantages within the subgroups tend to be numerically larger compared to the results within the ITT population. For secondary outcomes relating to relapse, these numerical advantages are significant within the ITT population, HDA-RRMS and RES-RRMS subgroups but not for the SOT-RRMS subgroup. For secondary outcomes relating to disability progression, these numerical advantages are significant within the ITT population and HDA-RRMS subgroup but not for the RES-RRMS and SOT-RRMS subgroups.
- Results of a post-hoc efficacy composite outcome NEDA-3, defined as no evidence of disease activity, showed numerically and statistically significant advantages for cladribine tablets compared to placebo in the ITT population and in all three post-hoc subgroups. The ERG advises caution when interpreting these results, due to the post-hoc nature of the analyses and the small participant numbers within the subgroups.

Indirect clinical evidence

Regarding the NMAs, the ERG considers that the general approach of the company is appropriate with regard to:

- The identification of trials for inclusion in the SLR and NMA
- The comparators included within the network for each subgroup of interest
- The outcomes considered in NMA
- The statistical approach to NMA for each outcome; with the exception of the arm-based approach of the NMA, which may have resulted in biased relative treatment effects due to over-inflated posterior variances
- The additional analyses and sensitivity analyses conducted by the company in consideration of inconsistency and heterogeneity of treatment effect due to trial or participant characteristics; however, these analyses were conducted only within the ITT population, therefore it is unclear whether inconsistency or heterogeneity is presented in analyses of the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups.
- The presentation of results from NMA models using random-effects for the ITT population due to anticipated heterogeneity between trials included in the network; however the ERG is uncertain whether important statistical inconsistency or heterogeneity is present within the results for the subgroups
- The company interpretations of the relative treatment effects from the NMA.

The ERG highlights the following points:

- Results of the NMAs undertaken for the efficacy outcomes of interest (qualifying ARR, 3 month CDP at 24 months and 6 month CDP at 24 months), generally show a numerical and/or statistically significant advantage for cladribine tablets compared to most comparators, aside from alemtuzumab and natalizumab, where NMA results generally showed a numerical disadvantage for cladribine tablets
- The company states that certain NMA results (such as the comparison of cladribine tablets against alemtuzumab) should be interpreted with caution due to difference in trial designs and participant characteristics of trials included in the network. The ERG considers that any heterogeneity present in the network will impact on all comparisons made within that network and therefore all NMA results should be interpreted with caution rather than just specific comparisons
- A major limitation of the NMAs performed by the company was the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations via a classic NMA approach. Therefore the company performed an additional meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS, by relating efficacy to baseline risk, and centering baseline risk to the expected value in each group
- In principle, the ERG considers the company approach to the meta-regression generally appropriate with regards to the trials and comparators included within the meta-regression, the statistical methodology employed, the model selection criteria and choice of most appropriate model and the interpretation of meta-regression results
- The company concludes that the meta-regression predicted that all comparators are less effective in the SOT-RRMS subgroup than in RES-RRMS subgroup and, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy
- However, the ERG is not convinced by the validations of the meta-regression presented by the company, and whether the application of this meta-regression approach, outlined in by the NICE DSU in the context of considering baseline risk as a source of between-trial heterogeneity, is appropriate and valid for the objectives of the company. Therefore, the ERG encourages caution when interpreting the results of this meta-regression for the RES-RRMS and SOT-RRMS subgroups.

5 COST EFFECTIVENESS

5.1 Introduction

A summary of the evidence provided by the company in support of the use of cladribine tablets for the treatment of RRMS is provided in Sections 5.2 to 5.5 of this report. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature (see Section 5.2) and (ii) a report of the company's de novo economic evaluation, which included the development of a model using Microsoft Excel (see Section 5.3 and Section 5.4). A structured critique of the economic evidence submitted by the company is provided in Section 5.5

5.2 Objective of the company's cost effectiveness review

The company's systematic review was carried out to identify studies that considered the cost effectiveness of treatments for RRMS. The company searched five databases (on 30 January 2017). These, and the interface used for each search, are listed in Table 34.

Table 34 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Embase.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Embase.com
MEDLINE® In-Process	Pubmed.com
National Health Service Economic Evaluation Database (NHS EED)	Cochrane library
EconLit®	AEAweb.org interface

Source: CS, Appendix G

The company also carried out searches to identify conference abstracts published between 2012 and 2016 from the following congresses:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): Annual International Meeting
- ISPOR: Annual European Congress
- ISPOR: Latin America Conferences
- 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 (ANA)
- European Federation of Neurological Societies (EFNS)
- European Neurological Society (ENS)
- Consortium of Multiple Sclerosis Centers (CMSC)
- Academy of Managed Care Pharmacy (AMCP).

In addition, hand searches of websites were performed to identify economic models submitted to HTA organisations. These searches were limited to appraisals reported after 2005.

5.2.1 Eligibility criteria used in study selection

The main inclusion criteria that were used to select studies are shown in Table 35. However, as the review was undertaken to identify information relevant to decision making in England, only peer-reviewed journal publications that reported cost effectiveness results in the UK were considered in detail.

Table 35 Economic review inclusion criteria

Characteristic	Inclusion criteria
Population	• Adults aged 18 and over
Interventions / comparators	• Cladribine tablets • IFN-ß 1a (Avonex, Rebif) • IFN-ß 1b(Betaferon, Betaseron) • Glatirmer acetate (Copaxone) • PEG-IFN- ß 1a (Plegridy) • Natalizumab (Tysabri) • Alemtuzumab (Lemtrada) • Fingolimod (Gilenya) • Dimethyl fumarate (Tecidera) • Teriflunomide (Aubagio) • BSC (author's definition) • Placebo • No treatment • Any other intervention
Outcomes	• All
Study design	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimization analyses • Cost-consequence studies • Budget impact models
Country	• No restriction
Exclusion	• Cost studies, surveys, database analyses

BSC=best supportive care
Source: CS Appendix G, Table 32

5.2.2 Included and excluded studies

The searches identified eight studies[64-71] reporting the cost effectiveness of the use of DMT to treat people with RRMS in the UK and eight NICE TA appraisals.[15-20,72,73] None of the identified studies reported the cost effectiveness of cladribine tablets. Seven[64-66,68-71] of the eight studies reported incremental cost effectiveness ratios (ICERs) per QALY gained. Only two studies[68,69] reported results for the populations considered by the company (people with RES-RRMS[69] and SOT-RRMS[68]). Cost effectiveness results for people treated with natalizumab were

reported in one study[69] and results for people treated with fingolimod were reported in two studies.[68,69] None of the identified studies reported cost effectiveness results for people treated with daclizumab or alemtuzumab.

The 11 economic models submitted to NICE as part of the technology appraisals process included six submitted to the STA process and five submitted to an ongoing MTA:

- Natalizumab (TA127)[17]
- Fingolimod (TA254)[72]
- Teriflunomide (TA303)[73]
- Alemtuzumab (TA312)[19]
- Dimethyl Fumarate (TA320)[18]
- Daclizumab (TA441)[20]
- Beta-interferon and glatiramer acetate (ID809 [ongoing] - review of TA32).[15]

5.2.3 Findings from the cost effectiveness review

Of the eight published studies[64-71] relevant to the UK that were identified via the electronic database searches, only two[68,69] reported the cost effectiveness of DMT in RES-RRMS or SOT-RRMS. Maruszczak[68] reported the cost effectiveness of treatment with fingolimod versus DMF in patients with highly active RRMS (as defined in the SmPC[8] for fingolimod, and considered by the company to represent the SOT-RRMS cohort). Reported results suggest that, the ICER for the comparison of the cost effectiveness of treatment with fingolimod versus dimethyl fumarate is £14,076 per QALY gained. The company report (CS, Table 58) that results from Montgomery[69] suggest that the ICER for the comparison of the cost effectiveness of treatment with fingolimod versus natalizumab in patients with RES-RRMS is £15,313 per QALY gained (the ERG was unable to find this figure in the quoted source). Further findings from the review of identified studies may be found in Appendix G of the CS.

The company examined the documents related to previous NICE TAs[10,17-20,72,73] in detail and used decisions that had previously been made by NICE ACs to inform the design of their economic analyses. In particular, the company took note of the following points:

- Inclusion of the long-term waning in drug efficacy for all therapies, including cladribine, rather than assuming that efficacy persists indefinitely
- Use of health state utility values from the CLARITY study (rather than from published studies)
- Re-initiation of treatment with alemtuzumab (and of cladribine)
- Use of the EMA preferred endpoint of 6-month (rather than 3-month) CDP
- Natural history improvements and progression in EDSS modelled based on analyses of data from the British Columbia registry (rather than the London Ontario registry)

- A faster rate of progression in those with SOT-RRMS or RES-RRMS when compared to less active disease
- Consideration of non-medical costs.

The company's review of information from previously conducted TAs also highlights that the following assumptions and inputs have been accepted by NICE Appraisal Committees (ACs):

- The high level of uncertainty around treatment pathways and insufficient data to populate a model necessitate focusing assessment on only one line of treatment
- Consideration should be given to the impact of disability progression on the health utility of caregivers
- Benefits of an oral drug may not be fully captured by QALY estimates.

5.3 ERG critique of the company's literature review

The company reports full details of the searches used to identify cost effectiveness evidence in Appendix G of the CS. These searches included an appropriate cost effectiveness filter. The ERG highlights that search terms were not used consistently between databases. This approach is not considered good practice as it means that, across databases, the searches are inconsistent. In addition, the ERG notes that the searches were carried out in January 2017 and therefore some relevant studies may have been missed. The ERG updated the company searches for the period between January and July 2017 and is satisfied that no relevant studies have been missed.

The company also undertook two additional literature reviews, one focusing on HRQoL data and the other on costs and health care resources, to identify appropriate parameter values to use in their economic model. The ERG considers that undertaking such reviews is good practice and recognises the workload that was required. Full details of the company searches, and the accompanying reviews of evidence are reported in Appendix H and Appendix I of the CS.

5.3.1 NICE reference case checklist

Table 36 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. Cost effectiveness results were only generated for two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS)
Comparator(s)	As listed in the scope developed by NICE	Partial. Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS subgroups
Perspective costs	NHS and PSS	Partial. The ERG considers the inclusion of informal care costs was inappropriate and outside of the NICE reference case
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial. The ERG considers the inclusion of carer disutility was inappropriate and outside of the NICE Reference Case
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Trial data as well as data from the company's NMAs and meta-regression were used to populate the company model
Outcome measure	Health effects should be expressed in QALYs.	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=Personal Social Services

5.3.2 Model structure

Overview of the model

The company's model has been designed to assess the incremental cost effectiveness of treatment with cladribine tablets versus alternative treatments for people with RES-RRMS and SOT-RRMS. A natural history reference model (developed using the disability and relapse status data of people receiving BSC) has been enhanced by incorporating trial data that provided evidence for the comparative efficacy of DMTs versus placebo. The basic structure comprises 11 health states: 10 EDSS states and a single state for death from all causes (see Figure 3). At model entry, patients are assigned to each of the EDSS health states based on the proportions of patients recruited to the CLARITY trial who were, at baseline, in each state. In each cycle period (1 year) the cohort is at risk of moving to a higher EDSS state, moving to a lower EDSS state, remaining in the current EDSS state, or dying. In addition, during each cycle, patients are at risk of experiencing one or more acute relapse events or discontinuing treatment. Patients who discontinue DMT are assumed to receive BSC (although it is recognised that this is a simplification as some people are likely to receive further DMT treatment). Costs are calculated based on EDSS state, number of relapses and time in each state. Health effects are modelled in terms of QALYs, which take into account the effect of disability status, relapses and drug-related AEs.

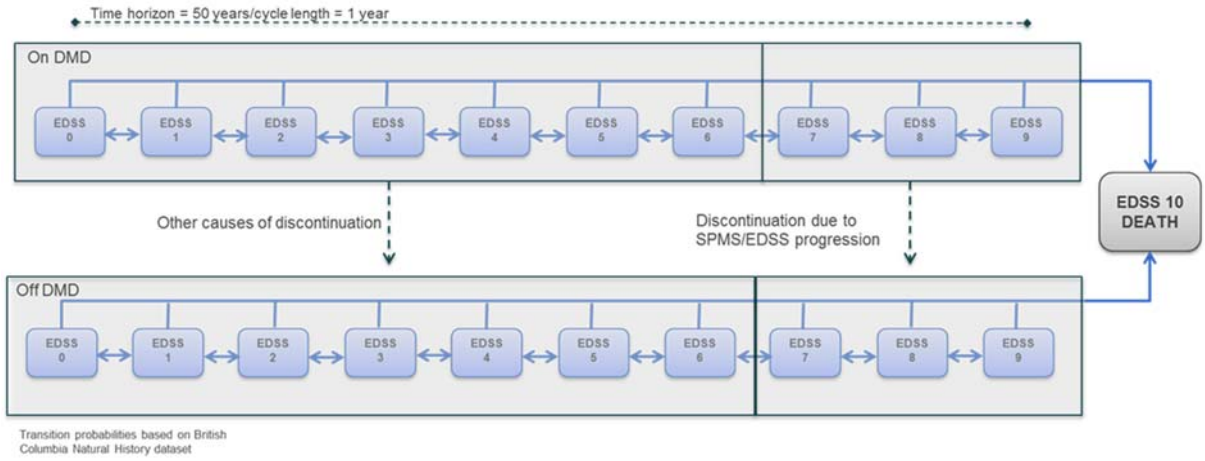


Figure 3 Health state structure of the company model

Source: CS, Figure 12

5.3.3 Population

Four subpopulations of people with RRMS are considered by the company. The company's analyses relate to people with RES-RRMS and SOT-RRMS, defined as follows:

- RES-RRMS: people with two or more relapses in the prior year, whether on treatment or not, and at least one T1 Gd+ lesion

- SOT-RRMS: people with one or more relapse in the prior year while on DMT, and at least one T1 Gd+ lesion or 9 T2 lesions.

These two populations are then subdivided, as shown in Table 37, depending on whether people are able to receive alemtuzumab.

Table 37 Modelled patient populations

Able to receive alemtuzumab	
Yes	**No**
RES-RRMSa	RES-RRMSb
SOT-RRMSa	SOT-RRMSb

Although people with active RRMS are included in the final scope issued by NICE, the company has not considered this population in any of their economic analyses as the anticipated EMA licence for cladribine was not expected to include this specific population.

Key baseline characteristics of the modelled populations, derived from the CLARITY trial, are provided in Table 38.

Table 38 Key model baseline population characteristics

Characteristic	**ITT (for reference)**	**RES-RRMS**	**SOT-RRMS**
Mean age (se)	38.7 years (0.474)	[redacted]	[redacted]
Female to male ratio:	1.933	[redacted]	[redacted]
Relapse in prior 12 months 0 1 2 >3	 0 (0.0%) 306 (70.0%) 110 (25.2%) 21 (4.8%)	[redacted]	[redacted]
Baseline EDSS			
EDSS 0	2.9%	[redacted]	[redacted]
EDSS 1.0	3.0%	[redacted]	[redacted]
EDSS 2.0	31.4%	[redacted]	[redacted]
EDSS 3.0	24.3%	[redacted]	[redacted]
EDSS 4.0	23.7%	[redacted]	[redacted]
EDSS 5.0	9.8%	[redacted]	[redacted]
EDSS 6.0	5.1%	[redacted]	[redacted]

EDSS=expanded disability status scale; ITT=intention-to-treat; se=standard error
Source: CS, Table 59 (Merck data on file)

5.3.4 Interventions and comparators

The company's economic evaluation compares the cost effectiveness of cladribine versus four of the comparators listed in the final scope issued by NICE (discussed in Section 3.6 of the ERG report). The methods used to deliver each of the DMTs considered in the company's analyses are summarised in Table 39. For each population considered in the company analyses, treatment with cladribine is compared with two comparator DMTs (see Table 40).

Table 39 Method of delivery of DMTs considered in the company's economic evaluation

DMT	Method of delivery
Cladribine tablets	Each treatment course consists of two treatment weeks, one at the beginning of the first month of year 1 and one at the beginning of the second month of year 2. Each treatment week consists of 4 or 5 days on which a patient receives one or two tablets (depending on body weight) as a single daily dose
Alemtuzumab	An infusion delivered on five consecutive days during week one of year one and on three consecutive days during week one of year 2
Daclizumab	A once monthly injection continued until treatment discontinuation
Fingolimod	One tablet a day until treatment discontinuation
Natalizumab	An infusion delivered once every 4 weeks until treatment discontinuation

DMT=disease modifying therapy

Table 40 Modelled comparators

Population	Comparator
RES-RRMSa	Natalizumab
	Alemtuzumab
RES-RRMSb	Natalizumab
	Daclizumab
SOT-RRMSa	Fingolimod
	Alemtuzumab
SOT-RRMSb	Fingolimod
	Daclizumab

Discontinuation

The company has assumed that any patient transitioning to EDSS state 7.0 or greater would have SPMS and, hence, would discontinue therapy. The company has explored the impact of varying the EDSS state 'cut-off' in a sensitivity analysis.

The modelling of treatment discontinuation due to reasons other than clinical diagnosis, for example, due to tolerability, has been captured through the implementation of a separate annual discontinuation probability. This is applied in each cycle and, in the base case, varies by treatment but is constant over time. The company has undertaken sensitivity analyses to explore the impact of varying the discontinuation probability over time.

Alemtuzumab and cladribine tablets are prescribed as two treatment courses administered over a 2-year period, with an interval of 12 months between the first and second course. Therefore, the concept of discontinuation is not relevant. The company has, however, applied the discontinuation probability to the first cycle to account for discontinuations between the first and second courses.

5.3.5 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and PSS. The cycle length was one year, the time horizon was set at 50 years and, in line with the NICE Guide to the Methods of Technology Appraisal,[31] both costs and outcomes have been discounted at 3.5% per annum.

5.3.6 Treatment effectiveness and extrapolation in the base case

Natural history model - acute relapse events

Relapse rates are modelled as a function of time and have been estimated by multiplying the number of patients alive by the qualifying ARR derived from published sources (CS, p99). The qualifying ARR in the first year is modelled using rate data from the placebo arm of the CLARITY trial (RES-RRMS: mean=[redacted], SOT-RRMS: mean=[redacted]). In the base case, the qualifying ARR in subsequent years relies on adjusting the first-year value using data from the British Columbia Multiple Sclerosis (BCMS) registry.[6]

Natural history model - duration of relapse events

Relapses have been divided into two categories depending on whether hospitalisation was required. Pooled ITT data from the CLARITY trial have been used to estimate duration of events (see Table 41). These estimates have been applied to relapses experienced on all treatments considered in the analyses.

Table 41 Length of relapse events

Relapse event	Mean (sd)
Duration of relapses requiring hospitalisation	34.41 days (6.38 days)
Duration of relapses not requiring hospitalisation	38.64 days (6.20 days

sd=standard deviation
Source: CS, Table 64

Natural history model – EDSS progression

Transition matrices for the natural history of RRMS were identified from previous NICE appraisals[18,19,72,73] and publications associated with the UK risk-sharing scheme.[74,75] The matrix with on a median age of onset of over 28 years was used in the base case, in keeping with the mean baseline age (38.7 years) and disease duration (5.18 years) of the modelled population (Table 42).

Table 42 Annual base case EDSS transition probabilities (multiple sclerosis age of onset ≥28 years)

State (from \to)	0	1–1.5	2–2.5	3–3.5	4–4.5	5–5.5	6–6.5	7–7.5	8–8.5	9–9.5
0	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000
1–1.5	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001
2–2.5	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004
3–3.5	0.00594	0.04960	0.12006	0.54422	0.09109	0.05845	0.11649	0.01030	0.00355	0.00030
4–4.5	0.00165	0.2214	0.06660	0.11519	0.48935	0.10388	0.16811	0.02580	0.00671	0.00056
5–5.5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.27310	0.03880	0.01883	0.00102
6–6.5	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74069	0.10897	0.04377	0.00423
7–7.5	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559
8–8.5	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01881	0.05574	0.90340	0.02066
9–9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832

Source: CS, Table 66 (Palace 2014[74])

Natural history model – progression rate adjustments

Progression rates in the natural history model have been adjusted for patients with RES-RRMS and SOT-RRMS. To account for faster progression, the model includes an acceleration parameter that is used to increase the probability of EDSS progression prior to the adjustment for the effect of DMT (see Table 43). The adjustment is applied to the probability of progression associated with each EDSS state. Based on advice from the company's clinical experts, the adjustment is applied to EDSS states 0 to 6 as progression rates are expected to return to baseline levels once patients develop SPMS (i.e. transition to EDSS 7.0 or greater). The adjustment was estimated using data from the CLARITY trial.

Table 43 Hazard rate adjustments

Group	Hazard rate adjustment EDSS 0 to 6	Note
RES-RRMS	[redacted]	Calculated by comparing progress by week 96 in RES-RRMS population versus progress in non-RES-RRMS population (placebo arm) in the placebo arm of the CLARITY trial
SOT-RRMS	[redacted]	Progression rates were lower in the placebo SOT-RRMS group than the placebo active RRMS population. This was considered not to be plausible and, therefore, the hazard rate adjustment was assumed to equal the ratio of the annualised relapse rates of the placebo group SOT-RRMS population versus the placebo group active population

EDSS=expanded disability status scale
Source: CS, Table 68

Natural history model – mortality risk

Transitions to the death state have been assumed to be independent of EDSS state. The annual probability of death was estimated by inflating Office for National Statistics (ONS) gender-averaged all-cause mortality rate by published excess mortality risk rates comparing

mortality in the population with RRMS versus the general population.[76] Next, the inflated mortality rates were converted into annual (cycle) probabilities.

Treatment adjusted model – relapse rate

The relapse rate ratios have mainly been obtained from the company's NMA (FE model), although the efficacy of alemtuzumab and daclizumab for the SOT-RRMS subgroup had to be assumed due to lack of available data. A summary of the ratios used in the model is provided in Table 44.

Table 44 Ratio of annualised relapse rates comparing DMT versus placebo

Treatment versus placebo	Median ratio of annualised relapse rates comparing treatment versus placebo [upper 95% crl to lower 95% crl value]	
	RES-RRMS	SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Fingolimod	Not in scope	[redacted]
Natalizumab	[redacted]	Not in scope
Daclizumab	[redacted]	[redacted]

*based on relapse rate ratio from CARE MS-II study
**assumed to have the same effect as cladribine
Crl=credible interval; DMT=disease modifying therapy
Source: CS, Table 69

Treatment adjusted model – EDSS progression

The effect of DMT on progression between EDSS states was modelled using data on confirmed disability at 6 months. A meta-regression analysis was used to generate hazard ratios between each DMT and placebo. The log-hazard ratios used in the model (see Table 45) correspond to the effect of DMT versus placebo for patients with a baseline probability of progression that is equal to the mean progression probability in the RES-RRMS population of CLARITY.

Table 45 Normalised progression hazard ratios

DMT	Normalised hazard ratio*	
	RES-RRMS	SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]
Fingolimod	Not applicable	[redacted]
Natalizumab	[redacted]	Not applicable
Population risk	[redacted]	[redacted]

DMT=disease modifying therapy
*Derived from log-hazard ratio and baseline risk
Source: CS, Table70

The company highlights that the results of their meta-regression analysis show significant overlap in the credible intervals for the hazard ratios of confirmed disability progression at 6 months for both subgroups, and that no therapy statistically dominates in terms of this outcome measure.

Treatment adjusted model – waning of drug efficacy

The long-term treatment effects of the intervention and comparators are unknown. The company has assumed that the effect of treatment will decrease over time (known as waning). This assumption has been modelled by adjusting the hazard ratio for drug effect. The annual proportions of drug effect for alemtuzumab, daclizumab, fingolimod and natalizumab are displayed in Table 46.

The company's assumptions relating to the waning effect of treatment with cladribine tablets are based on a post-hoc analysis of data collected during the CLARITY and CLARITY-EXT trials that explored whether the treatment effect observed during the CLARITY trial persists in the absence of additional treatment. The rank preserving structural failure time model (RPSFTM) and the iterative parameter estimation (IPE) algorithm have been used to estimate the effect of patients switching from placebo to intervention in the placebo/intervention group of the CLARITY-EXT trial.

Results from the company's analyses suggest that the effect of treatment with cladribine tablets was approximately constant over the 4 years for which data are available. However, the effectiveness beyond 4 years remains uncertain.

Table 46 Changes in drug effect over time

Years	Proportion of DMT effect	
	Cladribine	Alemtuzumab, daclizumab, fingolimod and natalizumab
0 to 2	100%	100%
2 to 4	100%	75%
4 to 5	75%	75%
5+	50%	50%

DMT=disease modifying therapy
Source: CS, Table 71 and Table 73

Treatment adjusted model – safety and tolerability

The company's probability estimates of experiencing drug-related AEs or tolerability issues are based on clinical trial data identified in the systematic literature review. Values used in the model are presented in Table 47.

Table 47 Absolute probabilities of adverse events by DMT and event type

Event type	Cladribine	Alemtuzumab	Natalizumab	Fingolimod	Daclizumab
Recurring events that apply to each year treated in the model					
Infusion site reaction	0%	90.1%	23.6%	0%	0%
Injection site reaction	0%	0%	0%	0%	2.0%
One-off events that apply at the start of the model time horizon					
PML	0%	0%	0.213%	0.001%	0%
Macular oedema	0%	0%	0%	0.394%	0%
Malignancy	0.60%	0.60%	0.60%	0.60%	0.60%
Hypersensitivity reaction	0%	0%	4.0%	0%	0%
Gastrointestinal disorder	24.5%	22.8%	22.8%	30.4%	22.8%
Thyroid related events	5.1%	11.3%	1.2%	1.2%	1.2%
Immune thrombocytopenic purpura	0%	1.8%	0%	0%	0%
Serious infection	2.8%	2.3%	1.9%	2.2%	10.1%
Influenza like illness	1.3%	1.1%	0.1%	0.5%	1.5%

PML=progressive multifocal leukoencephalopathy; DMT=disease modifying therapy
Source: CS, Table 74

Treatment adjusted model – discontinuation

The probability of treatment discontinuation has been estimated from reported all-cause discontinuation rates that occurred in the trials that are included in the company's 6-month CDP NMA. Fifteen of the 18 studies included in this NMA reported discontinuation data. The reported discontinuation probabilities have been converted to annualised probabilities and, for each DMT, a weighted mean probability was calculated based on the number of patients in each study. The probabilities used in the company model are presented in Table 48.

Table 48 Discontinuation probabilities used in the company model

DMT	Data sources (trials)	Discontinuation probability
Cladribine	CLARITY	4.854%
Alemtuzumab	CAMMS223, CARE-MS I, CARE-MS II	2.266%
Daclizumab	Decide	11.609%
Fingolimod	FREEDOMS, FREEDOMS II	13.595%
Natalizumab	AFFIRM	6.4%

DMT=disease modifying therapy
Source: CS, Table75

5.3.7 Health-related quality of life

As part of CLARITY and CLARITY-EXT trials, EQ-5D-3L questionnaires were administered on day 1, week 24, week 48, week 72, at the week 96/early termination visit, and at each relapse evaluation. Data from completed questionnaires were mapped to the health state utility

(HSU) index values using the UK social tariff. The company also carried out a systematic literature review to identify relevant HRQoL data.

Following an assessment of available evidence the company used data from the CLARITY trial to represent the HRQoL of people in EDSS 0 to 5, data from Hawton[24] for EDSS 6.0 to 8.0, and data from Orme[77] for EDSS 9.0. The company reports that this approach is in line with the approach taken in previously submitted company models.[17-20,72,73]

Table 49 Mean health state utility values used in the company model

Health state	CLARITY	Hawton[24]	Orme[77]
Age	38.3 years	50.7 years	51.4 years
EDSS 0	[redacted]	0.846 (0.026)	0.87 (0.045)
EDSS 1.0	[redacted]	0.762 (0.025)	0.799 (0.093)
EDSS 2.0	[redacted]	0.711 (0.019)	0.705 (0.093)
EDSS 3.0	[redacted]	0.608 (0.029)	0.574 (0.097)
EDSS 4.0	[redacted]	0.609 (0.028)	0.61 (0.093)
EDSS 5.0	[redacted]	0.531 (0.031)	0.518 (0.092)
EDSS 6.0	Not available	0.496 (0.012)	0.46 (0.093)
EDSS 7.0	Not available	0.392 (0.032)	0.297 (0.094)
EDSS 8.0	Not available	0.025 (0.038)	-0.049 (0.109)
EDSS 9.0	Not available	Not available	-0.195 (0.119)

EDSS=expanded disability status scale
Source: CS, Table 77

Impact of relapses on health state utility

Following their review of HRQoL literature, the company identified Ruutiainen[78] and Orme[77] to be their preferred sources of parameter values for the effect of relapses on HRQoL as the values in these papers had been generated by regression analyses that adjusted for EDSS staging. However, the same value was used for hospitalised and non-hospitalised events, as hospitalisation status was not reported in either paper. The values used in the model are presented in Table 50.

Table 50 Impact of relapse events on health state utility

Health state	Duration (days)	Orme[77]	Ruutiainen[78]
Relapse requiring hospitalisation	34.41	-0.071	-0.066
Relapse not requiring hospitalisation	38.64		

Source: CS, Table 80

Impact of adverse events on health state utility

The company's search for HRQoL literature did not identify any studies reporting the impact of treatment related AEs on health state utility. The company, therefore, carried out additional ad hoc searches to identify relevant data from previous appraisals of therapies for the treatment of RRMS and other chronic conditions. The company combined disutility estimates

with duration of event estimates to generate an estimate of QALY impact. The values used by the company have been taken from Boye,[79] NICE Technology Appraisal Guidance (TA312)[19] and Trogdon.[80]

Table 51 Adverse event disutilities

Adverse event	Duration (days)	Disutility
Infusion site reaction (alemtuzumab and natalizumab)	5	-0.011
Injection site reaction (monthly)	13	-0.011
PML	93.1	-0.200
Severe infection	14	-0.190
Macular oedema	84	-0.040
Gastrointestinal	8	-0.240
Hypersensitivity	7	-1.000
Autoimmune thyroid-related event	365.25	-0.110
Influenza-like symptoms	7	-0.210
Malignancy	365.25	-0.116
Immune thrombocytopenic purpura	28	-0.090

PML=progressive multifocal leukoencephalopathy; QALY=quality adjusted life year
Source: CS, Table 81

5.3.8 DMT related resource use and costs

Drug costs comprise three different components: acquisition, administration and monitoring. The costs of treatment with daclizumab, fingolimod and natalizumab are based on the number of people on therapy in each EDSS. All patients are assumed to adhere to therapy and take their full course in each cycle.

The costs of treatment with alemtuzumab and cladribine tablets are based on the proportion of patients eligible for therapy (EDSS<7) at the start of each cycle multiplied by the proportion treated. Given the uncertainty around long-term rates of relapse, re-initiation of treatment was only modelled up to year 6.

Model values for the proportions of patients treated with cladribine tablets have been based on time to first relapse in the intervention/placebo arm of the CLARITY and CLARITY-EXT trials. The estimates for re-treating patients with alemtuzumab are those used in TA441.[20] Proportions of patients eligible for treatment with cladribine tablets and alemtuzumab are provided in Table 52. Reasons for not completing a course of treatment include disease progression, and intolerance. Adjustments for these influences are accounted for separately within the model.

Table 52 Proportions of patients eligible for treatment with cladribine and alemtuzumab

Years	Proportion of eligible patients treated	
	Cladribine	Alemtuzumab
1	100%	100%
2	100%	100%
3	[redacted]	28%
4	[redacted]	11%
5	[redacted]	1%
6	[redacted]	0%

Source: CS, Table 84

Drug acquisition costs

Drug acquisition costs have been estimated using list prices for medications (British National Formulary [BNF][81]) and also for the model estimate of the mean total dose of therapy administered during each cycle. A summary of the total acquisition costs of each therapy considered in this appraisal is provided in Table 53. The company has varied the cost of cladribine tablets between the RES-RRMS and SOT-RRMS patients due to small differences in the weight distributions of the two cohorts in the CLARITY trial.

Table 53 Total drug acquisition costs (list prices)

Therapy	Pack size	Pack cost	Dose	Units per year year 1 / year 2+	Total annual cost	
					Year 1	Year 2+
Cladribine: RES-RRMS patients	1 x 10mg tab	£2,047	0.875mg/kg per dose	2 / 2	£25,917	£25,917
Cladribine: SOT-RRMS patients	1 x 10mg tab	£2,047	0.875mg/kg per dose	2 / 2	£26,373	£26,373
Alemtuzumab	12mg vial	£7,045	12mg per infusion	5 / 3	£35,225	£21,135
Daclizumab	1-syringe	£1,597	Once monthly	12.0	£19,160	
Fingolimod	28-cap	£1,470	1 tab per day	365.25	£19,176	
Natalizumab	15ml-vial	£1,130	Once every 4 weeks (300mgs equating to 1x 15ml-vial)	13.0	£14,690	

Source: CS, Table 85

Drug administration

Drug administration costs include the cost of admissions for infusions, additional medications provided alongside therapy, and any additional district nurse or neurologist visits required for the support of drug administration. The unit costs of drug administration are presented in Table 54.

Table 54 DMT administration costs

Therapy	Delivery method	Source	Administration resources consumed per year	Total cost	
				Year 1	Year 2+
Cladribine	Oral	Draft SmPC[28]	No administration requirements	£0	£0
Alemtuzumab	Infusion	TA312 CS[19]	5 x admissions in year 1 plus 3 x 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of aciclovir (200mg) 3 x admissions in subsequent years plus 3 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of aciclovir (200mg)	£2,782	£1,681
Fingolimod	Oral	TA312 CS[19]	Admission during first year to monitor ECG	£551	£0
Natalizumab	Infusion	SmPC[7]	Monthly admissions for infusions (13 in total)	£7,159	£7,159
Daclizumab	Subcutaneous	Assumption in line with that used in previous appraisals	Training for self-administration of device	£204	£0

CS=company submission; ECG=electrocardiogram; SmPC=summary of product characteristics
Source: CS, Table 86

Monitoring of patients receiving DMTs

The annual costs, first and subsequent years, of monitoring patients taking DMTs are provided in Table 55 and Table 56 respectively. The costs have been assumed to vary between first and subsequent years to take into account the increased testing that typically occurs when therapies are initiated. However, for patients receiving natalizumab, the costs remain high as receipt of this therapy is associated with a high risk of progressive multifocal leukoencephalopathy (PML) and, therefore, ongoing MRI monitoring is required.

Table 55 Year 1 costs of monitoring patients receiving DMTs

Therapy	Source	Administration resources consumed in first year	Total cost Year 1
Cladribine	Draft SmPC[28]	1 x MRI scan 3 x complete blood counts 2x neurology visits 1x tuberculin skin test 1x HBV test 1xHCV test	£584
Alemtuzumab	SmPC[82] TA312 CS[19]	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 1 x tuberculin skin test 0.65 x human papilloma virus test (females only – assumption 65%) 2x neurology visits	£444
Daclizumab	TA441 CS[20]	13 x biochemistry tests 4 x complete blood count 2 x neurology visit	£349
Fingolimod	SmPC[8] TA312 CS[19]	1 x MRI scan 4 x complete blood count 6 x biochemistry tests (month 0,1,3, 6,9 and 12) 1 x ophthalmology assessment 3 x neurology visits	£821
Natalizumab	McGuigan 2016[83] TA312 CS[19]	1 x JC virus test 2 x biochemistry test 1 x MRI scan 2 x neurologist visit	£540

MRI=magnetic resonance imaging; JC virus=John Cunningham virus; SmPC=summary of product characteristics
Source: CS, Table 87

Table 56 Costs of monitoring patients receiving DMTs during year 2+

Therapy	Source	Administration resources consumed in subsequent year	Total cost Year 2+
Cladribine	Draft SmPC[28]	3 x complete blood counts 1 x neurology visits 1 x HBV test 1 x HCV test	£215
Alemtuzumab	SmPC[82] TA312 CS[19]	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 0.65 x human papilloma virus test (females only – assumption 65%) 1 x neurology visits	£267
Daclizumab	TA441 CS[19]	12 x biochemistry tests 4 x complete blood count 1 x neurology visit	£187
Fingolimod	TA312 CS[19] SmPC[8]	2 x complete blood count 2 x biochemistry test 1 x neurology visits	£169
Natalizumab	McGuigan 2016[83] [redacted]TA312 CS[17]	2 x JC virus test (six monthly) 2 x biochemistry test 1 x MRI scan 2 x neurology visits	£547

HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; JC virus=John Cunningham virus; SmPC=summary of product characteristics
Source: CS, Table 87

5.3.9 EDSS related resource use and unit costs

The company carried out a systematic review to identify published costs. The review included published peer reviewed costing studies, costing data used in models submitted to NICE as part of other STAs and the company's own unpublished data.

Direct medical costs

A summary of the direct medical costs used in the company's base case analysis is provided in Table 57. These costs are those reported by Hawton[24] (n=289). The cost year for the costs is 2012. The total costs include the costs of contact with a chiropodist, clinical psychologist, continence advisor, district nurse, dietician, GP, MS specialist nurse, neurologist, occupational therapist, ophthalmologist, physiotherapist, rehabilitation doctor, social worker, speech therapist, pain management service and/or rehabilitation/respite care. The costs reported by Hawton[24] only cover a 6-month period and, therefore, the company multiplied these by two to generate an annual (model cycle) rate. In addition, the company inflated the Hawton[24] costs to 2015/2016 prices using the hospital and community health services index.[84]

Table 57 Annual direct medical costs

State	Annual mean cost (sd) *
EDSS 0	£1,020 (281)
EDSS 1.0	£910 (168)
EDSS 2.0	£716 (92)
EDSS 3.0	£668 (81)
EDSS 4.0	£1,002 (110)
EDSS 5.0	£1,006 (120)
EDSS 6.0	£1,304 (94)
EDSS 7.0	£1,316 (180)
EDSS 8.0	£3,320 (395)
EDSS 9.0	Not reported

EDSS=expanded disability status scale; sd=standard deviation
*Costs are reported for a 6-month period and so have been multiplied by 2 to provide annual costs
Source: CS, Table 88

Direct non-medical costs

The company highlights that there is uncertainty around the extent to which non-medical costs can be considered to fall under the headings of an NHS and PSS perspective. The company, therefore, adopted the approach used in the CS for TA441,[20] namely that 80% of social and community care costs, and 47% of investment costs, should be considered in the analysis.

The company identified two studies that reported non-medical costs (Karampama[85] and Tyas[86]). The company uses the costs reported by Karampama[85] (inflated to 2015/2016 prices using the hospital and community care index[84]) in their model. These costs were used as insufficient detail was supplied by Tyas[86] to allow the costs reported in that paper to be adjusted so as to only include components relevant to an NHS and PSS perspective. A summary of the direct non-medical costs used in the company model is provided in Table 58.

Table 58 Annual non-medical direct costs used in the company model

	Unadjusted costs		Adjusted and inflated costs
	Investment	Professional and informal care	Total direct non-medical
Proportion of cost considered relevant to an NHS and PSS perspective	47%	80%	-
EDSS: 0 to 3.0	£23	£1,492	£1,675
EDSS: 4.0 to 6.5	£693	£7,074	£8,569
EDSS: 7.0 to 9.0	£1,405	£30,603	£35,592

EDSS=Expanded Disability Status Scale
Source: CS, Table 90

Costs of relapses

The company used costs reported by Hawton[24] (rather than those reported by Karampama[85]) in their base case analysis as these data are in line with the data they have chosen to use to model costs by EDSS state in the model. The costs associated with hospitalised and non-hospitalised relapse events have been estimated by subtracting the costs for those who had a relapse from the costs for those without relapse. Resultant costs have been inflated to 2015/2016 cost year using the hospital and community health services index.[84] The costs of relapse used in the company model are provided in Table 59.

Table 59 Cost of relapse events

Relapse state	Inflated cost per event
Relapse without hospitalisation	£526
Relapse with hospitalisation	£3,463

Source: CS, Table 92

5.3.10 Adverse events

The company has estimated resource use associated with AEs based on assumptions and information from published studies. Associated costs have been taken from the BNF,[81] NHS Reference Costs (2016)[87] and Unit Costs of Health and Social Care (2016).[84] The costs used in the company model are provided in Table 60.

Table 60 Adverse event costs

Adverse event	Cost
Infusion site reaction	£0
Injection site reaction	£6.79
PML	£1,268.11
Severe infection	£3,287.62
Macular oedema	£245.46
Gastrointestinal	£707.28
Hypersensitivity	£156.68
Autoimmune thyroid-related event	£543.63
Influenza-like symptoms	£6.79
Malignancy	£11,427.59
Immune thrombocytopenic purpura	£939.54

PML=progressive multifocal leukoencephalopathy
Source: CS, Table 93

5.3.11 Cost effectiveness results

Results from all the company's analyses show that treatment with cladribine tablets is cheaper than any of the comparators and generates more QALYs (see Table 61, Table 62, Table 63, and Table 64). However, as the company has used the list prices for daclizumab and fingolimod, the results from analyses involving these comparators are not relevant to the NICE AC's decision. Results generated by the company model using the PAS prices for daclizumab

and fingolimod and the company's base case assumptions, have been generated by the ERG and are included in the confidential appendix that accompanies this ERG report. In addition, cost effectiveness results, using PAS prices and following the ERG's amendments to the company model, are also included in this confidential appendix.

Table 61 Base case results for RES-RRMSa (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£480,441	22.176	8.098				
Alemtuzumab	£499,575	22.176	7.916	-£19,134	0.000	0.182	Cladribine dominant
Natalizumab	£611,117	22.176	7.586	-£130,676	0.000	0.512	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 97

Table 62 Base case results for RES-RRMSb (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£480,441	22.176	8.098				
Daclizumab	£569,623	22.176	7.174	-£89,182	0.000	0.924	Cladribine dominant
Natalizumab	£611,117	22.176	7.586	-£130,676	0.000	0.512	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 98

Table 63 Base case results for SOT-RRMSa (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£467,361	21.318	7.570				
Alemtuzumab	£484,910	21.318	7.417	-£17,549	0.000	0.153	Cladribine dominant
Fingolimod	£539,427	21.318	6.626	-£72,066	0.000	0.944	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 99

Table 64 Base case results for SOT-RRMSb (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£467,361	21.318	7.570				
Daclizumab	£533,758	21.318	7.022	-£66,397	0.000	0.548	Cladribine dominant
Fingolimod	£539,427	21.318	6.626	-£72,066	0.000	0.944	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 100

5.3.12 Sensitivity analyses

Deterministic univariate sensitivity analyses

The company carried out a wide range of univariate sensitivity analyses to show the impact of variation in parameters on the incremental net health effects. Each parameter was varied between its lower and upper 95% confidence, or credible, interval value, or by 50% of its mean value, if statistical measures of variance were not available. Tornado diagrams are presented in the CS (CS, Figure 23 to Figure 26). Results show that the base case analyses are most sensitive to variation in the effect of DMT on 6-month CDP. Other key drivers include the rate at which costs and outcomes are discounted, baseline risk, the adjustment factor applied to the natural history model to account for the faster EDSS progression of patients with RES-RRMS and treatment discontinuation.

Probabilistic sensitivity analysis

The company undertook probabilistic sensitivity analyses (PSAs) to assess the uncertainty surrounding the parameter values used in the model. Results from these analyses are displayed in Table 65 to Table 68. The results support the base case results as, for each analysis, the company shows that treatment with cladribine dominates all other treatments.

Table 65 Probabilistic results for RES-RRMSa (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£475,162				63.7%
Alemtuzumab	£495,655	-£20,492	0.202	Cladribine dominant	36.3%
Natalizumab	£604,411	-£129,249	0.491	Cladribine dominant	0.0%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 101

Table 66 Probabilistic results for RES-RRMSb (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£471,594				96.9%
Daclizumab	£559,064	-£87,470	0.920	Cladribine dominant	2.6%
Natalizumab	£600,923	-£129,328	0.498	Cladribine dominant	0.5%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 102

Table 67 Probabilistic results for SOT-RRMSa (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£472,273				60.8%
Alemtuzumab	£491,914	-£19,641	0.198	Cladribine dominant	35.7%
Fingolimod	£538,566	-£66,293	0.873	Cladribine dominant	3.1%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 103

Table 68 Probabilistic results for SOT-RRMSb (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£472,012				84.5%
Daclizumab	£534,318	-£62,306	0.489	Cladribine dominant	11.9%
Fingolimod	£538,296	-£66,283	0.845	Cladribine dominant	3.6%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 104

5.3.13 Scenario analyses

The company carried out scenario analyses to test the robustness of the model to variations in model assumptions and the use of alternative input parameters (including different utility values and different transition matrices for the natural history of disease). Analyses also considered use of societal perspective, alternative time horizons, assumptions on the durability of drug effect, and using a 21 health-state model.

5.3.14 In all of the scenarios except one, treatment with cladribine tablets was shown to dominate all other treatments. The exception was a scenario in which the cost effectiveness of treatment with cladribine tablets was compared with alemtuzumab in the population with RES-RRMS. In this scenario, results from a conventional NMA that used a different network to that used in the base case meta-regression analysis, were used in the model. Results showed that treatment with cladribine tablets was costed more (+£36,519) and was less effective (-1.071) than treatment with alemtuzumab. However, the company highlights that results from the NMA show that there was significant overlap in the 95% credible intervals for 6-month CDP and hence neither DMT was shown to be statistically superior to the other. Model validation and face validity check

The company employed a number of approaches to validate their economic model, including asking clinical experts and external health economists to check the face validity of the structure, assumptions and data used to populate the model. In addition, an external meta-analysis expert checked the meta-analysis regression model. Internal validity was tested through application of extreme value testing and by examination of model calculations by an independent modeller. Where possible, results were compared with published studies[63,88] and analyses of British Columbia registry data (CS, Figure 15).

5.3.15 Drummond checklist

Table 69 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partially	No. Effectiveness data from the CLARITY trial were used to demonstrate the effectiveness of treatment with cladribine tablets versus placebo. The two outcomes used in the model are qualifying ARR and 6-month CDP. The results show the following: • **RES-RRMS** subgroup: treatment with cladribine tablets is not statistically significantly superior to placebo in terms of 6-month CDP but is statistically significantly superior in terms of qualifying ARR • **SOT-RRMS** subgroup: treatment with cladribine tablets is not statistically significantly superior to placebo in terms of either 6-month CDP or qualifying ARR Comparative effectiveness of treatment with cladribine tablets versus other DMTs was derived from the company's NMAs and meta-regression. The ERG has concerns about the reliability of results from these analyses

Were all the important and relevant costs and consequences for each alternative identified?	Yes	Partial. The ERG considers the inclusion of cost of informal care and carer disutility were inappropriate as both are outside of the NICE reference case
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	No. The company did not fully explain the limitations of the available clinical evidence

ARR=annualised relapse rate; CDP=confirmed disability progression; DMT=disease modifying therapy; ERG=evidence review group; NMA=network meta-analysis; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy

5.4 Detailed critique of the company's economic model

The company submitted a cost effectiveness model built in MS Excel. This model is a simplified version of economic models that, since 2005, have formed part of company submissions for NICE STAs of drugs for treating MS. Previously submitted models had a 21-health state structure: 10 states were based on EDSS state for patients with RRMS and a further 10 states were for patients with SPMS, with one additional state for death from all causes. The submitted company model comprises 11 health states: 10 EDSS based states and one additional state for death from all causes. The company's justification for employing a simplified 11 health-state model is that:

- HRQoL is more closely related to EDSS state than to the clinical form of MS
- It is difficult to identify the transition from RRMS into the SPMS subtype, making it challenging to reliably model the conversion from one form to the other
- The use of SPMS-specific health states requires the use of SPMS-specific transition rates. The only source of these data is the London Ontario registry and the company considered that these data were too limited to accurately estimate SPMS-specific transition rates.

The ERG is satisfied with the company's rationale for using the simplified 11 health-state model rather than a 21 health-state model. Clinical advice to the ERG is that SPMS subtype does not significantly impact on costs or HRQoL. Whilst EDSS state transition probabilities for the SPMS subtype would differ from those for the RRMS subtype, the ERG considers that any incorporation of this detail into the model is limited by available data on transition to the SPMS subtype and is satisfied that the 11 state simplification does not unduly influence model results.

Whilst an 11 health-state model is, by design, less complicated then a 21 health-state model, the algorithms required to build the model are extensive and have made it impossible for the ERG to fully check that they had all been correctly implemented. The Excel model frequently crashed when undertaking standard formula checking processes (e.g., checking the precedents and dependents of values in cells). The checks that the ERG was able to perform suggest that the model results are generated by accurate algorithms; however, the ERG is unable to guarantee that this is true for all the algorithms in the company model.

5.4.1 Natural history of EDSS state progression

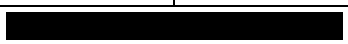
The ERG notes that the company approach to modelling the natural history for EDSS state progression involves adjusting data from the British Columbia MS register by acceleration factors for the RES-RRMS and SOT-RRMS subgroups. These acceleration factors have been estimated using data from the placebo arm of the CLARITY trial using the 6-month CDP hazard rate at 96 week, i.e., by calculating the difference between the RES-RRMS and non RES-RRMS subgroups, and between the SOT-RRMS and non SOT-RRMS subgroups. The ERG considers that, whilst there is no clear alternative, this is a simplistic approach that is reliant on hazards being proportional for 6-month CDP between the RES-RRMS and non RES-RRMS, and between the SOT-RRMS and non SOT-RRMS subgroups. If the hazards are not proportional then the approach may over or underestimate the rate of disease progression in the model. Failure to test the validity of the PH assumption further adds to the uncertainty around the validity of the submitted model results.

5.4.2 Clinical effectiveness

The statistical evidence on clinical effectiveness from the CLARITY trial for qualifying ARR and 6-month CDP for the RES-RRMS and SOT-RRMS subgroups is provided in

Table 70.

Table 70 Time to 6-month CDP and qualifying ARR in CLARITY trial post-hoc subgroup analyses

	Cladribine tablets	Placebo
RES-RMMS		
6-month CDP: K-M estimate of progression-free patients, % (95% CI)		
HR for cladribine tablets vs placebo (95% CI)		
SOT-RRMS		
6-month CDP K-M estimate of progression-free patients, % (95% CI)		
HR for cladribine tablets vs placebo (95% CI)		
RES-RMMS		
Qualifying ARR (95% CI)		
Rate ratio (95% CI)		
SOT-RRMS		
Qualifying ARR (95% CI)		
Rate ratio (95% CI)		

RES=rapidly-evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy; ARR=annualised relapse rate; CI=confidence interval; K-M=Kaplan-Meier; CDP=confirmed disease progression
Source: CS, adapted from Table 30 and Table 35

RES-RRMS

Inevitably, there is considerable uncertainty around the reliability of point estimate results from analyses of small datasets, and interpretation of the associated wide credible/confidence intervals is problematic. Results from analyses of CLARITY trial data show that, at 2 years, people retrospectively described as having RES-RRMS who were treated with cladribine tablets had statistically significantly better qualifying ARR than those receiving placebo. However, results from analyses of 6-month CDP data from this population show that there is no statistically significant difference in effect between arms. This is not surprising given that clinical advice to the ERG is that there is no relationship between relapse frequency and disability progression. However, the ERG highlights that this effect may be due to the RES-RRMS definition used by the company; the company's definition relates to people with two or more relapses, not two or more *disabling* relapses, the wording used in previous submissions.[17,72] The ERG notes that, for patients who had been experiencing frequent disabling relapses, reducing qualifying ARR could, by default, also reduce disability progression. The ERG considers that data to support the conclusion that treatment with cladribine tablets is more effective than placebo in the population with RES-RRMS are limited to qualifying ARR only.

If only qualifying ARR effectiveness for cladribine tablets compared to placebo is included in the model, results show that treatment with cladribine tablets is dominated by alemtuzumab

and is less costly but generates fewer QALYs versus natalizumab (an ICER of £32,997 per QALY **lost** with cladribine tablets) or daclizumab (an ICER of £2,167 per QALY **lost** with cladribine tablets).

SOT-RRMS

Results from analyses of CLARITY trial data show that, at 2 years, for people retrospectively described as having SOT-RRMS, there is no statistically significant difference in terms of either qualifying ARR or 6-month CDP between arms. There is, therefore, no statistical basis to suggest that treatment with cladribine tablets is more effective than placebo for this patient group. Where sample sizes from a trial are so small that there is no statistically significant evidence that the intervention is more effective than placebo, there is no robust basis on which to construct an economic model.

5.4.3 Comparators: clinical effectiveness evidence

The company undertook an NMA to generate evidence to enable the qualifying ARR associated with treatment with cladribine tablets to be compared with the qualifying ARRs associated with the comparator treatments included in the company's economic model. The company also undertook a meta-regression to provide comparative estimates of 6-month CDP for treatment with cladribine tablets versus all comparators. In Section 5.6, the ERG has set out methodological concerns about the robustness of both the NMAs and the meta-regression. Briefly, the ERG considers that the results of the company's NMAs and meta-regression analyses should be treated with caution for the following reasons:

- RES-RRMS and SOT-RRMS effectiveness data for cladribine tablets in the NMAs were based on post-hoc subgroup analyses
- RES-RRMS and SOT-RRMS were post-hoc classifications of patients in the CLARITY trial
- Definitions of RES-RRMS and SOT-RRMS may have differed between included trials in the network. Importantly, the definition for RES-RRMS used in the CLARITY trial does not specify that people had to have had a *disabling* relapse, a term that was used in definitions of RES-RRMS in previous NICE MS TA submissions.[17,72]
- The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS.

The ERG highlights that even if the results from the company's statistical analyses were robust for both the RES-RRMS and SOT-RRMS subgroups, the credible intervals for 6-month CDP for all DMTs overlap and the point estimates are similar. Indeed, within the CS (p110) the company notes that results show that there is 'no therapy statistically dominating in terms of efficacy'.

Similarly, an examination of the risk ratios compared to placebo of qualifying ARR results for the SOT-RRMS subgroup shows that the point estimates for each DMT are close and reside within the credible intervals of every other DMT (see CS, Table 69).

The picture is slightly less clear for the RES-RRMS subgroup. The qualifying ARR point estimates for the rate ratio compared to placebo for cladribine tablets, alemtuzumab and daclizumab are further apart than those for the SOT-RRMS subgroup but still reside in each other's credible intervals (CS, Table 69), with the point estimate for natalizumab only residing in the alemtuzumab credible interval.

The ERG considers that, in situations where confidence/credible intervals overlap and point estimates are close, the appropriate approach is to assume that all treatment options have equal efficacy. As such, regardless of treatment, the ERG has assumed that the 6-month CDP normalised hazard ratios for all treatments are the same as those generated by the company's meta-regression for cladribine tablets, i.e., 0.489 for the RES-RRMS subgroup.

The ERG has assumed that the RES-RRMS population qualifying ARR is the same for all DMTs other than natalizumab (which has a risk ratio compared to placebo of 0.19), with the effect set to be the same as for cladribine tablets (i.e., risk ratio 0.31). This change has no effect on the company's base case cost effectiveness results, i.e., treatment with cladribine tablets dominates all of the other comparators.

For the SOT-RRMS subgroup, the ERG has also assumed equal qualifying ARR effectiveness for all DMTs, with the rate ratio again set equal to cladribine tablets (0.48). This change has no effect on the company's base case cost effectiveness results, i.e., treatment with cladribine tablets still dominates all other comparators.

5.4.4 Waning of treatment effect

The DMTs considered by the company all have different modes of action and are delivered in different ways. As stated in the CS (p110), previous NICE appraisals of drugs for treating MS have incorporated assumptions about the waning of drug efficacy over time. In the absence of long-term follow-up data, in previously submitted models, the waning of effectiveness over time has been assumed to be the same for all DMTs, namely 100% during the first 2 years, 75% between years 2 and 4, and 50% from year 5 onwards.

The company has carried out analyses of CLARITY-EXT data in an attempt to provide robust evidence about the extent to which the effect of cladribine tablets on 6-month CDP wanes over a 4-year time horizon. The ERG commends the company for trying to provide evidence rather than simply relying on assumptions but highlights two issues with their analysis:

1. The confidence intervals, from the ITT analysis, for the HRs used to support no waning between years 2 and 4 are wide and include a reduction in effectiveness between years 2 and 4 of 75%. There is therefore evidence that the waning for cladribine tablets is the same as has been assumed for other DMTs in previous appraisals.
2. The company's analysis of waning, that is presented in the CS, was only carried out using 6-month CDP data and the results are only available for the ITT population, not for the RES-RRMS and SOT-RRMS subgroups. During the clarification process, the ERG requested analyses of waning using 6-month CDP and qualifying ARR for the RES-RRMS and SOT-RRMS subgroups. The ERG commends the company for providing what was an extensive re-analysis in a timely fashion. For SOT-RRMS, the company stated in the clarification response that the numbers were too small (there were only two patients in the intervention/placebo arm) for the treatment-switching algorithm to be robustly applied (although this analysis was undertaken anyway). Therefore, for the SOT-RRMS subgroup, there is no evidence on the waning of effectiveness of cladribine tablets. For the RES-RRMS group, the numbers were larger, although still small (10 or fewer patients in the trial arms), with a small number of outcomes, meaning that the confidence intervals were even wider than those for the ITT population waning analysis. In line with the results of the ITT analysis, the confidence intervals included a reduction in effectiveness between years 2 and 4 of 75%.

Clinical advice to the ERG is that there is almost complete uncertainty around the extent and timing of any waning of treatment effect for people in the RES-RRMS and SOT-RRMS subgroups (or for any patients with MS) who receive any of the DMTs included in the company model, for the period beyond 2 years. Results from the analyses carried out by the company add some information to the evidence base, but only over a 4-year period and only for the whole CLARITY-EXT trial population (i.e., the information is not specific to the RES-RRMS and SOT-RRMS subgroups) with wide confidence intervals. The ERG considers that the evidence provided by the company is not strong enough to merit the application of a waning effect for cladribine tablets that is different from that used for the other DMTs. Setting all treatments to have the same waning effect (100% up to year 2, 75% over years 2 to 4 and 50% thereafter) has no effect on the company's base case cost effectiveness results, i.e., cladribine tablets dominate all the comparator treatments for the RES-RRMS and SOT-RRMS subgroups.

Adoption of the waning assumption used in previous STAs should not mask the complete uncertainty around the medium- to long-term efficacy of any of the DMTs. With a time horizon

of 50 years, modelled effectiveness is essentially based on an absence of any information for 48 out of 50 (96%) of those years. Given there is no robust evidence of treatment effectiveness waning (6-month CDP or qualifying ARR) over a 2-year period for all of the DMTs considered in this appraisal, small differences in medium- and long-term efficacy will have a significant impact on the relative cost effectiveness of different DMTs.

5.4.5 Treatment discontinuation

The company estimated annualised discontinuation rates for patients treated with fingolimod, natalizumab and daclizumab using data from 15 of the 18 studies included in their NMA (CS, p116). These estimates are based on all cause discontinuation rates over the whole included trial periods. The all cause annualised discontinuation rates used in the model considered during TA441[20] were taken from the main trial and applied to the whole time horizon; this approach was criticised by both the ERG and the AC who considered that this approach was unrealistic. Their rationale was that discontinuation rates associated with taking any DMT are likely to be higher during the first year than during subsequent years because, during the early stages of a trial, patients are more likely to discontinue treatment due to AEs than during the later stages of the trial. The ERG and the AC for TA441[20] considered that it would be more appropriate to apply the discontinuation rates that occurred during the last year, rather than the first year, of a trial over the whole model time horizon. The ERG accepts that it was inappropriate to apply all cause annualised discontinuation rates for natalizumab and daclizumab that were derived over the whole trial period. However, in a scenario with only one line of treatment (as in this and previous MS submissions), with no alternative treatment to move onto, clinical advice to the ERG is that treatment would only stop when there was perceived to be no further clinical benefit to a patient even if a patient was still having relapses. The ERG considers that a more realistic approach to modelling discontinuation is, therefore, to use trial treatment discontinuation rates where available and then assume treatment would continue whilst the patient receives benefit, which, in the company model, is up until a patient reaches EDSS state 7.

This change in modelling approach increases both the costs and QALYs associated with treatment with natalizumab and daclizumab for both the RES-RRMS and SOT-RRMS subgroups. However, this change in discontinuation assumption has no effect on the company's base case cost effectiveness results i.e., for both the RES-RRMS and SOT-RRMS subgroups, treatment with cladribine tablets dominate all the comparator treatments.

5.4.6 Re-exposure to cladribine tablets and alemtuzumab

During TA441[20] and TA312[19] re-initiation rates for alemtuzumab following relapse in years 3 to 5 were included in the company's economic analysis. Reflecting this, the company model

incorporates rates of re-exposure to alemtuzumab that are equal to those used in TA441[20] and TA312,[19] whilst re-exposure rates for cladribine tablets are based on the company's projection of relapse rates for patients on cladribine tablets. Clinical advice to the ERG is that patients may be re-exposed to alemtuzumab after relapse but there is no published evidence to show whether this approach is effective. The way in which the company has modelled the effect of re-exposure means that re-exposure increases the costs of treatment and administration as well as the costs and QALY losses that arise from AEs; however, reflecting the absence of effectiveness evidence on re-exposure, this approach does not influence rates of qualifying ARR or 6-month CDP. As such, the ERG considers that it is more appropriate to remove re-exposure to cladribine tablets and alemtuzumab from the base case analyses. This isolated change reduces the costs and increases the QALYs associated with treatment with both cladribine tablets and alemtuzumab. However, there is no effect on the company's base case results, i.e. cladribine tablets dominate all the comparator treatments.

5.4.7 Adverse events

The ERG considers that the method used by the company to calculate the incidence of AEs included in the company model, whilst is well described for malignancies, is poorly described for several other AEs (such as gastrointestinal disorder and influenza). Reference is made in the CS to a series of NMAs, details of which are not included in the CS, that were used to calculate odds ratios for AEs for all DMTs compared to placebo. Although the values calculated for cladribine tablets produce AE rates that are comparable to those reported in the CLARITY trial, incidence rates reported in the CLARITY trial are for all patients with RRMS and do not specifically relate to the RES-RRMS and SOT-RRMS subgroups. The severity of events included in the NMAs to generate the AE rates is also unclear. This has implications for the validity of costs and disutilities associated with AEs. The ERG was not able to produce alternative AE rates for the DMTs considered in the model that were specific to the RES-RRMS and SOT-RRMS subgroups and thus the event rates, costs and disutility values associated with AEs that are used in the company model add further uncertainty to the cost effectiveness results.

5.4.8 EDSS state costs

The EDSS state costs presented in the CS are substantially higher than the costs used in previous MS STA submissions[17,18] and are also higher than the EDSS state costs that are used in a scenario analysis in the ongoing MS MTA (TA32).[15] A comparison of the different EDSS state costs used in selected previous submissions[17,18] to NICE, the ongoing MTA (TA32)[15] and in the CS is provided in Table 71.

Table 71 EDSS state costs used in NICE multiple sclerosis technology appraisal submissions

EDSS state	Costs			
	TA127[17] 2005/06 prices	TA320[18] (unit costs from TA127 updated to 2011/12 prices using the HCHS index)	Ongoing MTA (TA32)[15] (costs from TA320[18] inflated to 2015/16 using the HCHS index)	Cladribine tablets submission 2015/16 prices
0	£638	£903	£949	£2,729
1	£927	£939	£987	£2,615
2	£883	£688	£724	£2,415
3	£2,758	£3,765	£3,958	£2,365
4	£1,756	£1,824	£1,917	£9,625
5	£2,543	£3,094	£3,253	£9,629
6	£3,146	£4,130	£4,342	£9,937
7	£7,384	£10,871	£11,429	£36,753
8	£17,370	£26,478	£27,838	£38,824
9	£16,307	£21,187	£22,274	£38,824

EDSS state=Expanded Disability Status Scale; HCHS=Hospital and Community Health Services
Source: Email correspondence from NICE and company model

As shown in Table 71, the EDSS state costs in the cladribine tablets CS are substantially higher than the costs that have used in previous STAs[17,18] and in the ongoing MTA (TA32).[15] The bulk of the difference in these costs can be accounted for by the non-medical costs included in the current CS (derived from the analysis carried out by Karampampa[85]), specifically, the informal care element of professional and informal care estimated by Karampampa.[85]

The company argues that 80% of the costs of informal and professional care should be included in the economic evaluation as previous ACs have suggested that 80% of non-medical care would be paid for by PSS and, as such, this cost is relevant to the NICE reference case.[31]

Details of how the value of 80% was derived have not been provided; however, the ERG considers that this is likely to represent the proportion of professional domiciliary and personal care that is generally funded by PSS. However, professional domiciliary and personal care is not the same as informal care. This is exemplified by the fact that Karampampa[85] costed informal care by multiplying the hours of care provided by the average hourly wage rate in UK, whereas professional care was costed via unit costs reported by the PSSRU.[84] The ERG considers that only the professional care costs should have been included in the company

model as the costs of informal care are not met by PSS and are, therefore, not relevant to the NICE Reference Case.[31]

The ERG estimates that the informal care costs used in the company model amount to approximately £1,600 per year for EDSS state 0 to 3, £7,000 per year for EDSS state 4 to 6 and £17,000 per year for EDSS state 7 to 9, after the ERG adjusted the costs to 2015/16 prices. Excluding these informal care costs brings the costs of being in each EDSS state in line with the EDSS state costs used in previous STAs[17,18] and in the ongoing MTA (TA32).[15] The ERG, therefore, considers it appropriate to use the EDSS state costs used in the ongoing MTA (TA32)[15] updated to 2015/16 prices.

Using the MTA (TA32)[15] EDSS state costs substantially reduces the lifetime costs of all treatments by between 40% and 55%, with the greatest reductions seen for natalizumab and daclizumab. However, using the MTA (TA32)[15] values in isolation does not change the dominant position of cladribine tablets over all comparators for patients in the RES-RRMS and SOT-RRMS subgroups.

5.4.9 Health-related quality of life

The utilities incorporated into the company model are driven by EDSS state and are derived using data from the CLARITY trial and results from a literature review. Whilst the values are not specifically for patients with RES-RRMS or SOT-RRMS, the ERG considers that the primary driver of utility would be the EDSS state and so is satisfied that the values implemented in the company model are reasonable.

In addition to patient utility, carer utility is also incorporated into the company model by via a disutility applied to the carer that varies by the cared for patient's EDSS state. Whilst carers' utility has been included in previous submissions, the NICE reference case[31] states that outcomes should reflect all direct health effects, whether for patients or for other people. Whilst 'other people' could include carers, the NICE reference case[31] explicitly states that only the direct health effects of an intervention should be included in the analysis. The ERG considers that carers only benefit indirectly from any improvement in the EDSS state of a person taking DMTs and so their health outcomes should not be included.

Whilst reducing the QALYs gained for all treatments, removing carers' disutility from the model in isolation has no effect on the company's base case results, i.e., for both the RES-RRMS and SOT-RRMS subgroups, treatment with cladribine tablets dominates all the comparator treatments.

5.4.10 Time horizon

The company has assumed only a single line of treatment. This approach, which is one that has been adopted in previous NICE MS TAs, is acknowledged by the company to be unrealistic as, in NHS clinical practice, patients would be offered alternative DMTs at relapse or progression, or if treatment were stopped due to a lack of tolerability. As modelling of treatment sequencing is beyond the remit of the ERG, the ERG considers it informative to explore time horizons significantly shorter than lifetime to reflect the facts that (i) patients are unlikely to be on a single treatment for life and (ii) that the effectiveness data available for the DMTs are limited to, at the most, 4 years.

The ERG has produced analyses using time horizons of 2 years (the length of the CLARITY trial) and 4 years (the length of the CLARITY trial plus the length of the CLARITY-EXT trial).

For the RES-RRMS subgroup, use of a 2-year time horizon resulted in treatment with cladribine tablets remaining dominant compared to alemtuzumab, but being dominated by natalizumab. Compared to daclizumab, treatment with cladribine tablets generated an additional QALY gain of 0.005 at an incremental cost of £15,931, with an ICER of £3,121,856 per QALY gained. When a 4-year time horizon was used, treatment with cladribine tablets dominated all comparators.

For the SOT-RRMS subgroup, use of a 2-year time horizon resulted in treatment with cladribine tablets being dominant over alemtuzumab, but being dominated by daclizumab. Compared to fingolimod, treatment with cladribine tablets generated an additional QALY gain of 0.019 at an incremental cost of £16,977, with an ICER of £897,693 per QALY gained. When a 4-year time horizon was used, treatment with cladribine tablets dominated all comparators.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

A summary of the effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with cladribine tables versus alemtuzumab, natalizumab and daclizumab for patients in the RES-RRMS subgroup are provided in Table 72 to Table 74.

For the RES-RRMS subgroup, none of the ERG's individual changes (except for shortening the time horizon) stop cladribine tablets from dominating all the other comparators. However, all of the ERG's individual changes (except stopping re-exposure to cladribine tablets or alemtuzumab) either reduce the cost savings or reduce the QALY gain associated with treatment with cladribine tablets compared to the other DMTs.

In the ERG scenario where treatment effectiveness for cladribine tablets compared with placebo is limited to qualifying ARR only (with effectiveness for alemtuzumab and daclizumab set equal to cladribine, as discussed in Section 5), then together with the other ERG model amendments over a 50-year time horizon:

- Treatment with cladribine tablets becomes dominated by alemtuzumab
- Treatment with cladribine tablets no longer dominates natalizumab, costing less (-£133,754) than natalizumab but generating fewer QALYs (-1.650) with an ICER per QALY **lost** of £81,050
- Treatment with cladribine tablets no longer dominates daclizumab, costing less (-£87,566) than daclizumab but generating fewer QALYs (-1.362) with an ICER per QALY **lost** of £64,269.

For interventions that are less costly and less effective (in terms of QALYs gained) than a comparator, the ICERs relate to the amount of money saved for every QALY that is lost by using the intervention rather than the comparator. When this is the case, an intervention will be considered cost effective if the ICER generated is **above** the willingness to pay threshold rather than below it. This contrasts with the common scenario in which treatment with an intervention results in higher costs and more QALYs than treatment with a comparator and the intervention is considered cost effective when the value of the ICER per QALY gained is lower than the willingness to pay threshold.

Table 72 Cost effectiveness results for cladribine tablets versus alemtuzumab with ERG revisions to company base case (list prices) – RES-RRMS

Model scenario and ERG revisions	Cladribine tablets		Alemtuzumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£480,441	8.098	£499,575	7.916	-£19,134	0.182	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£567,079	6.251	£500,409	7.906	£66,670	-1.655	*Cladribine dominated*
R1b) For qualifying ARR and 6-month CDP, the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£496,602	7.990	-£16,162	0.108	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£499,575	7.916	-£12,257	0.033	Cladribine dominant
R3) No re-exposure to cladribine or alemtuzumab	£474,494	8.098	£491,747	7.916	-£17,253	0.182	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years	N/A	N/A	N/A	N/A	N/A	N/A	N/A
R5) TA32 EDSS state costs	£298,718	8.098	£314,615	7.916	-£15,897	0.182	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£499,575	9.777	-£19,134	0.165	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£72,796	1.200	-£9,328	0.004	Cladribine dominant
R8) 4-year time horizon	£81,567	2.272	£96,395	2.251	-£14,828	0.021	Cladribine dominant
(R1b-R6)	£297,128	9.807	£305,320	9.844	-£8,192	-0.037	£219,549*
(R1b-R7)	£56,817	1.343	£66,409	1.338	-£9,592	0.005	Cladribine dominant
(R1b-R6, R8)	£65,078	2.529	£74,567	2.527	-£9,490	0.002	Cladribine dominant
ERG scenario (R1a, R2-R6)	£346,045	8.227	£307,622	9.768	£38,423	-1.541	*Cladribine dominated*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; N/A=not applicable

* The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 73 Cost effectiveness results for cladribine tablets versus natalizumab with ERG revisions to company base case (list prices)– RES-RRMS

Model scenario & ERG revisions	Cladribine tablets		Natalizumab		Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case	£480,441	8.098	£611,117	7.586	-£130,676	0.512	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo	£567,079	6.251	£611,117	7.586	-£44,038	-1.335	£32,997*
R1b) For 6-month CDP, the effectiveness of natalizumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£613,939	7.463	-£133,498	0.635	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£611,117	7.586	-£123,799	0.363	Cladribine dominant
R3) No re-exposure to cladribine	£474,494	8.098	£611,117	7.586	-£136,623	0.512	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years for natalizumab	£480,441	8.098	£662,978	8.027	-£182,537	0.071	Cladribine dominant
R5) TA32 EDSS state costs	£298,718	8.098	£419,579	7.586	-£120,861	0.512	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£611,117	9.462	-£130,676	0.480	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£53,471	1.215	£9,997	-0.011	Cladribine dominated
R8) 4-year time horizon	£81,567	2.272	£101,063	2.268	-£19,496	0.004	Cladribine dominant
(R1b-R6)	£297,128	9.807	£478,521	9.720	-£181,393	0.087	Cladribine dominant
(R1b-R7)	£56,817	1.343	£46,878	1.349	£9,939	-0.006	*Cladribine dominated*
(R1b-R6, R8)	£65,078	2.529	£88,453	2.531	-£23,375	-0.002	£11,291,887*
ERG scenario (R1a, R2-R6)	£346,045	8.227	£479,799	9.877	-£133,754	-1.650	£81,050*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 74 Cost effectiveness results for cladribine tablets versus daclizumab with ERG revisions to company base case (list prices)– RES-RRMS

Model scenario & ERG revisions	Cladribine tablets		Daclizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£480,441	8.098	£569,623	7.174	-£89,182	0.924	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£567,079	6.251	£569,092	7.180	-£2,013	-0.929	£2,167*
R1b) For qualifying ARR and 6-month CDP, the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£569,973	7.152	-£89,532	0.946	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£569,623	7.174	-£82,305	0.775	Cladribine dominant
R3) No re-exposure to cladribine	£474,494	8.098	£569,623	7.174	-£95,129	0.924	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years for daclizumab	£480,441	8.098	£622,959	7.708	-£142,518	0.390	Cladribine dominant
R5) TA32 EDSS state costs	£298,718	8.098	£370,829	7.174	-£72,110	0.924	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£569,623	9.079	-£89,182	0.864	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£47,537	1.199	£15,931	0.005	£3,121,856
R8) 4-year time horizon	£81,567	2.272	£87,551	2.226	-£5,984	0.046	Cladribine dominant
(R1b-R6)	£297,128	9.807	£433,490	9.546	-£136,363	0.261	Cladribine dominant
(R1b-R7)	£56,817	1.343	£40,550	1.341	£16,267	0.002	£7,206,437
(R1b-R6, R8)	£65,078	2.529	£74,817	2.510	-£9,739	0.020	Cladribine dominant
ERG scenario (R1a, R2-R6)	£346,045	8.227	£433,611	9.589	-£87,566	-1.362	£64,269*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

A summary of the effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with cladribine tables versus alemtuzumab, fingolimod and daclizumab for patients in the SOT-RRMS subgroup are provided in Table 75 to Table 77.

As discussed in Section 5, the ERG considers that, in the absence of statistically significant trial evidence to show that treatment with cladribine is more effective than placebo for patients with SOT-RRMS, there is no robust basis for any cost effectiveness results produced by an economic model. Table 75 to Table 77 do not include any cost effectiveness estimates based on an ERG scenario.

Table 75 Cost effectiveness results for cladribine tablets versus alemtuzumab with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Alemtuzumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£484,910	7.417	-£17,549	0.153	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£480,655	7.507	-£13,294	0.063	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£484,910	7.417	-£13,476	0.067	Cladribine dominant
R3) No re-exposure to cladribine tablets or alemtuzumab after 2 years	£461,531	7.570	£477,257	7.417	-£15,726	0.153	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years	N/A	N/A	N/A	N/A	N/A	N/A	N/A
R5) TA32 EDSS costs	£289,050	7.570	£303,970	7.417	-£14,921	0.153	Cladribine dominant
R6) No carer disutility	£467,360	9.416	£484,910	9.274	-£17,550	0.142	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£74,531	1.125	-£8,887	0.009	Cladribine dominant
R8) 4-year time horizon	£85,775	2.131	£99,937	2.108	-£14,162	0.023	Cladribine dominant
(R1-R6)	£285,791	9.336	£293,681	9.358	-£7,889	-0.021	£372,802*
(R1-R7)	£57,874	1.296	£66,648	1.290	-£8,774	0.006	Cladribine dominant
(R1-R6, R8)	£66,689	2.434	£75,400	2.430	-£8,711	0.004	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 76 Cost effectiveness results for cladribine tablets versus fingolimod with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Fingolimod		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£539,427	6.626	-£72,065	0.944	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of fingolimod is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£528,912	6.941	-£61,552	0.629	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£539,427	6.626	-£67,992	0.858	Cladribine dominant
R3) No re-exposure to cladribine	£461,531	7.570	£539,427	6.626	-£77,896	0.944	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years for fingolimod	£467,360	7.570	£594,828	6.756	-£127,468	0.814	Cladribine dominant
R5) ID890 EDSS costs	£289,050	7.570	£343,415	6.626	-£54,366	0.944	Cladribine dominant
R6) No carer disutility	£467,360	9.416	£539,427	8.537	-£72,066	0.879	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£48,668	1.116	£16,977	0.019	£897,693
R8) 4-year time horizon	£85,775	2.131	£88,813	2.048	-£3,038	0.083	Cladribine dominant
(R1-R6)	£285,791	9.336	£403,086	9.137	-£117,295	0.199	Cladribine dominant
(R1-R7)	£57,874	1.296	£40,480	1.296	£17,394	0.000	£37,479,159*
(R1-R6, R8)	£66,689	2.434	£73,331	2.420	-£6,642	0.013	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 77 Cost effectiveness results for cladribine tablets versus daclizumab with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Daclizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£533,758	7.022	-£66,397	0.548	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£534,750	6.991	-£67,388	0.579	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£533,758	7.022	-£62,323	0.462	Cladribine dominant
R3) No re-exposure to cladribine	£461,531	7.570	£533,758	7.022	-£72,227	0.548	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years for daclizumab	£467,361	7.570	£590,474	7.359	-£123,112	0.211	Cladribine dominant
R5) TA32 EDSS state costs	£289,050	7.570	£345,024	7.022	-£55,974	0.548	Cladribine dominant
R6) No carer disutility	£467,361	9.416	£533,758	8.903	-£66,397	0.513	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£48,359	1.136	£17,285	-0.001	*Cladribine dominated*
R8) 4-year time horizon	£85,775	2.131	£88,813	2.110	-£3,038	0.020	Cladribine dominant
(R1-R6)	£285,791	9.336	£408,028	9.172	-£122,237	0.164	Cladribine dominant
(R1-R7)	£57,874	1.296	£40,560	1.297	£17,314	0.000	*Cladribine dominated*
(R1-R6, R8)	£66,689	2.434	£74,439	2.423	-£7,749	0.010	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

6.1 Conclusions of the cost effectiveness section

The ERG considers that the economic model submitted by the company is well designed and commends the company on the efforts that they have made to identify data with which to populate it.

However, the ERG considers that the usefulness of the model to decision makers is limited. The two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets versus placebo and versus other DMTs, and (ii) the inclusion of costs and benefits that are outwith the NICE reference case.[31] Whilst changes to the model can address the latter of these issues, no data are available to address the clinical evidence related issues.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence using data from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 17 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively. This means that the samples have low power to detect statistically significant changes in outcomes.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model). This means that any model results, for patients in the SOT-RRMS subgroup, showing that treatment with cladribine tablets is cost effective compared with any comparator should be viewed with caution.
- Evidence allowing the clinical effectiveness of cladribine tablets to be compared with other DMTs has been drawn from a set of NMAs and a meta-regression. The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS (see Section 4.7).

- For qualifying ARR in the RES-RRMS subgroup, CLARITY trial data showed that cladribine tablets were demonstrated to be statistically significantly better than placebo. However, the results from the company's NMA show that the qualifying ARR confidence intervals for cladribine tablets and the other DMTs are wide. This makes the assessment of comparative effectiveness of cladribine tablets versus other DMTs essentially speculation.
- For 6-month CDP there is no evidence that cladribine tablets are any more (or less) effective than any other DMT for the RES-RRMS and SOT-RRMS subgroups over 2 years.
- Effectiveness evidence for all of the DMTs included in the company's economic analyses, for both the RES-RRMS and SOT-RRMS subgroups, is limited to 2 years. The company has then extrapolated this evidence out to 50 years. This means that there is no clinical evidence for 96% of the model time horizon. After 2 years, the modelling of waning of treatment effectiveness, treatment discontinuation rates and efficacy of re-exposure to cladribine tablets or alemtuzumab, all of which have an effect on clinical effectiveness, are all almost entirely based on assumptions.
- As in models that have informed previous NICE MS TAs, the model submitted by the company only considers a single line of treatment. In reality, upon relapse or treatment failure, other lines of treatment or re-exposure with a previous treatment would be offered to patients and, therefore, the model is overly simplistic. However, the ERG recognises that data to populate a more realistic lifetime model that includes multiple lines of treatment are not currently available.

The NICE reference case

- The NICE reference case[31] stipulates that outcomes should reflect all direct health effects, whether for patients or for other people. However, costs (in the form of lost income) and health benefits (in the form of disutility associated with EDSS states and progression) to carers are included in the company model. The ERG considers that carers' lost income is not a direct cost and that health benefits to carers cannot be considered to be direct health benefits from treatment with cladribine tablets and that, therefore, neither should have been included in the company model.

7 END OF LIFE CRITERIA

End of life considerations do not apply.

8 OVERALL CONCLUSIONS

8.1 Clinical: overall conclusions

Discrepancies between the evidence submitted and the final scope issued by NICE

The ERG considers that the evidence submitted by the company reflects the decision problem defined in the final scope issued by NICE for the RES-RRMS and SOT-RRMS populations only. The company did not provide evidence for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

Direct clinical evidence

The company presented direct clinical effectiveness evidence (cladribine tablets versus placebo) from the CLARITY trial. This trial was of good quality and was well conducted. The RES-RRMS and SOT-RRMS subgroups and three outcomes (NEDA-3, time to 6-month CDP and proportion of people with 6-month CDP) were defined retrospectively. The ERG considers that the post-hoc definitions and analyses were necessary to address the final scope issued by NICE.

Indirect clinical evidence

The ERG considers that the company's general approach to undertaking NMAs and meta-regression) were appropriate in terms of the trials and comparators included, the statistical methodology employed, the model selection criteria, the choice of most appropriate model, and the interpretation of results. The results of the NMAs carried out by the company should be viewed with caution due to the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab in the RES-RRMS and SOT-RRMS populations. The company also performed a meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS. However, in light of the company's stated objectives, the ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

8.2 Economics: overall conclusions

The effect of DMTs on slowing disability progression is by far the biggest driver of cost effectiveness in the economic model for cladribine tablets submitted by the company. The company and the ERG agree that, for 6-month CDP, evidence presented in the CS for the RES-RRMS and SOT-RRMS subgroups suggests that there is no difference between cladribine tablets and any of the other DMTs. The point estimates in the model for 6-month CDP are close for all DMTs. However, due to the company applying a lower treatment effect for waning to cladribine tablets compared with that applied to other DMTs, as well as significantly higher discontinuation rates for natalizumab, fingolimod and daclizumab,

cladribine tablets are shown to dominate all comparators. The ERG considers that even if key effectiveness evidence from the CLARITY trial was statistically significant versus placebo (which it is not for either RES-RRMS or SOT-RRMS), the waning and discontinuation rates applied in the model are not supported by evidence and are overestimating the cost effectiveness of cladribine tablets over other DMTs.

RES-RRMS

If cladribine tablets are ineffective at reducing 6-month CDP as suggested by the lack of statistically significant evidence from the CLARITY trial, but alemtuzumab, natalizumab and daclizumab are effective at reducing 6-month CDP with effectiveness parameters as estimated by the company meta-regression, then cladribine tablets would be dominated by alemtuzumab and be less costly and less effective than natalizumab and daclizumab, albeit at favourable ICERs per QALYs lost.

If cladribine tablets were assumed to be as effective at reducing 6-month CDP as suggested by the point estimate in the meta-regression, with alemtuzumab, natalizumab and daclizumab assumed to have equal effectiveness to cladribine tablets, then cladribine tablets would dominate natalizumab and daclizumab but would be less costly and less effective than alemtuzumab, again at a favourable ICER per QALY lost.

Given substantial uncertainties in the long-term evidence of all DMTs on disability progression and qualifying ARR, the ERG considers that any economic findings produced by the company model, even after ERG modifications, should be treated with caution.

SOT-RRMS

There is no statistically significant evidence of effectiveness of cladribine tablets over placebo in the SOT-RRMS subgroup for either 6-month CDP or qualifying ARR. There is therefore no basis on which to undertake economic analysis.

8.3 Implications for research

The ERG considers that:

- Currently, evidence does not allow a direct comparison of effectiveness of treatment with cladribine tablets versus any other DMT. A head-to-head trial considering these treatments and placebo would generate results that would be valuable to decision makers
- Future studies of people with RRMS should pay careful consideration to the classification of patient subgroups and use that classification as a randomisation stratification factor

- It would be useful to record, and report, HRQoL outcomes from any future clinical study of cladribine tablets and other DMTs. In particular, data should be collected, using the EQ-5D questionnaire, throughout the whole trial period, not only from patients whose disease has not progressed
- It would be useful to explore how cladribine tablets should be positioned in the treatment pathway.

9 REFERENCES

1. Merck. Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]: company evidence submission to NICE. 2017.
2. Compston A, Coles A. Multiple sclerosis. Lancet. 2008; 372:1502-17.
3. Zuvich RL, McCauley JL, Pericak-Vance MA, Haines JL. Genetics and pathogenesis of multiple sclerosis. Semin Immunol. 2009; 21:328-33.
4. Compston A, Coles A. Multiple sclerosis. Lancet. 2002; 359:1221-31.
5. Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron. 2006; 52:61-76.
6. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. Neurology. 2010; 74:2004-15.
7. European Medicines Agency. Tysabri. Summary of product characteristics. 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf [accessed August 2017].
8. European Medicines Agency. Gilenya. Summary of product characteristics. 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf [accessed August 2017].
9. Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R*, et al.* Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain. 2008; 131:808-17.
10. National Institute for Health and Care Excellence (NICE). Cladribine for treating relapsing-remitting multiple sclerosis [final scope] 2017.
11. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M*, et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69:292-302.
12. Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A*, et al.* Association of British neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol. 2015; 15:273-9.
13. European Medicines Agency (EMA). Movectro. 2011; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001197/wapp/Initial_authorisation/human_wapp_000114.jsp&mid=WC0b01ac058001d128&source=homeMedSearch&category=human [accessed August 2017].
14. European Medicines Agency. Mavenclad. Summary of opinion (initial authorisation). 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004230/WC500229786.pdf [Accessed August 2017].
15. National Institute for Health and Care Excellence (NICE). Multiple sclerosis - interferon beta, glatiramer acetate (review TA32) [ID809]. 2017; Available from: https://www.nice.org.uk/search?q=ID809 [accessed August 2017].
16. National Institute for Health and Care Excellence (NICE). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis [TA32]. NICE; 2002; Available from: https://www.nice.org.uk/Guidance/ta32 [accessed August 2017]
17. National Institute for Health and Care Excellence (NICE). Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis [TA127]. 2007; Available from: https://www.nice.org.uk/search?q=TA127 [accessed August 2017].
18. National Institute for Health and Care Excellence (NICE). Dimethyl fumarate for treating relapsing‐remitting multiple sclerosis [TA320]. 2014; Available from: https://www.nice.org.uk/guidance/ta320 [accessed August 2017].
19. National Institute for Health and Care Excellence (NICE). Alemtuzumab for treating relapsing‐remitting multiple sclerosis [TA312]. 2014; Available from: https://www.nice.org.uk/search?q=TA312 [accessed August 2017].

20. National Institute for Health and Care Excellence (NICE). Daclizumab for treating relapsing–remitting multiple sclerosis [TA441]. 2017; Available from: https://www.nice.org.uk/guidance/ta441 [accessed August 2017].
21. Office for National Statistics. Population projections. 2017; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections [accessed August 2017].
22. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the general practice research database. J Neurol Neurosurg Psychiatry. 2014; 85:76-84.
23. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Epidemiology of multiple sclerosis: results from a large observational study in the UK. J Neurol. 2015; 262:2033-41.
24. Hawton A, Green C. Health Utilities for Multiple Sclerosis. Value Health. 2016; 19:460-8.
25. Zajicek JP, Ingram WM, Vickery J, Creanor S, Wright DE, Hobart JC. 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.
26. Merck. CLARITY GEVD subgroup analyses. 2017.
27. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sorensen P*, et al.* A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010; 362:416-26.
28. European Medicines Agency. Mavenclad. Summary of product characteristics. 2017.
29. Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. Clin Neuropharmacol. 2011; 34:28-35.
30. Merck. CLARITY EXT clinical trial report, Study 27820. 2016.
31. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. 2013; Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. [Accessed August 2017].
32. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ*, et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996; 17:1-12.
33. Merck. PREMIERE registry clinical trial report, Study EMR700568-0122016.
34. Leist TP, Comi G, Cree BAC, Coyle PK, Freedman MS, Hartung H-P*, et al.* Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol. 2014; 13:257-67.
35. Cook S, Comi G, Rieckmann P, Rammohan K, Soelberg-Sorensen P, et al. Safety and tolerability of cladribine tablets in patients with relapsing-remitting multiple sclerosis (RRMS): final results from the 120-week phase IIIb extension trial to the CLARITY study. American Academy of Neurology Annual Conference (AAN) 15-21 April. 2016: Abstract No. 3326.
36. Merck. CLARITY clinical trial report, Study 25643. 2010.
37. Merck. CLARITY clinical study protocol, Study 25643. 2008.
38. Merck. CLARITY statistical analysis plan. Final analysis for study 25643. 2010.
39. Bevan CJ, Cree BA. Disease activity free status: a new end point for a new era in multiple sclerosis clinical research? JAMA neurology. 2014; 71:269-70.
40. Lublin FD. Disease activity free status in MS. Multiple sclerosis and related disorders. 2012; 1:6-7.
41. Havrdova E, Galetta S, Stefoski D, Comi G. Freedom from disease activity in multiple sclerosis. Neurology. 2010; 74 Suppl 3:S3-7.
42. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. 2015.

43. Ebers GC. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. Lancet. 1998; 352:1498-504.
44. National Research Council. The prevention and treatment of missing data in clinical trials (panel on handling missing data in clinical trials, committee on national statistics, division of behavioral and social sciences and education). Washington, DC: 2010.
45. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. Qual Life Res. 1995; 4:187-206.
46. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16:199-208.
47. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). 1. conceptual framework and item selection. Medical care. 1992; 30:473-83.
48. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L*, et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014; 20:705-16.
49. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP*, et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014; 13:247-56.
50. O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C*, et al.* A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006; 66:894-900.
51. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP*, et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011; 365:1293-303.
52. Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K*, et al.* A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012; 18:1269-77.
53. Dias S, Ades AE. Absolute or relative effects? Arm-based synthesis of trial data. Res Synth Methods. 2016; 7:23-8.
54. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997; 50:683-91.
55. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010; 29:932-44.
56. Knobler RL, Greenstein JI, Johnson KP, Lublin FD, Panitch HS, Conway K*, et al.* Systemic recombinant human interferon-beta treatment of relapsing-remitting multiple sclerosis: pilot study analysis and six-year follow-up. J Interferon Res. 1993; 13:333-40.
57. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung H-P*, et al.* Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012; 380:1819-28.
58. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ*, et al.* Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012; 380:1829-39.
59. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH*, et al.* Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008; 359:1786-801.
60. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD*, et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001; 50:121-7.

61. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L*, et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005; 58:840-6.
62. NICE Decision Support Unit. Technical support document 3 (TSD3): heterogeneity: subgroups, meta-regression, bias and bias-adjustment. 2011.
63. Polman CH, O'Connor P, Havrdova E, Hutchinson M, Kappos L, Miller D*, et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006; 354:899-910.
64. Bose U, Ladkani D, Burrell A, Sharief M. Cost-effectiveness analysis of glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis. J Med Econ. 2001; 4:207-19.
65. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J. 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; 26:617-27.
66. Hernandez L, Guo S, Kinter E, Fay M. Cost-effectiveness analysis of peginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States. J Med Econ. 2016; 19:684-95.
67. Lepen C, Coyle P, Vollmer T, Blumhardt L, Lilliu H, Beresniak A. Long-term cost effectiveness of interferon-beta-1a in the treatment of relapsing-remitting multiple sclerosis : an econometric model. Clin Drug Investig. 2003; 23:571-81.
68. Maruszczak MJ, Montgomery SM, Griffiths MJ, Bergvall N, Adlard N. Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England. J Med Econ. 2015; 18:874-85.
69. Montgomery SM, Maruszczak MJ, Slater D, Kusel J, Nicholas R, Adlard N. A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK. J Med Econ. 2017; 20:474-82.
70. Phillips C, Gilmour L, Gale R, Palmer M. A cost utility model of interferon beta-1b in the treatment of relapsing-remitting multiple sclerosis. J Med Econ. 2001; 4:35-50.
71. Versteegh M. Impact on the incremental cost-effectiveness ratio of using alternatives to EQ-5D in a markov model for multiple sclerosis. Pharmacoeconomics. 2016; 34:1133-44.
72. National Institute for Health and Care Excellence (NICE). Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis [TA254]. 2012; Available from: https://www.nice.org.uk/guidance/ta254 [accessed August 2017].
73. National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing–remitting multiple sclerosis [TA303]. 2014; Available from: https://www.nice.org.uk/guidance/ta303 [accessed August 2017].
74. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M*, et al.* UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open. 2014; 4:e004073.
75. Palace J, Duddy M, Bregenzer T, Lawton M, Zhu F, Boggild M*, et al.* Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK multiple sclerosis risk sharing scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol. 2015; 14:497-505.
76. Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. J Neurol Neurosurg Psychiatry. 2016; 87:324-31.
77. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007; 10:54-60.

78. Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. J Med Econ. 2016; 19:21-33.
79. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. Eur J Health Econ. 2011; 12:219-30.
80. Trogdon JG, Ekwueme DU, Chamiec-Case L, Guy GP, Jr. Breast cancer in young women: health state utility impacts by race/ethnicity. Am J Prev Med. 2016; 50:262-9.
81. British National Formulary. BNF online. 2017; Available from: http://www.bnf.org/products/bnf-online/. [Accessed August 2017].
82. European Medicines Agency. Lemtrada. Summary of product characteristics. 2017; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003718/WC500150521.pdf [accessed August 2017].
83. McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P*, et al.* Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. 2016; 87:117.
84. Curtis L, Burns A. Unit costs of health and social care 2016. 2016; Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php. [Accessed August 2017].
85. Karampampa K, Gustavsson A, Miltenburger C, Tyas D. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from the United Kingdom. Mult Scler. 2012; 18:41-5.
86. Tyas D, Kerrigan J, Russell N, Nixon R. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? Value Health. 2007; 10:386-9.
87. Department of Health. NHS reference costs 2015 to 2016. 2016; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. [Accessed August 2017].
88. Gani R, Nixon RM, Hughes S, Jackson CH. Estimating the rates of disability progression in people with active relapsing-remitting multiple sclerosis. J Med Econ. 2007; 10.
89. Singer B, Bandari D, Cascione M, LaGanke C, Huddlestone J, Bennett R*, et al.* Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonbeta-1a versus subcutaneous interferonbeta-1b: results of the randomized, multicenter, phase IIIb REFORMS study. BMC Neurol. 2012; 12:154.
90. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F*, et al.* Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012; 18:418-24.
91. De Stefano N, Sormani MP, Stubinski B, Blevins G, Drulovic JS, Issard D*, et al.* Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: further outcomes from the IMPROVE study. J Neurol Sci. 2012; 312:97-101.
92. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A*, et al.* Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002; 359:1453-60.
93. Wroe SJ. Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis. J Int Med Res. 2005; 33:309-18.
94. Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E*, et al.* A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987; 317:408-14.

95. The IFNB multiple sclerosis study group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993; 43:655-61.
96. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM*, et al.* Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The multiple sclerosis collaborative research group (MSCRG). Ann Neurol. 1996; 39:285-94.

10 APPENDICES

10.1 Differences in statistical approaches for the original analysis and analysis for the CS of the CLARITY trial

The ERG notes several slight differences in numerical results presented within the CS compared to the results of efficacy outcomes reported in the CSR of the CLARITY trial and the primary publication which were prepared in 2010.[27]

The company state that within submissions to regulatory authorities including the present CS, the approach to handling missing data was amended to an approach the company consider more appropriate to the original approach specified within the TSAP. Additionally, original analyses were conducted with region as a fixed-effect within statistical models, however this fixed-effect was omitted from the re-analyses conducted for the CS, due to concerns regarding statistical model convergence within the smaller post-hoc subgroups.

Detailed reasons for the differences in the numerical results due to the differences in statistical modelling are presented in Table 78 and further details of the differences in the approach to missing data between the original analysis and the re-analysis of the CLARITY trial are provided in Table 79.

Table 78 Differences between reported results in primary publication and reported results in the CS for the CLARITY trial

CS Table	Estimate presented	Imputation and model used in the primary publication[27]	Imputation and model used in the CS
18	Qualifying ARR	- Numbers of qualifying relapses were imputed for rescued subjects (after the rescue time). - The relapse count was modelled through a Poisson regression model with fixed effects for treatment group and region and with log of time on study as an offset variable.	- Numbers of qualifying relapses were not imputed. Reported numbers of qualifying relapses were used for all subjects. - The relapse count was modelled through a Poisson regression model with fixed effect for treatment group and the log of time on study as an offset variable.
18	Time to first qualifying relapse Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effect for treatment group.
19	Proportion of relapse-free patients	- Missing data was imputed for the proportion of qualifying relapse-free subjects - The proportion of relapse-free patients was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 18. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.
20	Time to 3-month confirmed disability progression Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effect for treatment group.
21	Proportion of patients with 3-month confirmed disability progression	- Missing data was imputed for the proportion of patients without a 3-month sustained disability progression - The proportion of patients without a 3-month sustained disability progression was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 20. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.

ARR=annualised relapse rate; CS=company submission; K-M=kaplan-meier;
Source; adapted from company response to ERG clarification letter;

Table 79 Differences in analysis of missing data in the original analysis and the re-analysis of the CLARITY trial

TSAP page number	Original CLARITY analysis	CLARITY reanalysis for CS
p130-131	Imputation of number of qualifying relapses after rescue for subjects who received rescue medications	For all subjects, including those who received rescue medications, their reported qualifying relapses were used without exclusions or alterations.
p131-132	Imputation of missing data for the proportion of qualifying relapse-free subjects during 96 weeks (for subjects who prematurely withdrew from the study and had not had a relapse before withdrawing)	Subjects with no qualifying relapses but who withdrew from the study early were considered of unknown status and were excluded from logistic regression analyses (in the CS analyses). In the CS analyses, the proportions were presented descriptively and in addition, K-M estimates were provided (in which subjects that withdrew prematurely without having had a qualifying relapse were considered censored at the time of withdrawal).
p132	Imputation of missing data for the proportion of subjects without a 3-month sustained change in EDSS score (for subjects who prematurely withdrew from the study and had not had a sustained change before withdrawing)	The same approach as for the proportion of qualifying relapse-free subjects was taken.
p132	Imputation of missing data for the proportion of subjects with no CU, no active T1 Gd+ or no active T2 lesions (for subjects with missing mean lesion numbers)	For proportion of subjects with no active T1 Gd+ lesions and for proportion of subjects with no active T2 lesions: the same approach as for the proportion of qualifying relapse-free subjects was taken. The proportion of subjects with no CU lesions was analysed descriptively only in the CS analyses.
p132-133	Missing MRI data (baseline data and follow-up data)	Missing data were not imputed. For the definition of HDA populations: subjects with missing baseline number of T2 lesions were considered in the <9 T2 lesions category. Subjects with missing baseline number of T1 Gd+ lesions were considered in the <1 T1 Gd+ category.

CS=company submission; CU=combined unique; EDSS=expanded disability status scale Gd+=gadolinium enhancing; HDA=high disease activity; K-M=kaplan-meier;
Source; adapted from company response to ERG clarification letter; TSAP (p130-133)

10.2 Trials and participants included in network meta-analyses

Summary results and treatment networks for key efficacy outcomes ARR, 3-month CDP at 24 months and 6-month CDP at 24 months are provided in this section.

Table 80 Summary of trials used in the network meta-analysis for ARR (ITT population)

Study	Treatment 1	Events 1	Person years 1	Treatment 2	Events 2	Person years 2	Treatment 3	Events 3	Person years 3	Number of arms
ADVANCE trial	Placebo	181	445.25	INF-β-1a (Plegridy)	116	435.74	NA	NA	NA	2
AFFIRM trial	Placebo	472	738	Natalizumab, 300mg, q4w	294	1338	NA	NA	NA	2
BECOME trial	GA, 20mg, qd	23	69.7	INF-β-1b (Betaferon)	25	67.57	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	374	1099.5	INF-β-1b (Betaferon)	814	2260	NA	NA	NA	2
Bornstein 1987	Placebo	62	46	GA, 20mg, qd	16	47	NA	NA	NA	2
BRAVO trial	Placebo	275	808.82	INF-β-1a (Avonex)	215	826.92	NA	NA	NA	2
Calabrese 2012	GA, 20mg, qd	52	103	INF-β-1a (Avonex)	51	102	INF-β-1a (Rebif 44µg)	40	101	3
CARE-MS I trial	Alemtuzumab, 12mg, qd	119	661.11	INF-β-1a (Rebif 44µg)	122	312.82	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	236	907.69	INF-β-1a (Rebif 44µg)	201	386.54	NA	NA	NA	2
CombiRx trial	GA, 20mg, qd	70	650.7	INF-β-1a (Avonex)	97	604.4	NA	NA	NA	2
CONFIRM trial	Placebo	212	561.43	DMF, 240mg, bid	124	552.99	GA, 20mg, qd	163	569.62	3
Copolymer1 trial	Placebo	210	250	GA, 20mg, qd	161	272.88	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	500	2274.17	INF-β-1a (Avonex)	873	2238.16	NA	NA	NA	2
DEFINE Trial	Placebo	246	612.35	DMF, 240mg, bid	128	628.61	NA	NA	NA	2
Etemadifar 2006	INF-β-1a (Avonex)	57	60	INF-β-1a (Rebif 44µg)	66	60	INF-β-1b (Betaferon)	65	60	3
European and Canadian Glatiramer trial	Placebo	91	75.21	GA, 20mg, qd	61	75.31	NA	NA	NA	2
EVIDENCE trial	INF-β-1a (Avonex)	195	304.2	INF-β-1a (Rebif 44µg)	165	304.71	NA	NA	NA	2

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
FREEDOMS trial	Placebo	359	897.5	Fingolimod, 0.5mg, qd	172	955.6	NA	NA	NA	2
Gala trial	Placebo	215	445.5	GA, 40mg, tiw	290	901	NA	NA	NA	2
Gate trial	Placebo	24	61.88	GA, 20mg, qd	182	512.26	NA	NA	NA	2
IFNB MS trial	Placebo	266	209.2	INF-β-1b (Betaferon)	173	207	NA	NA	NA	2
IMPROVE trial	Placebo	6	18.14	INF-β-1a (Rebif 44µg)	5	35.96	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	126	180	INF-β-1b (Betaferon)	95	190	NA	NA	NA	2
Kappos 2011	Placebo	16	24.38	INF-β-1a (Avonex)	9	24.84	NA	NA	NA	2
Knobler 1993	Placebo	5	2.8	INF-β-1b (Betaferon)	2	2.3	NA	NA	NA	2
MSCRG trial	Placebo	235	286	INF-β-1a (Avonex)	212	316	NA	NA	NA	2
O`Connor 2006	Placebo	33	40.85	Teriflunomide, 14mg, od	19	35.31	Teriflunomide, 7mg, od	24	41.19	3
PRISMS trial	Placebo	479	364	INF-β-1a (Rebif 22µg)	344	366	INF-β-1a (Rebif 44µg)	318	363	3
REFORMS trial	INF-β-1a (Rebif 44µg)	10	13.92	INF-β-1b (Betaferon)	7	14.61	NA	NA	NA	2
REGARD trial	GA, 20mg, qd	194	669.5	INF-β-1a (Rebif 44µg)	201	669.5	NA	NA	NA	2
Saida 2012	Placebo	27	27	Fingolimod, 0.5mg, qd	13	26.25	NA	NA	NA	2
SELECT trial	Placebo	88	191.3	Daclizumab , 150mg, q4w	43	204.8	NA	NA	NA	2
TEMSO trial	Placebo	335	620.37	Teriflunomide, 14mg, od	227	613.51	Teriflunomide, 7mg, od	233	629.73	3
TENERE Trial	INF-β-1a (Rebif 44µg)	29	126.09	Teriflunomide, 14mg, od	39	144.44	Teriflunomide, 7mg, od	63	143.18	3
TOWER trial	Placebo	296	592	Teriflunomide, 14mg, od	177	553.125	Teriflunomide, 7mg, od	235	602.56	3

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
TRANSFORMS trial	Fingolimod, 0.5mg, qd	89	423.81	INF-β-1a (Avonex)	179	416.28	NA	NA	NA	2
CLARITY trial	Placebo	252	741.1	Cladribine tablets	109	767.1	NA	NA	NA	2
Saida 2017	Placebo	36	20.7	Natalizumab, 300mg, q4w	11	21.39	NA	NA	NA	2

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A1.1, company response to ERG clarification letter

Table 81 Summary of trials used in the network meta-analysis for ARR (HDA-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.31	0.23	0.42
CONFIRM trial	DMF, 240mg, bid	Placebo	0.66	0.42	1.04
CONFIRM trial	GA, 20mg, qd	Placebo	0.80	0.53	1.22
DEFINE Trial	DMF, 240mg, bid	Placebo	0.45	0.30	0.67
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.37	0.27	0.51
TOWER trial	Teriflunomide, 7 mg, od	Placebo	0.68	0.49	0.94
TOWER trial	Teriflunomide, 14 mg, od	Placebo	0.55	0.39	0.79
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.52	0.37	0.73
CLARITY trial	Cladribine tablets	Placebo	0.35	0.24	0.50
CAMMS223 trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.26	0.11	0.59
CARE-MS I trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.53	0.37	0.67
CARE-MS II trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.51	0.39	0.77
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.72	0.53	0.96

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; RR=rate ratio; UCI=upper bound of 95% confidence interval
Source: Table A2.1, company response to ERG clarification letter

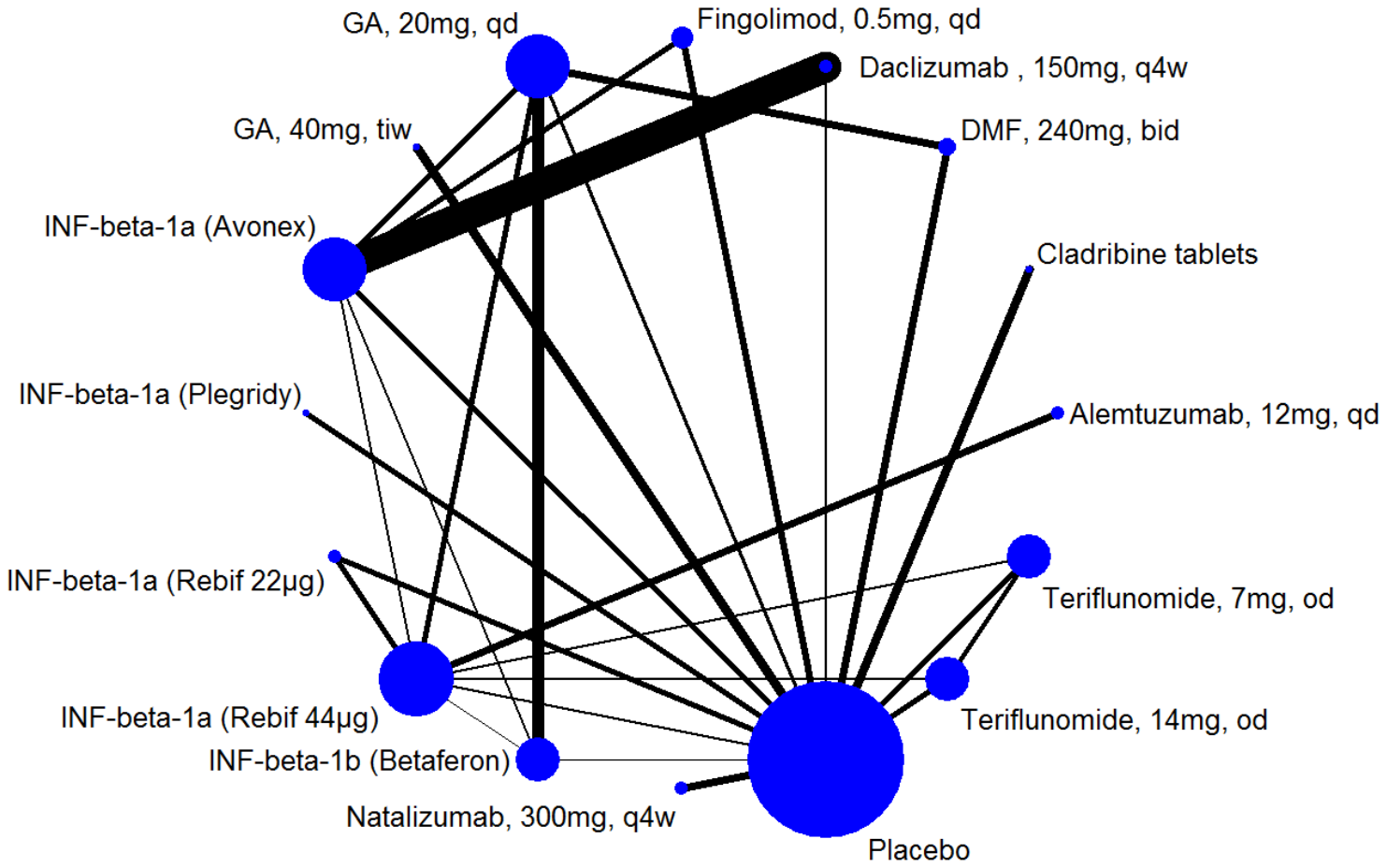


Figure 4 Network plot for the network meta-analysis of ARR (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total patient years contributing to the pairwise comparison.

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF=interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of **Error! Reference source not found.**

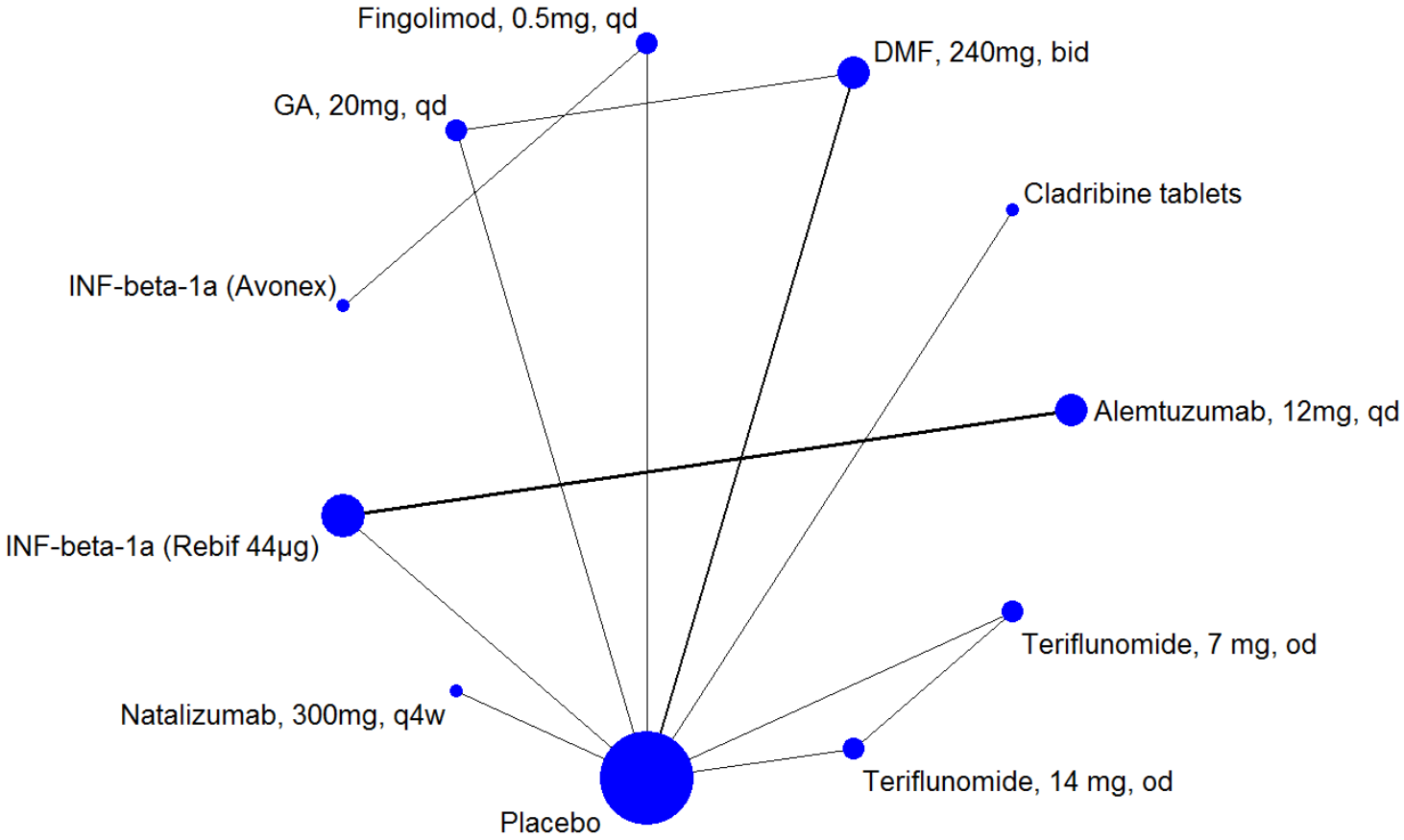


Figure 5 Network plot for the network meta-analysis of ARR (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; INF= interferon; RR=rate ratio.

Source: produced by the ERG, based on the numbers of Table 80 Summary of trials used in the network meta-analysis for ARR (ITT population)

Study	Treatment 1	Events 1	Person years 1	Treatment 2	Events 2	Person years 2	Treatment 3	Events 3	Person years 3	Number of arms
ADVANCE trial	Placebo	181	445.25	INF-β-1a (Plegridy)	116	435.74	NA	NA	NA	2
AFFIRM trial	Placebo	472	738	Natalizumab, 300mg, q4w	294	1338	NA	NA	NA	2
BECOME trial	GA, 20mg, qd	23	69.7	INF-β-1b (Betaferon)	25	67.57	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	374	1099.5	INF-β-1b (Betaferon)	814	2260	NA	NA	NA	2
Bornstein 1987	Placebo	62	46	GA, 20mg, qd	16	47	NA	NA	NA	2
BRAVO trial	Placebo	275	808.82	INF-β-1a (Avonex)	215	826.92	NA	NA	NA	2
Calabrese 2012	GA, 20mg, qd	52	103	INF-β-1a (Avonex)	51	102	INF-β-1a (Rebif 44µg)	40	101	3
CARE-MS I trial	Alemtuzumab, 12mg, qd	119	661.11	INF-β-1a (Rebif 44µg)	122	312.82	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	236	907.69	INF-β-1a (Rebif 44µg)	201	386.54	NA	NA	NA	2
CombiRx trial	GA, 20mg, qd	70	650.7	INF-β-1a (Avonex)	97	604.4	NA	NA	NA	2
CONFIRM trial	Placebo	212	561.43	DMF, 240mg, bid	124	552.99	GA, 20mg, qd	163	569.62	3
Copolymer1 trial	Placebo	210	250	GA, 20mg, qd	161	272.88	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	500	2274.17	INF-β-1a (Avonex)	873	2238.16	NA	NA	NA	2
DEFINE Trial	Placebo	246	612.35	DMF, 240mg, bid	128	628.61	NA	NA	NA	2
Etemadifar 2006	INF-β-1a (Avonex)	57	60	INF-β-1a (Rebif 44µg)	66	60	INF-β-1b (Betaferon)	65	60	3
European and Canadian Glatiramer trial	Placebo	91	75.21	GA, 20mg, qd	61	75.31	NA	NA	NA	2
EVIDENCE trial	INF-β-1a (Avonex)	195	304.2	INF-β-1a (Rebif 44µg)	165	304.71	NA	NA	NA	2

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
FREEDOMS trial	Placebo	359	897.5	Fingolimod, 0.5mg, qd	172	955.6	NA	NA	NA	2
Gala trial	Placebo	215	445.5	GA, 40mg, tiw	290	901	NA	NA	NA	2
Gate trial	Placebo	24	61.88	GA, 20mg, qd	182	512.26	NA	NA	NA	2
IFNB MS trial	Placebo	266	209.2	INF-β-1b (Betaferon)	173	207	NA	NA	NA	2
IMPROVE trial	Placebo	6	18.14	INF-β-1a (Rebif 44µg)	5	35.96	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	126	180	INF-β-1b (Betaferon)	95	190	NA	NA	NA	2
Kappos 2011	Placebo	16	24.38	INF-β-1a (Avonex)	9	24.84	NA	NA	NA	2
Knobler 1993	Placebo	5	2.8	INF-β-1b (Betaferon)	2	2.3	NA	NA	NA	2
MSCRG trial	Placebo	235	286	INF-β-1a (Avonex)	212	316	NA	NA	NA	2
O`Connor 2006	Placebo	33	40.85	Teriflunomide, 14mg, od	19	35.31	Teriflunomide, 7mg, od	24	41.19	3
PRISMS trial	Placebo	479	364	INF-β-1a (Rebif 22µg)	344	366	INF-β-1a (Rebif 44µg)	318	363	3
REFORMS trial	INF-β-1a (Rebif 44µg)	10	13.92	INF-β-1b (Betaferon)	7	14.61	NA	NA	NA	2
REGARD trial	GA, 20mg, qd	194	669.5	INF-β-1a (Rebif 44µg)	201	669.5	NA	NA	NA	2
Saida 2012	Placebo	27	27	Fingolimod, 0.5mg, qd	13	26.25	NA	NA	NA	2
SELECT trial	Placebo	88	191.3	Daclizumab , 150mg, q4w	43	204.8	NA	NA	NA	2
TEMSO trial	Placebo	335	620.37	Teriflunomide, 14mg, od	227	613.51	Teriflunomide, 7mg, od	233	629.73	3
TENERE Trial	INF-β-1a (Rebif 44µg)	29	126.09	Teriflunomide, 14mg, od	39	144.44	Teriflunomide, 7mg, od	63	143.18	3
TOWER trial	Placebo	296	592	Teriflunomide, 14mg, od	177	553.125	Teriflunomide, 7mg, od	235	602.56	3

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
TRANSFORMS trial	Fingolimod, 0.5mg, qd	89	423.81	INF-β-1a (Avonex)	179	416.28	NA	NA	NA	2
CLARITY trial	Placebo	252	741.1	Cladribine tablets	109	767.1	NA	NA	NA	2
Saida 2017	Placebo	36	20.7	Natalizumab, 300mg, q4w	11	21.39	NA	NA	NA	2

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A1.1, company response to ERG clarification letter

Table 81

Table 82 Summary of trials used in the network meta-analysis for ARR (RES-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.19	0.15	0.25
Decide Trial	Daclizumab , 150mg, q4w	INF-β-1a (Avonex)	0.42	0.31	0.57
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.37	0.24	0.57
TEMSO trial	Teriflunomide, 7mg, od	Placebo	0.51	0.32	0.81
TEMSO trial	Teriflunomide, 14mg, od	Placebo	0.81	0.51	1.28
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.48	0.24	0.95
CLARITY trial	Cladribine tablets	Placebo	0.31	0.18	0.53
CARE-MS I trial	Alemtuzumab	INF-β-1a (Rebif 44µg)	0.49	0.33	0.74
CARE-MS II trial	Alemtuzumab	INF-β-1a (Rebif 44µg)	0.51	0.35	0.74
SELECT trial	Daclizumab , 150mg, q4w	Placebo	0.48	0.22	1.04
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.44	0.21	0.91

ARR=annualised relapse rate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β=interferon-beta; LCI=lower bound of 95% confidence interval; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; RR=rate ratio; UCI=upper bound of 95% confidence interval
Source: Table A4.1, company response to ERG clarification letter

Table 83 Summary of trials used in the network meta-analysis for ARR (SOT-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.52	0.37	0.74
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.49	0.31	0.78
CLARITY trial	Cladribine tablets	Placebo	0.48	0.20	1.11

ARR=annualised relapse rate; mg=milligram; qd=per day; INF- β=interferon-beta; LCI=lower bound of 95% confidence interval; RR=rate ratio; SOT-RRMS=suboptimal therapy relapsing remitting multiple sclerosis; UCI=upper bound of 95% confidence interval
Source: Table A3.1, company response to ERG clarification letter

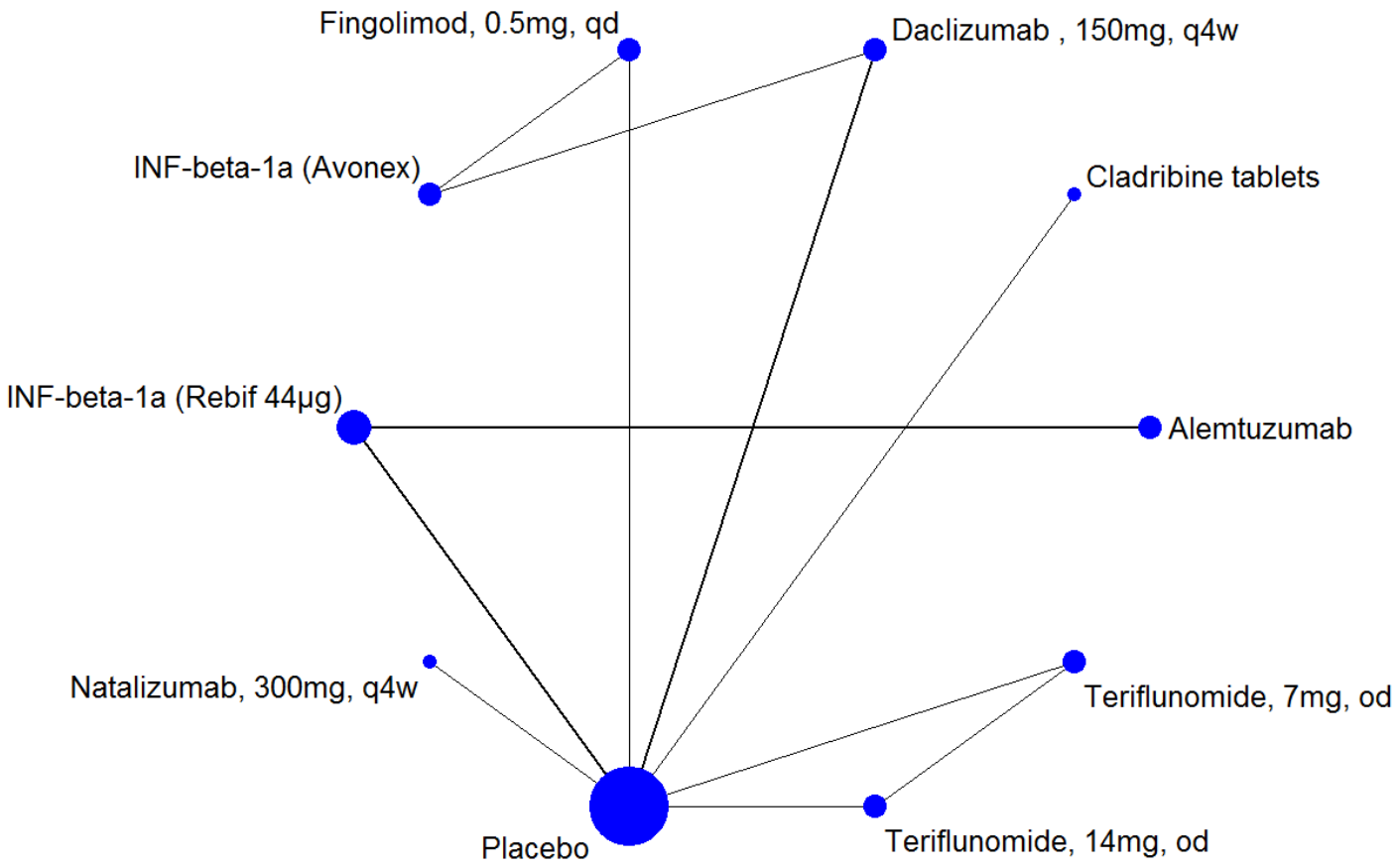


Figure 6 Network plot for the network meta-analysis of ARR (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.

ARR=annualised relapse rate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF=interferon; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; RR=rate ratio;
Source: produced by the ERG, based on the numbers of Table 82

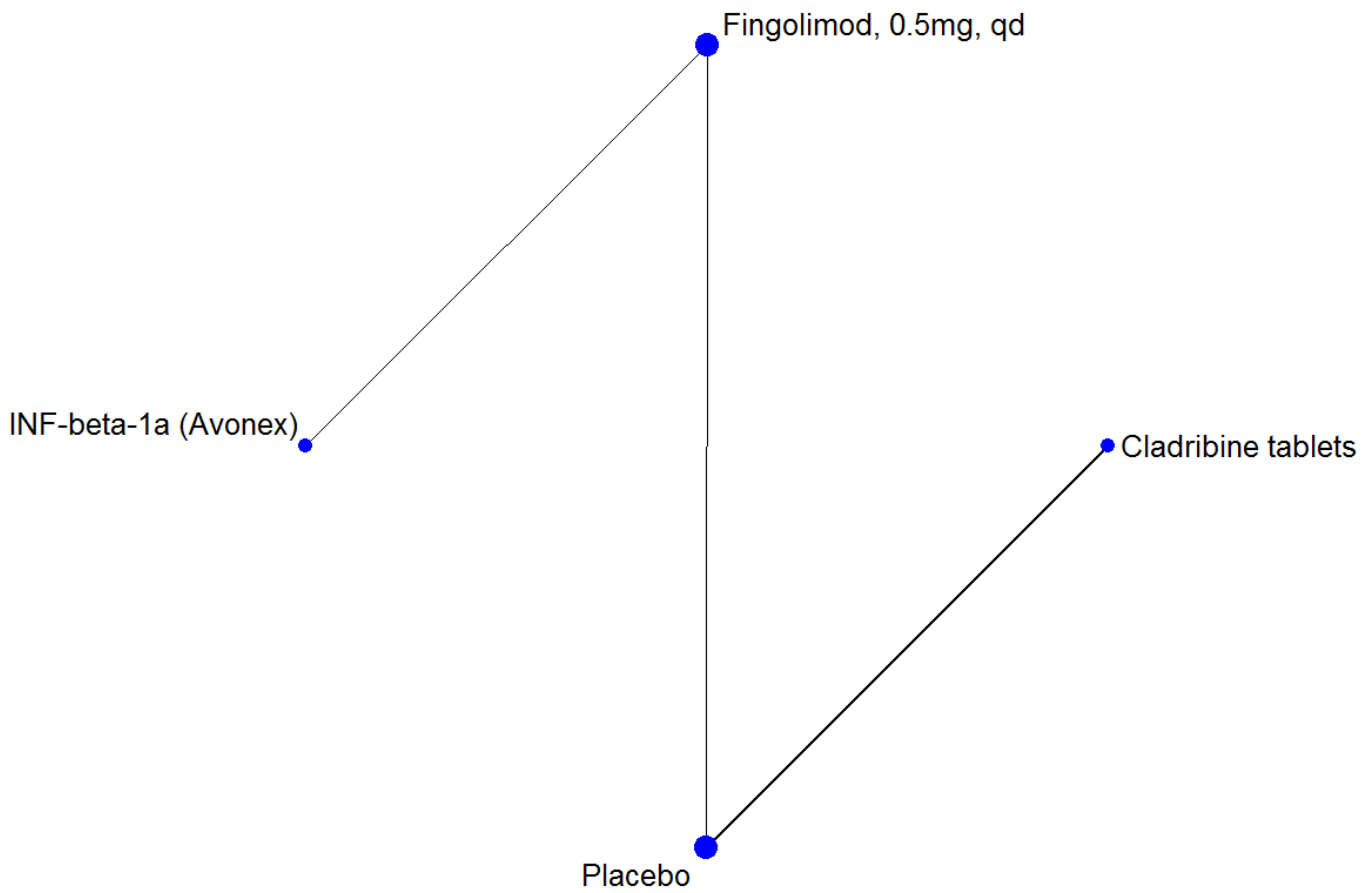


Figure 7 Network plot for the network meta-analysis of ARR (SOT-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.
ARR=annualised relapse rate; mg=milligram; qd=per day; INF=interferon; RR=rate ratio; SOT-RRMS=suboptimal therapy relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 83

Table 84 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (ITT population)

Study	Treatment 1	Events 1	Total 1	Treatment 2	Events 2	Total 2	Treatment 3	Events 3	Total 3	Number of arms
AFFIRM trial	Placebo	91	315	Natalizumab, 300mg, q4w	107	627	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	92	448	INF-β-1b (Betaferon)	244	897	NA	NA	NA	2
Bornstein 1987	Placebo	11	25	GA, 20mg, qd	5	25	NA	NA	NA	2
BRAVO trial	Placebo	60	450	INF-β-1a (Avonex)	47	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab, 12mg, qd	11	113	INF-β-1a (Rebif 44µg)	24	111	NA	NA	NA	2
CONFIRM trial	Placebo	62	363	DMF, 240mg, bid	47	362	GA, 20mg, qd	56	360	3
Copolymer1 trial	Placebo	31	126	GA, 20mg, qd	27	125	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	118	919	INF-β-1a (Avonex)	138	922	NA	NA	NA	2
DEFINE Trial	Placebo	89	410	DMF, 240mg, bid	57	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	103	355	Fingolimod, 0.5mg, qd	91	358	NA	NA	NA	2
FREEDOMS trial	Placebo	101	418	Fingolimod, 0.5mg, qd	75	425	NA	NA	NA	2
IFNB MS trial	Placebo	56	123	INF-β-1b (Betaferon)	43	124	NA	NA	NA	2
PRISMS trial	Placebo	68	187	INF-β-1a (Rebif 22µg)	49	189	INF-β-1a (Rebif 44µg)	47	184	3
TEMSO trial	Placebo	99	363	Teriflunomide, 14mg, od	72	359	Teriflunomide, 7mg, od	79	366	3
TOWER trial	Placebo	76	389	Teriflunomide, 14mg, od	58	372	Teriflunomide, 7mg, od	86	408	3
CLARITY trial	Placebo	103	437	Cladribine tablets	65	433	NA	NA	NA	2

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A2.1, company response to ERG clarification letter

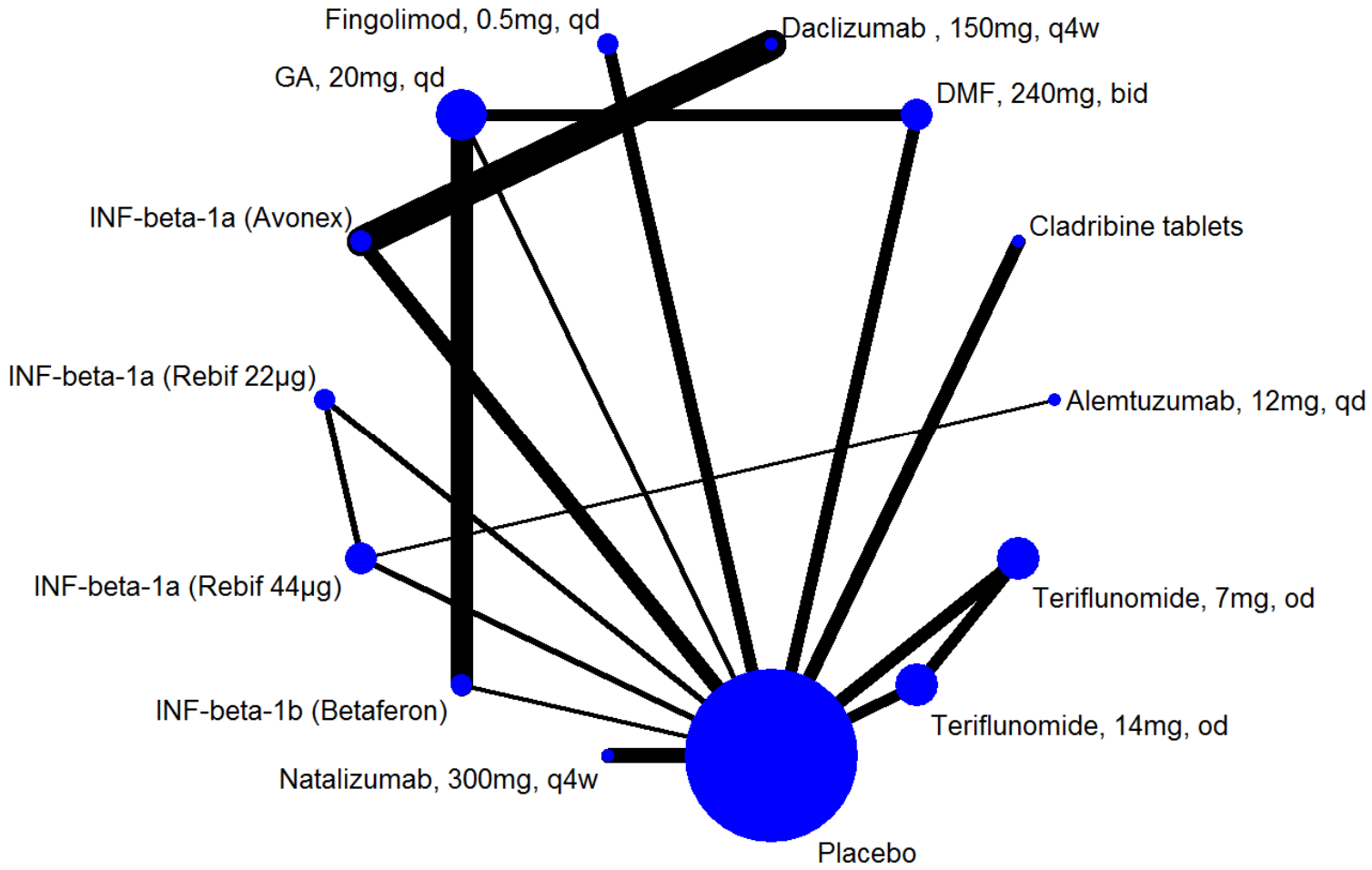


Figure 8 Network plot for the network meta-analysis of 3-month CDP at 24 months (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF= interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of Table 84

Table 85 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (HDA-RRMS subgroup)

Study	Treatment	Comparator	HR	LCI	UCI
AFFIRM trial	Natalizumab, 300 mg, q4w	Placebo	0.55	0.35	0.86
CONFIRM trial	DMF, 240 mg, bid	Placebo	0.62	0.30	1.28
CONFIRM trial	GA, 20 mg, qd	Placebo	0.44	0.20	0.95
DEFINE Trial	DMF, 240 mg, bid	Placebo	0.67	0.38	1.19
FREEDOMS trial	Fingolimod, 0.5 mg, qd	Placebo	0.62	0.37	1.04
CLARITY trial	Cladribine tablets	Placebo	0.28	0.15	0.53

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; mg=milligram; qd=per day; q4w=every 4 weeks; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; UCI=upper bound of 95% confidence interval
Source: Table A2.2, company response to ERG clarification letter

Table 86 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (RES-RRMS subgroup)

Study	Treatments	Comparator	HR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.47	0.24	0.93
CLARITY trial	Cladribine tablets	Placebo	0.77	0.34	1.74
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.78	0.36	1.68
TEMSO trial	Teriflunomide, 7 mg, od	Placebo	0.61	0.25	1.51
TEMSO trial	Teriflunomide, 14 mg, od	Placebo	0.65	0.26	1.59

CDP=confirmed disability progression; mg=milligram; od=once daily; qd=per day; q4w=every 4 weeks; HR=hazard ratio; LCI=lower bound of 95% confidence interval; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; UCI=upper bound of 95% confidence interval
Source: Table A4.2, company response to ERG clarification letter

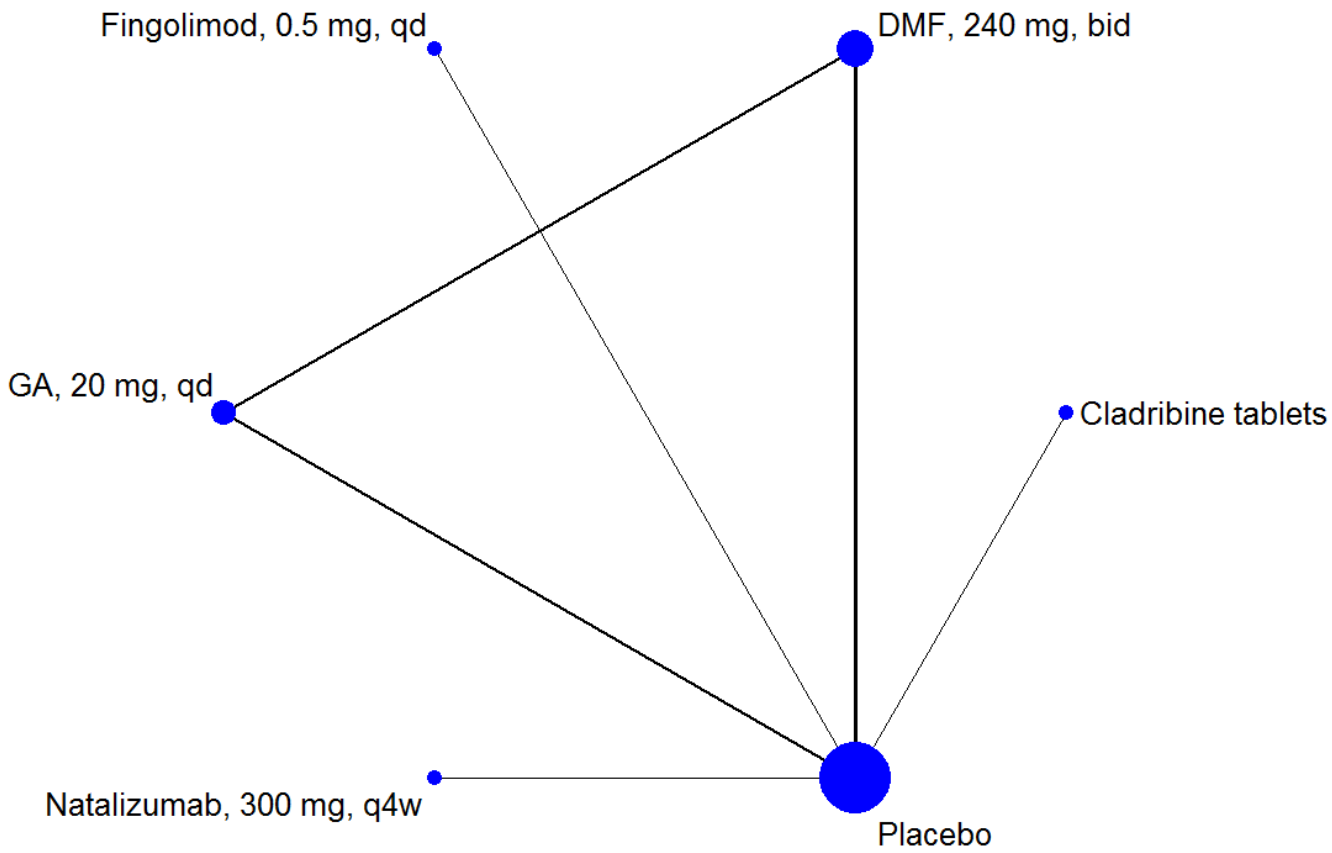


Figure 9 Network plot for the network meta-analysis of 3-month CDP at 24 months (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; mg=milligram; qd=per day; q4w=every 4 weeks; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF= interferon;
Source: produced by the ERG, based on the numbers of Table 85

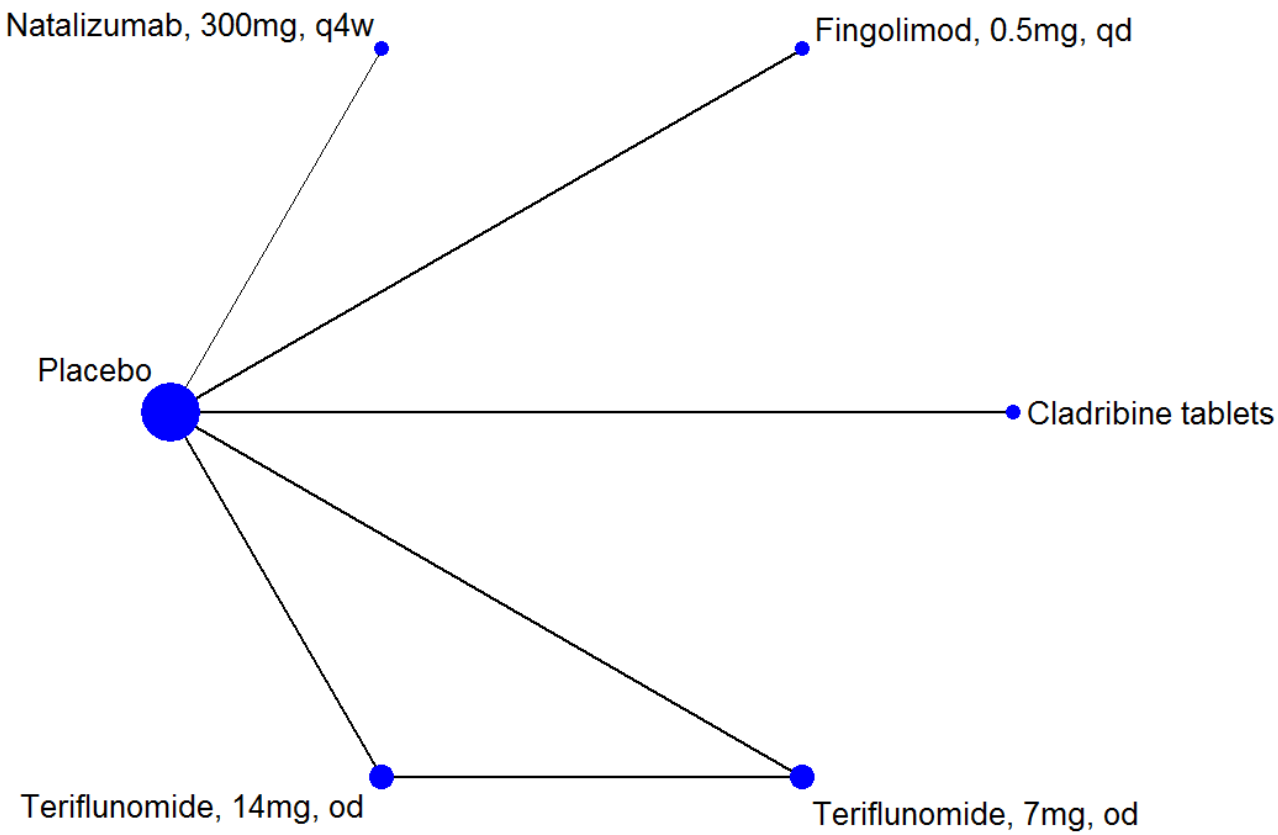


Figure 10 Network plot for the network meta-analysis of 3-month CDP at 24 months (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
CDP=confirmed disability progression; mg=milligram; od=once daily; qd=per day; q4w=every 4 weeks; HR=hazard ratio; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 86

Table 87 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (ITT population)

Study	Treatment 1	Event 1	Total 1	Treatment 2	Event 2	Total 2	Treatment 3	Event 3	Total 3	Number of arms
AFFIRM trial	Placebo	72	315	Natalizumab	69	627	NA	NA	NA	2
BECOME trial	GA, 20 mg, qd	6	39	INF-β-1b (Betaferon)	4	36	NA	NA	NA	2
BRAVO trial	Placebo	46	450	INF-β-1a (Rebif 44µg)	35	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab 12mg	4	113	INF-β-1a (Rebif 44µg)	19	111	NA	NA	NA	2
CARE-MS I trial	Alemtuzumab 12mg	30	386	INF-β-1a (Rebif 44µg)	21	195	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab 12mg	54	436	INF-β-1a (Rebif 44µg)	43	231	NA	NA	NA	2
CONFIRM trial	Placebo	45	363	Dimethyl fumurate	28	362	GA, 20 mg, qd	38	360	3
Decide Trial	Daclizumab	83	919	INF-β-1a (Avonex)	111	922	NA	NA	NA	2
DEFINE	Placebo	69	410	Dimethyl fumurate	52	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	63	355	Fingolimod	49	358	NA	NA	NA	2
FREEDOMS trial	Placebo	79	418	Fingolimod	53	425	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	28	92	INF-β-1b (Betaferon)	13	96	NA	NA	NA	2
MSCRG trial	Placebo	50	143	INF-β-1a (Avonex)	35	158	NA	NA	NA	2
REGARD trial	GA, 20 mg, qd	33	378	INF-β-1a (Rebif 44µg)	45	386	NA	NA	NA	2
TEMSO trial	Placebo	68	363	Teriflunomide 14mg	49	359	Teriflunomide 7mg	51	366	3
TOWER trial	Placebo	46	389	Teriflunomide 14mg	43	372	Teriflunomide 7mg	61	408	3
CLARITY trial	Placebo	[redacted]	[redacted]	Cladribine tablets	[redacted]	[redacted]	NA	NA	NA	2
PRISMS trial (unpublished data)	Placebo	[redacted]	[redacted]	INF-β-1a (Rebif 44µg)	[redacted]	[redacted]	NA	NA	NA	2

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: CS, Appendix L, Table 60

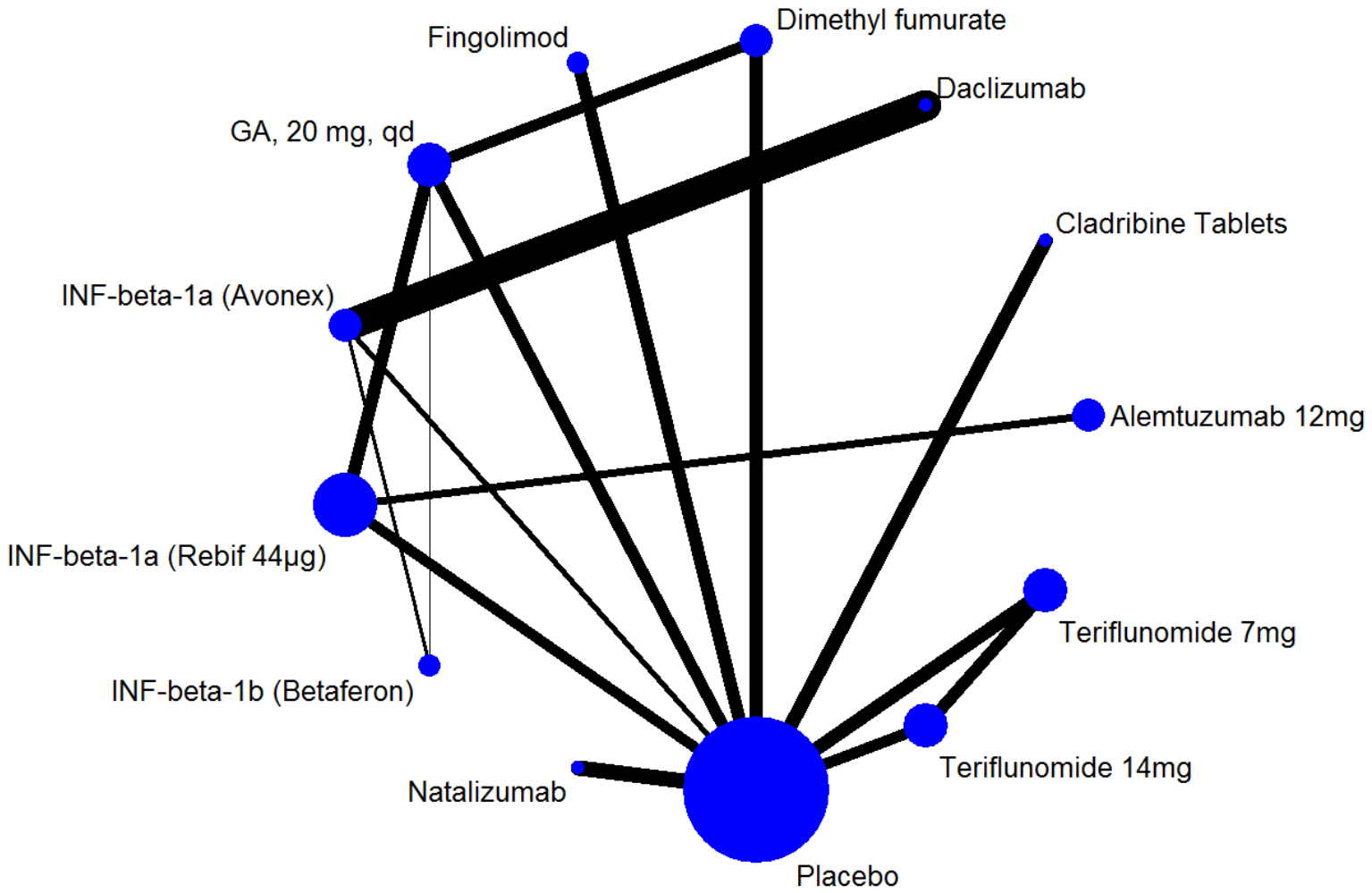


Figure 11 Network plot for the network meta-analysis of 6-month CDP at 24 months (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF= interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of Table 87

Table 88 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (HDA-RRMS subgroup)

Study	Treatment	Comparator	HR	LCI	UCI
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.56	0.37	0.86
CLARITY trial	Cladribine tablets	Placebo	0.18	0.08	0.44
CARE-MS I trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.83	0.40	1.88

CDP=confirmed disability progression; µg=microgram; qd=per day; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; UCI=upper bound of 95% confidence interval
Source: Table A2.4, company response to ERG clarification letter

Table 89 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (RES-RRMS subgroup)

Study	Treatment 1	Events 1	Total1	Treatment 2	Events 2	Total2	Number of arms
AFFIRM trial	Placebo	16	61	Natalizumab, 300mg, q4w	15	148	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	7	101	INF-β-1a (Rebif 44µg)	7	42	2
CLARITY trial	Placebo	9	41	Cladribine tablets	6	50	2
PRISMS trial (unpublished data)	Placebo	13	19	INF-β-1a (Rebif 44µg)	7	14	2

CDP=confirmed disability progression; mg=milligram; µg=microgram od=once daily; qd=per day; q4w=every 4 weeks; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: Table A4.4, company response to ERG clarification letter

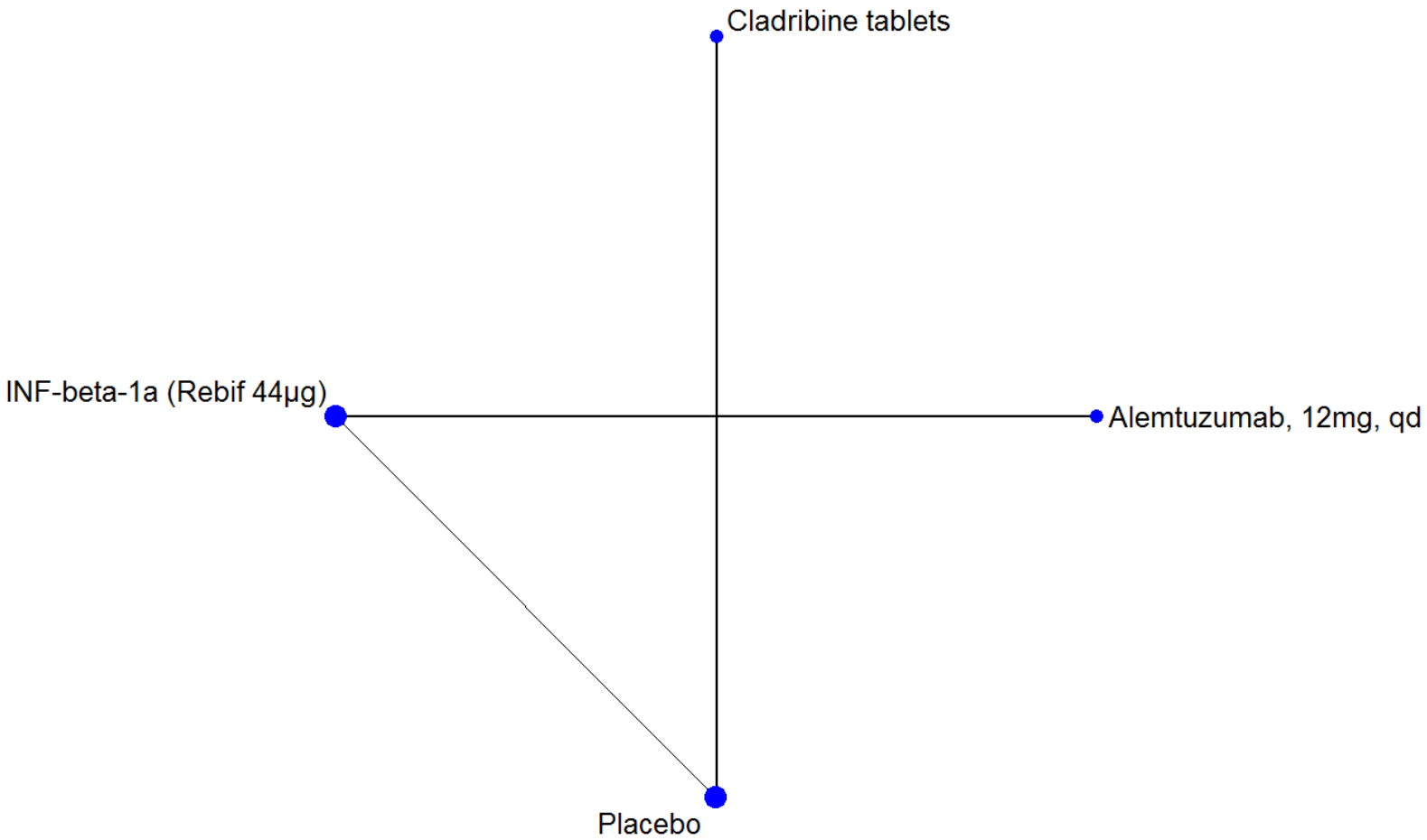


Figure 12 Network plot for the network meta-analysis of 6-month CDP at 24 months (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
CDP=confirmed disability progression; µg=microgram; qd=per day; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF= interferon;
Source: produced by the ERG, based on the numbers of Table 88

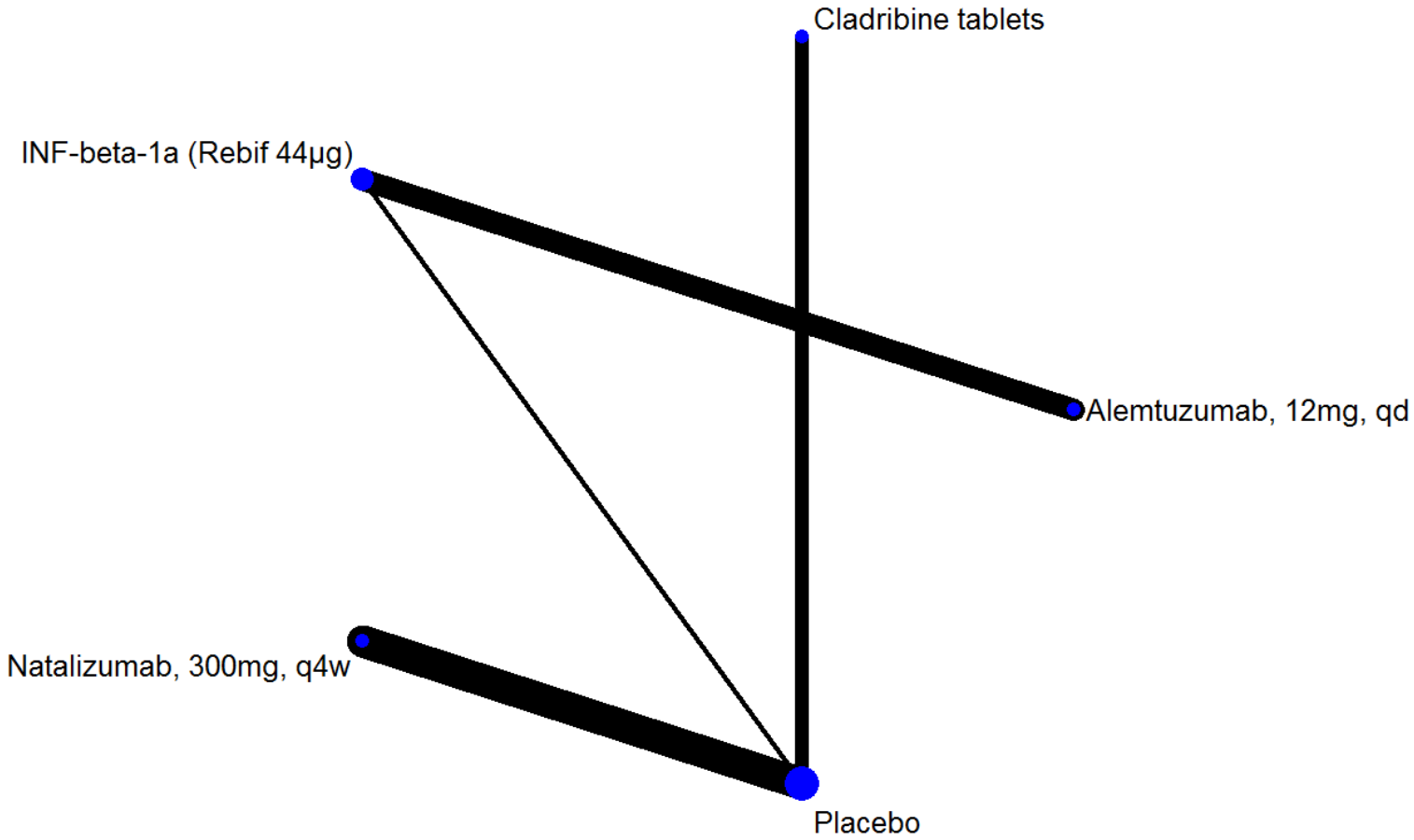


Figure 13 Network plot for the network meta-analysis of 6-month CDP at 24 months (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
CDP=confirmed disability progression; mg=milligram; µg=microgram od=once daily; qd=per day; q4w=every 4 weeks; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 89

10.3 Sensitivity analyses of key efficacy outcomes

The company conducted sensitivity analyses to evaluate the impact of study characteristics on the results of the base-case NMA. Sensitivity analyses were conducted based on following parameters where applicable:

- Diagnostic criteria: Sensitivity analysis was conducted after excluding studies utilizing Poser diagnostic criteria and studies for which diagnostic criteria was unclear
- Year of publication: Sensitivity analysis was conducted after excluding studies published prior to the year 2000
- Blinding: Sensitivity analysis was conducted after excluding open-label studies and studies for which blinding status was unclear
- Study phase: Sensitivity analysis was conducted after excluding phase II studies

Results of these sensitivity analyses for key efficacy outcomes (ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are presented in this section. Results of sensitivity analyses for the proportion of participants relapse-free at 12 and 24 months and for tolerability outcomes (all cause and AE related study withdrawals and treatment withdrawals) are presented in Appendix B of the company response to the ERG clarification letter.

For ARR, there was no change in the direction of the relative treatment difference between cladribine tablets and comparators, however, alemtuzumab 12mg qd which presented numerically favourable results compared to cladribine tablets in the original analysis was significantly favourable after sensitivity analysis based on diagnostic criteria (Table 90). The company reason that this difference is due to sensitivity analysis with a lower number of studies, indicating reduced power to detect the difference.

For both 3-month CDP at 24 months and 6-month CDP at 24 months, the treatment difference versus placebo, which was significantly favouring cladribine tablets in the original analysis was no longer significant in the sensitivity analyses of diagnostic criteria and publication year. All other results of sensitivity analyses were in line with the base-case results.

Table 90 Summary of sensitivity analysis results for ARR in the ITT population (rate ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Blinding status	Year of publication
Placebo	0.42 (0.32, 0.54)	0.42 (0.31, 0.56)	0.42 (0.32, 0.54)	0.42 (0.32, 0.53)	0.42 (0.32, 0.54)
Alemtuzumab, 12 mg, qd	1.3 (0.93, 1.83)	1.48 (1, 2.3)	1.33 (0.96, 1.87)	1.34 (0.98, 1.85)	1.28 (0.89, 1.84)
Daclizumab HYP, 150 mg, q4w	0.92 (0.66, 1.25)	0.89 (0.62, 1.3)	0.89 (0.64, 1.23)	0.93 (0.69, 1.24)	0.91 (0.65, 1.26)
DMF, 240 mg, bid	0.78 (0.57, 1.07)	0.78 (0.54, 1.12)	0.78 (0.56, 1.05)	0.79 (0.58, 1.04)	0.78 (0.56, 1.08)
Fingolimod, 0.5 mg, qd	0.91 (0.67, 1.22)	0.91 (0.65, 1.26)	0.9 (0.66, 1.26)	0.9 (0.69, 1.19)	0.9 (0.67, 1.22)
GA, 20 mg, qd	0.64 (0.48, 0.85)	0.61 (0.43, 0.85)	0.61 (0.46, 0.83)	0.64 (0.48, 0.81)	0.61 (0.45, 0.83)
GA, 40mg, tiw	0.62 (0.44, 0.87)	0.63 (0.42, 0.92)	0.62 (0.45, 0.88)	0.63 (0.45, 0.86)	0.63 (0.44, 0.87)
IFN beta-1a, 22 mcg, tiw	0.58 (0.42, 0.81)	-	0.59 (0.43, 0.81)	0.57 (0.43, 0.77)	-
IFN beta-1a, 30 mcg, q1w	0.52 (0.39, 0.68)	0.5 (0.36, 0.7)	0.5 (0.38, 0.67)	0.53 (0.4, 0.68)	0.51 (0.38, 0.69)
IFN beta-1a, 44 mcg, tiw	0.63 (0.47, 0.84)	0.67 (0.47, 0.99)	0.64 (0.48, 0.86)	0.61 (0.47, 0.8)	0.62 (0.45, 0.85)
IFN beta-1b, 250 mcg, eod	0.62 (0.47, 0.83)	0.57 (0.38, 0.88)	0.6 (0.44, 0.82)	0.6 (0.45, 0.78)	0.6 (0.43, 0.83)
Natalizumab, 300 mg, q4w	1.22 (0.89, 1.68)	1.24 (0.86, 1.8)	1.21 (0.88, 1.67)	1.21 (0.91, 1.64)	1.23 (0.89, 1.71)
PEG IFN beta-1a, 125 mcg, q2w	0.64 (0.44, 0.92)	0.64 (0.42, 0.97)	0.63 (0.44, 0.91)	0.62 (0.45, 0.9)	0.64 (0.44, 0.95)
Teriflunomide, 14 mg, od	0.62 (0.46, 0.84)	0.63 (0.45, 0.88)	0.63 (0.47, 0.84)	0.63 (0.47, 0.84)	0.63 (0.46, 0.84)
Teriflunomide, 7 mg, od	0.54 (0.4, 0.72)	0.54 (0.38, 0.75)	0.54 (0.4, 0.72)	0.58 (0.43, 0.75)	0.54 (0.4, 0.72)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; Red highlighted cells represent statistically significant results in favour of comparator; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; EOD=every other day; GA=glatiramer acetate; HYP=high yield process; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; PEG=pegylated; qd=per day; q1w=once a week; q2w=every 2 weeks; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 13, Appendix B, company response to ERG clarification letter

Table 91 Summary of sensitivity analysis results for 3-month CDP at 24 months in the ITT population (hazard ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Year of publication
Placebo	0.6 (0.38, 0.95)	0.61 (0.34, 1.06)	0.6 (0.38, 0.95)	0.61 (0.34, 1.06)
Alemtuzumab, 12 mg, qd	2.25 (0.81, 6.49)	-	-	-
Daclizumab HYP, 150 mg, q4w	0.92 (0.41, 2.04)	0.93 (0.35, 2.46)	0.92 (0.42, 2.01)	0.93 (0.35, 2.46)
DMF, 240 mg, bid	0.94 (0.54, 1.66)	0.91 (0.45, 1.81)	0.93 (0.53, 1.64)	0.91 (0.45, 1.81)
Fingolimod, 0.5 mg, qd	0.78 (0.45, 1.35)	0.78 (0.39, 1.54)	0.77 (0.45, 1.35)	0.78 (0.39, 1.54)
GA, 20 mg, qd	0.84 (0.49, 1.47)	0.71 (0.32, 1.54)	0.8 (0.46, 1.39)	0.71 (0.32, 1.54)
IFN beta-1a, 22 mcg, tiw	0.91 (0.47, 1.79)	0.78 (0.35, 1.78)	0.91 (0.47, 1.76)	-
IFN beta-1a, 30 mcg, q1w	0.78 (0.39, 1.54)	0.78 (0.35, 1.78)	0.78 (0.4, 1.53)	0.78 (0.35, 1.78)
IFN beta-1a, 44 mcg, tiw	0.93 (0.47, 1.83)	-	0.92 (0.47, 1.81)	-
IFN beta-1b, 250 mcg, eod	0.68 (0.39, 1.26)	0.51 (0.2, 1.3)	0.66 (0.37, 1.21)	0.51 (0.2, 1.3)
Natalizumab, 300 mg, q4w	1.1 (0.58, 2.07)	1.1 (0.5, 2.41)	1.1 (0.59, 2.05)	1.1 (0.5, 2.41)
Teriflunomide, 14 mg, od	0.82 (0.47, 1.43)	0.82 (0.41, 1.63)	0.82 (0.47, 1.43)	0.82 (0.41, 1.63)
Teriflunomide, 7 mg, od	0.67 (0.38, 1.16)	0.67 (0.33, 1.31)	0.66 (0.38, 1.15)	0.67 (0.33, 1.31)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies.
Sensitivity analysis of blinding was not conducted due to lack of studies contributing to the network which were open-label or had unclear methods of blinding.

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 14, Appendix B, company response to ERG clarification letter

Table 92 Summary of sensitivity analysis results for 6-month CDP at 24 months in the ITT population (hazard ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Blinding status	Year of publication
Placebo	0.54 (0.29, 0.99)	0.54 (0.28, 1.03)	0.54 (0.33, 0.88)	0.54 (0.31, 0.94)	0.54 (0.29, 1)
Alemtuzumab, 12 mg, qd	1.37 (0.58, 3.32)	0.81 (0.25, 2.93)	0.52 (0.25, 1.08)	0.61 (0.28, 1.43)	0.86 (0.28, 2.97)
Daclizumab HYP, 150 mg, q4w	1.07 (0.42, 2.65)	0.97 (0.32, 3.01)	1.12 (0.52, 2.37)	1.11 (0.47, 2.61)	0.91 (0.31, 2.51)
DMF, 240 mg, bid	0.85 (0.41, 1.81)	0.8 (0.36, 1.8)	0.77 (0.42, 1.43)	0.77 (0.39, 1.55)	0.81 (0.38, 1.76)
Fingolimod, 0.5 mg, qd	0.79 (0.37, 1.64)	0.79 (0.35, 1.73)	0.79 (0.43, 1.43)	0.79 (0.4, 1.54)	0.79 (0.37, 1.66)
GA, 20 mg, qd	0.81 (0.37, 1.73)	0.62 (0.25, 1.53)	0.55 (0.29, 1.03)	0.54 (0.27, 1.12)	0.65 (0.29, 1.57)
IFN beta-1a, 30 mcg, q1w	0.79 (0.37, 1.64)	0.72 (0.28, 1.85)	0.82 (0.44, 1.52)	0.82 (0.41, 1.64)	0.67 (0.27, 1.57)
IFN beta-1a, 44 mcg, tiw	0.76 (0.35, 1.61)	0.46 (0.14, 1.42)	0.34 (0.19, 0.64)	0.34 (0.17, 0.7)	0.48 (0.17, 1.46)
IFN beta-1b, 250 mcg, eod	1.79 (0.65, 4.73)		0.8 (0.18, 3.77)	0.79 (0.17, 4.06)	1.47 (0.5, 4.21)
Natalizumab, 300 mg, q4w	1.21 (0.52, 2.77)	1.2 (0.49, 2.96)	1.21 (0.61, 2.38)	1.21 (0.56, 2.57)	1.21 (0.51, 2.84)
Teriflunomide, 14 mg, qd	0.66 (0.31, 1.38)	0.66 (0.3, 1.47)	0.66 (0.36, 1.22)	0.66 (0.33, 1.3)	0.66 (0.31, 1.4)
Teriflunomide, 7 mg, qd	0.57 (0.27, 1.18)	0.57 (0.25, 1.25)	0.57 (0.31, 1.04)	0.56 (0.29, 1.11)	0.57 (0.26, 1.2)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies.

bid=twice a day; CDP=confirmed disability progression; eod=every other day; DMF=dimethyl fumarate; GA=glatiramer acetate; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 15, Appendix B, company response to ERG clarification letter

10.4 Assessment of risk of bias in the trials included in the network meta-analysis

The company performed an assessment of study quality and risk of bias using the NICE checklist[31] for all trials included in the NMAs. Detailed information for each domain of quality can be found in Appendix D.1.1.3 and Appendix D.1.1.4 of the CS. A summary of the risk of bias domains is also provided in Appendix 10.4 of this ERG report.

Of the 42 trials included in at least one NMA, the method of generation of random sequence number was adequate in 32 (76%); in the remaining 10 trials (24%), this information was unclear. Concealment of allocation was adequate in 34 (81%) of the included trials; in the remaining eight trials (19%), allocation concealment was unclear. Baseline characteristics within the treatment groups were judged to be comparable across the 42 included studies.

Overall, 28 (67%) of the included trials were double-blind and eight (19%) were single-blind (outcome assessors blinded). These 36 trials were judged to have a low risk of bias. One of the included trials (the REFORMS trial[89]) was open-label except for blinded assessments of injection site reactions and therefore judged to be at high risk of bias The risk of bias associated with blinding was judged to be unclear in five studies[56,90-93] where the method of blinding and/or who was blinded was unclear. The company conducted a sensitivity analysis excluding the six trials[56,89-93] that were open-label or for which blinding status was unclear, results are presented in Appendix 11.3 and Appendix B of the company response to the ERG clarification letter.

Across the 42 included trials, reasons for withdrawals were adequately reported in 36 (86%), one trial (the CARE-MS II trial[58]) was judged to be at high risk of bias as there were some unexpected imbalances in drop-outs between the treatment groups and in the remaining five trials[90,91,94-96] the number and/or reasons for withdrawals were inadequately reported. In 27 of the trials (64%), the reporting of outcomes was adequate and was associated with low risk of bias, while outcome selection and reporting were not clear in the remaining 15 (36%) trials.

All except one of the 42 included trials (98%) reported an ITT or modified ITT analysis for evaluating efficacy or safety outcomes, while the remaining trial (Calabrese 2012[90]) reported using a per-protocol approach to statistical analysis which was judged to be at high risk of bias.

10.5 ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model. To generate results for the RES-RRMS subgoup, the population in the "Settings" sheet of the company model needs to be set to "RES". Similarly, to generate results for the SOT-RRMS subgroup, the population in the "Settings" sheet of the company model needs to be set to "SOT".

ERG revisions	Implementation instructions
RES-RRMS ONLY R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of alemtuzumab, and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy cell L43 In range L43:L47 Paste values In cell U44 set value = 0.31 In cell U47 set value = 0.31 In cell N34 set value = NMA
RES-RRMS ONLY R1b) For qualifying ARR, the effectiveness of alemtuzumab and daclizumab is set equal to the effectiveness of cladribine tablets. For 6-month CDP, the effectiveness of alemtuzumab, natalizumab and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy range L43:L47 In range L43:L47 Paste values In cell L48 set value = 1.000 In cell U44 set value = 0.31 In cell U47 set value = 0.31 In cell N34 set value = NMA
SOT-RRMS ONLY R1) For qualifying ARR and 6-motnh CDP, the effectiveness of alemtuzumab, fongolinod and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy cell L43 In range L43:L47 Paste values In cell U44 set value = 0.48 In cell U45 set value = 0.48 In cell N34 set value = NMA

ERG revisions	Implementation instructions
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	In Sheet “Costs - drug” In range “AB9:AE10” set values = 0
R3) No re-exposure to cladribine or alemtuzumab	In Sheet “Clinical – treatment effect” In cell P76 set value = 0.75 In cell T76 set value = 0.75
R4) Treatment discontinuation only at EDSS state 7 after 2 years	In Sheet “Clinical – treatment persistence” In range “R47:R49” set values = 0 In range “W47:W49” set values = 0
R5) TA32 EDSS state costs	In Sheet “Costs - disease” In cell P27 set value = No cost In cell K30 set value = £949 In cell K31 set value = £987 In cell K32 set value = £724 In cell K33 set value = £3958 In cell K34 set value = £1917 In cell K35 set value = £3253 In cell K36 set value = £4342 In cell K37 set value = £11429 In cell K38 set value = £27838 In cell K39 set value = £22274
R6) No carer disutility	In Sheet “Health utility” In cell K46 set value = No
R7) 2-year time horizon	In sheet “Settings” In cell K10 set value = 2
R8) 4-year time horizon	In sheet “Settings” In cell K10 set value = 4

ID64 STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/10

Erratum completed 11 September 2017

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

The company identified 9 overall issues in relation to factual inaccuracies in the original Evidence Review Group (ERG) report. Not all were considered by the ERG to be factual inaccuracies but some were considered to require minor changes to the text. The pages of the ERG report that have been affected are presented here. Please note:

- Additional or replacement text added by the ERG is highlighted in grey
- Text deleted completely (as opposed to being reworded) is blacked out (for example, [redacted]).

symptoms are mild or disappear altogether) followed by relapses (which may or may not result in residual disability). Some people with RRMS can progress to develop secondary progressive multiple sclerosis (SPMS).

2.2 Critique of company's overview of current service provision

The company presents a brief overview of the clinical care pathway in Sections B.1.3.2 and B.1.3.3 of the CS and provides details of the McDonald diagnostic criteria for MS in Table 5 of the CS.[11] The ERG considers that the overview of the clinical care pathway in the CS is largely accurate.

The ERG notes that there is no current cure for MS and that RRMS is managed using disease-modifying therapies (DMTs). The aim of treatment with DMTs is to reduce the frequency / severity of relapses and delay progression of the disease.

The company reports that the Association of British Neurologists (ABN)[12] classifies DMTs into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles). The DMTs in each category are listed in the CS (CS, Figure 6), and reproduced here in Figure 1. The company does not know whether the ABN will designate cladribine tablets as a Category 1 or Category 2 DMT. The company suggests that a new category might be needed (CS, p24). Clinical advice to the ERG is that cladribine tablets are likely to be considered as a Category 2 drug. Cladribine tablets would be the only Category 2 drug that is administered orally and the only oral drug available as a treatment option for rapidly-evolving severe RRMS (RES-RRMS).

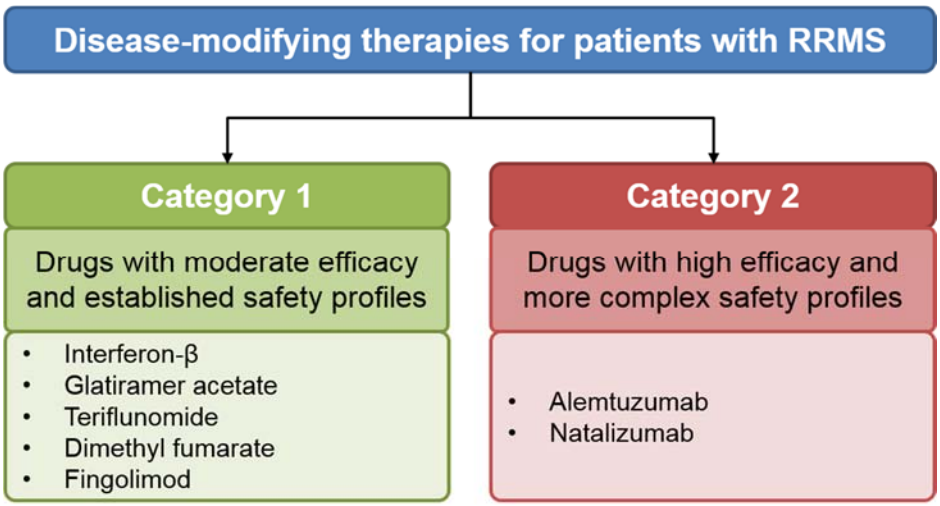


Figure 1 Categorisation of disease-modifying therapies according to the ABN guidelines

Source: CS, Figure 6

2.3 Indication / market authorisation

The company received a negative opinion in response to its 2009 marketing authorisation application to the European Medicines Agency (EMA)[13] for the treatment of people with RRMS and to a subsequent application for conditional approval for the treatment of people with high disease activity RRMS (HDA-RRMS) in 2010 (CS, pp18-20). The company states that the Committee for Medicinal Products for Human Use (CHMP) acknowledged the efficacy benefits of treatment with cladribine tablets, but raised concerns about the safety profile (CS, p19). The company reports that the Food and Drug Administration (FDA) issued a complete response letter following the company's request in 2010 for conditional approval of the use of cladribine tablets to treat people with MS in the USA with HDA-RRMS.

A new marketing authorisation application was submitted to the EMA in June 2016 following the availability of new data (i.e. from the integrated safety analysis performed on combined data from the CLARITY, CLARITY-EXT and ORACLE trials, and the PREMIERE registry), which the company states 'has substantiated the positive clinical efficacy of cladribine tablets while also mitigating safety concerns previously identified by the CHMP' (CS, p20).

At the time the CS was submitted to NICE (26th June 2017), cladribine tablets did not have a marketing authorisation in Europe. The company had anticipated that the marketing authorisation for cladribine tablets would be for adults with HDA-RRMS (CS, p11). However, on the 22nd June 2017, the CHMP of the EMA[14] issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features. The company states throughout the CS that they were assuming that the marketing authorisation granted by the EMA would be for the HDA-RRMS population, which includes people with [redacted]RES-RRMS and people with RRMS sub-optimal therapy (SOT-RRMS). The HDA-RRMS is a narrower population than the highly active relapsing MS population.

2.4 Summary of relevant clinical guidance and guidelines

The CS does not include details of relevant published guidance and treatment guidelines for MS. A summary of the available NICE guidance for technologies included as comparators in the final scope issued by NICE is provided in **Error! Reference source not found.**.

The ERG notes that although beta interferon and glatiramer acetate are not currently recommended by NICE for the treatment of people with MS, these therapies are available in the NHS through a risk sharing scheme arranged by the Department of Health.[10] Beta interferon and glatiramer acetate are being assessed as part of an ongoing multiple technology appraisal (TA32).[15]

5.3.1 NICE reference case checklist

Table 1 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	[redacted] Cost effectiveness results were only generated for two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS)
Comparator(s)	As listed in the scope developed by NICE	[redacted] Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS subgroups
Perspective costs	NHS and PSS	Partial. The ERG considers the inclusion of informal care costs was inappropriate and outside of the NICE reference case
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial. The ERG considers the inclusion of carer disutility was inappropriate and outside of the NICE Reference Case
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Trial data as well as data from the company's NMAs and meta-regression were used to populate the company model
Outcome measure	Health effects should be expressed in QALYs.	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=Personal Social Services

6.1 Conclusions of the cost effectiveness section

The ERG considers that the economic model submitted by the company is well designed and commends the company on the efforts that they have made to identify data with which to populate it.

However, the ERG considers that the usefulness of the model to decision makers is limited. The two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets versus placebo and versus other DMTs, and (ii) the inclusion of costs and benefits that are outwith the NICE reference case.[31] Whilst changes to the model can address the latter of these issues, no data are available to address the clinical evidence related issues.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence using data from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 19 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively. This means that the samples have low power to detect statistically significant changes in outcomes.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model). This means that any model results, for patients in the SOT-RRMS subgroup, showing that treatment with cladribine tablets is cost effective compared with any comparator should be viewed with caution.
- Evidence allowing the clinical effectiveness of cladribine tablets to be compared with other DMTs has been drawn from a set of NMAs and a meta-regression. The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS (see Section 4.7).

ADDENDUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]:

Addendum to the ERG report

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/194/10

Completed 28th September 2017

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Additional analyses of annualised relapse rate and 6-month confirmed disability progression

The company submitted complementary evidence of the effect of cladribine tablets for patients with high disease activity relapsing-remitting multiple sclerosis (HDA-RRMS), rapidly evolving severe RRMS (RES-RRMS) and sub-optimal therapy relapsing-remitting multiple sclerosis (SOT-RRMS). The outcomes evaluated in this additional submission were annualised relapse rate (ARR) and 6-month confirmed disability progression (CDP). Considering that the company only submitted cost effectiveness evidence for the RES-RRMS and SOT-RRMS subgroups, only the additional analyses submitted by the company related with these populations were taken into account by the Evidence Review Group (ERG).

As mentioned in Sections 4.3.2 of the ERG report, due to the small numbers of participants within the SOT-RRMS subgroup (19 and 32 for 3.5 mg/kg cladribine tablets and placebo, respectively), it is unlikely that any of the post-hoc analyses of the efficacy outcomes has the statistical power to detect a difference between the treatments, including ARR. The comparative risk of 6-month CDP in the treatment groups could not be evaluated in the SOT-RRMS subgroup as no participants in the cladribine tablets group had confirmed 6-month CDP within this subgroup (Section 4.3.4 of the ERG report). For patients with RES-RRMS, cladribine tablets were associated with a statistically significant relative reduction in qualifying ARR compared with placebo within the RES-RRMS-subgroup (Section 4.3.2 of the ERG report). However, cladribine tablets were not associated with a statistically significant delay in time to 6-month CDP compared with placebo within the RES-RRMS subgroup (Section 4.3.4 of the ERG report).

The company submitted a pooled analysis of cladribine tablets 3.5 or 5.25 mg/kg versus placebo for ARR and 6-month CDP. The licensed dose for cladribine tablets is 3.5 mg/kg and only effectiveness data of patients administered a 3.5 mg/kg dose of cladribine tablets were considered in the initial company submission and ERG report. The ERG considers that since 5.25 mg/kg is not a licensed dose for cladribine tablets, there is no clinical justification to pool the data from the 3.5 and 5.25 mg/kg doses.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Cladribine tablets for treating relapsing-remitting multiple sclerosis [ID64]

Merck's response to the ERG report (identification of factual inaccuracies)

Issue 1 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Omission from the summary section (Section 1.1-1.8) of key detail from and conclusions of the main body of the ERG report. 1. No mention of innovative nature of Cladribine Tablets. 2. Omission of detail behind ERG's summary of their exploratory analyses. 3. Overall objection to ERG's analyses given the assumption that Cladribine Tablets has no effect on disability progression versus placebo (see Issue	As the ERG have concluded, Cladribine is an innovative treatment. Administration and monitoring is simple and minimal compared with other available DMT's for highly active RMS (e.g. max 20 days treatment that is oral, lowest monitoring burden for patients, HPCs and health systems). Administration (20 days max oral treatment) over first 2 years can sustain disease control for up to 4 years. Merck propose that the ERG include within the summary section, the conclusion they themselves reach, namely that "an oral MS treatment only given in two cycles that are 12 months apart, with no treatment in between or after, and with no unique monitoring above the standard, represents a step change and innovative treatment for people with MS." Further, in Section 1.8 of the summary section	Whilst Merck fully appreciates the objective nature of the ERG report, there is a disconnect between the tone of the summary section and the full document. We understand that the report is essential to critique the company's submission, but the omission of key factual sections and clarifying statements from the summary may lead to an overall negative impression and will not provide the Committee with fair balance of essential information.	These points are not factual errors. No changes were made.

2) and the inconsistent application of this logic to other DMTs (see Issue 3).	(page 18 of 166), Merck propose that the ERG explicitly detail the main assumptions behind the alternative analysis they present by amending the non-specific phrase "Modifications to qualifying ARR and 6-month CDP parameter values for cladribine tablets, alemtuzumab and daclizumab". Importantly, we have significant reservations about the analysis which concludes that versus natalizumab and daclizumab, Cladribine Tablets results in ICERs in the SW quadrant; given the underlying assumption here that Cladribine Tablets has no effect on disability progression versus placebo (see Issue 2) and the inconsistent application of the ERG's logic to other DMTs (see Issue 3).		

Issue 2 Interpretation of statistical significance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 8.2, the ERG state that the lack of statistically significant evidence of effect in the subgroups of CLARITY suggests that there is no effect of Cladribine Tablets versus placebo in these populations. Merck are strongly against this view and highlight that this is a factually inaccurate interpretation of statistical	Merck suggest that the ERG recognise within their conclusions and summary that assuming equivalent efficacy between Cladribine Tablets and placebo on the basis of non-significant results alone, and despite showing meaningful differences in point estimates, is an overtly conservative assumption that will ultimately yield a "worst case" set of ICERs. Further, the company request that the analyses conducted by the ERG assuming equivalence	As noted in Greenland et al, a p-value > 0.05 does not imply that the test hypothesis, e.g. no difference between Cladribine Tablets and placebo, is true. This result merely suggests that "a discrepancy from the hypothesis prediction (e.g., no difference between treatment groups) would be as large or larger than that observed more than 5 % of the	These are not a factual errors. No changes made. The company submission is on the basis of the RES and SOT-RRMS subgroups and evidence. Statistical significance in a wider and larger group does not mean that statistically significant

significance. In addition it is an illogical conclusion considering that there are strongly positive, statistically significant results confirming the efficacy of Cladribine Tablets versus placebo in the HDA-RRMS (of which RES and SOT-RRMS are subgroups).	between Cladribine Tablets and other DMTs (i.e. ERG model scenarios 'R1b'), rather than point estimates, (described in the overall conclusions but not in the executive summary) be recognised as a more plausible basis for decision-making. It is suggested that this set of analyses be presented as part of the conclusion section of the summary, in line with this proposed change. Consistent with a correction to the factually inaccurate interpretation of statistical significance (which is the basis for the ERG's conclusion about the trial evidence for SOT-RRMS), we request that the ERG amend the final paragraph of Section 1.8 and their approach in Section 6 to provide a more valid conclusion about the results of modelling in this subgroup.	time if only chance were creating the discrepancy." Greenland et al further notes that "unless the point estimate (observed association) equals the null value exactly, it is a mistake to conclude from $p > 0.05$ that a study found "no association" or "no evidence" of an effect". On this basis, the ERG conclusion that Cladribine Tablets confers no benefit in 6 month CDP in RES and SOT-RRMS, due to showing non-significant differences between groups (e.g. p-value >0.05) is factually incorrect. The company also wishes to highlight that the assumption that Cladribine Tablets is of equivalent efficacy to placebo in cases of non-significant results is contradictory to the ERG's approach to assuming equivalence between DMTs: "The ERG considers that, in situations where confidence/credible intervals overlap and point estimates are close, the appropriate approach is to assume that all treatment options have equal efficacy." While the company agrees, in principle, with this approach for DMTs, in the case of Cladribine Tablets versus placebo, the	evidence of effect should also be observed in subgroups. The ERG states in Section 8.2 that in the absence of statistically significant evidence of effectiveness against placebo there is no statistical basis to model a difference. The ERG does not state or conclude that there is no difference but that there is no statistically significant evidence of difference. The company – as is the norm in frequentist analysis – uses the phrase 'statistical significance' throughout their submission in the same way and with the same meaning that the ERG has done in the report. The ERG does not consider that the committee will be misled or is being misinformed in the discussion about the statistical evidence available on cladribine effectiveness in the RES or SOT-RRMS subgroups. Regarding the ERG statement: "The ERG considers that, in situations where confidence/credible intervals

		requirement that point estimates are “close”, or otherwise equal to 1.0 is not met. The company highlights that in the case of RES-RRMS and HDA-RRMS, which includes RES-RRMS and SOT-RRMS, the hazard ratios of 6 month CDP are 0.46 and 0.18 respectively, demonstrating meaningful improvements in effect with Cladribine Tablets compared to placebo. The ERG’s assumption here is therefore also counter logic. The company acknowledges that there is uncertainty surrounding the effect of Cladribine Tablets versus placebo in RES-RRMS and SOT-RRMS, but wish to re-iterate that these sub-populations were defined retrospectively to comply with the scope of the appraisal. In the licensed population for cladribine, HDA-RRMS, which includes RES- and SOT-RRMS, Cladribine Tablets was associated with a statistically significant and highly meaningful improvement in both CDP6 and ARR. Further, as acknowledged on page 83 of the ERG report, “the advantages within the subgroups tend to be numerically larger compared to the results within the ITT population” where the effects of Cladribine Tablets are not disputed.	overlap and point estimates are close, the appropriate approach is to assume that all treatment options have equal efficacy.” The ERG does not consider that this is a contradiction of the position regarding efficacy compared to placebo. The necessary condition is that confidence intervals overlap. If point estimates are close this adds further weight but all that is required for treatments to be considered equal is that there is no statistically significant difference between them.

		Reference: Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations, Greenland et al, European Journal of Epidemiology	

Issue 3 Incorrect and inconsistent application of assumptions (which unfairly biases against Cladribine Tablets)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
An assumption which underpins the ERG's additional economic analyses (Tables 72, 73 and 74) is inconsistently applied across Cladribine Tablets and other DMTs. As we have outlined in Issue 2, we object to the conclusion that Cladribine Tablets has no effect on disability versus placebo (a factually inaccurate interpretation of non-significant results). In addition, the ERG do not appear to apply this same assumption to the effectiveness of the other DMTs in the subgroups, assuming in their 'ERG scenarios, R1a, R2-R6)' that the other DMTs have an effect on CDP6M in spite of absence of significance in their own results.	As above.	The company is concerned that the ERG is 1) misinterpreting statistical significance, and 2) applying two different criteria when assuming efficacy of other DMTs, and for Cladribine Tablets. In the companies view, this leads to a biased and factually incorrect result.	This is not a factual error, no change made. As detailed above, the ERG has not inaccurately interpreted statistically insignificant results. Whilst it is true that the other drugs in R1a were assumed to be effective for 6 month CDP, this is because NICE has recommended the comparators in RES-RRMS on the basis that the evidence supports an improvement in 6 month CDP. Alternative analyses are provided in the ERG report (R1b) where effectiveness of cladribine for 6 month CDP against placebo is assumed.

Issue 4 Conclusions and details in the description of the meta-regression analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Validity of methodological approach On page 79 of the ERG report, the ERG states: "The ERG notes that the meta-regression approach outlined in the TSD3 document is used to explore treatment-covariate interactions, such as an interaction between treatment effect and baseline risk, as a source of heterogeneity. The company has used the approach outlined in TSD3 to model treatment-covariate interactions to allow baseline risk estimates to predict treatment effect estimates for specific subgroups. The ERG is uncertain whether the approach outlined in TSD3 is valid for the company's objectives."	Merck suggests that this paragraph and reference to the same point throughout the document is revised, specifically to remove the implication that our application of this methodology is in some way different to its intended use (as described in TSD3).	The meta-regression methodology was adopted following advice from Professor Keith Abrams and TSD3 describes an identical application of it. On page 43 of TSD3 (section 4.4.1) the DSU states when referring to the example network meta-regression on baseline risk (Certolizumab example): "The analysis used centred covariate values, achieved by subtracting the mean covariate value (mean of the observed log-odds on treatment 1,x=- 2.421) from each of the estimated mui. The treatment effects obtained are then the estimated log-odds ratios at the mean covariate value, which can be un-centred and transformed to produce the estimate at baseline risk z" Following this guidance, Merck's economic model uses the log-hazard ratios at mean covariate level for RES-RRMS, which are un-centred and transformed to produce effect estimates at the baseline risk for RES-RRMS and SOT-RRMS. The company is therefore unclear why the ERG	This is not a factual error, no change made.

		considers this approach to be invalid given that DSU methods have been followed.	
Suggestion that Merck is providing contradictory interpretations of the assumptions underpinning the meta-regression On page 81 of 166, the ERG describe Merck's conclusion - *that the meta-regression's under-estimation of the AFFIRM HR may be due to the relationship between baseline risk and effect size estimate differing in this trial than the relationship between baseline risk and effect size in other studies* - as contradictory to a former conclusion	Merck proposes that the ERG delete the following statement from page 81 of 166: "This suggestion contradicts the company's interpretation of their first validation (i.e., that the similar slope trend lines of natalizumab and Cladribine Tablets indicate that the relationship between effect size and baseline risk may also be consistent across drugs)."	The company highlights that the statement that the slopes are "similar" (as opposed to equal) remains valid, and is not contradictory to the statement which concludes" The relationship between baseline risk and effect size estimate in AFFIRM may therefore differ to those estimated from other studies, including CLARITY and PRISMS." Both statements provide the necessary circumspection and their message is consistent and not contradictory.	This is not a factual error, no change made. The ERG also uses the word 'similar' on page 81 of the ERG report rather than equal.
Use of a meta-regression analysis at all	We propose that the ERG amend the tone and conclusions of their discussion about the meta-regression throughout the report, particularly in light of the preceding factual inaccuracies; it is inappropriate to communicate that this analysis is unsound given the context and given the associated shortcomings of a submission that is unable to fully address the decision problem in question.	As acknowledged by the ERG, the meta-regression analysis was necessary to allow for comparisons specified by the scope for this STA and was conducted well. The discussion on the meta-regression is incomplete without an acknowledgement of the lengths that Merck has gone to in order to be able to address the specifics of the decision problem under consideration and the strong	The ERG does not consider the two points above to be factual inaccuracies, therefore no changes were made.

		academic context in which this methodology was considered and applied. Merck had investigated the appropriateness of the use of the meta-regression with an external technical advisor, Professor Keith Abrams and other external experts through advisory boards. Additionally, in our original NICE/ERG teleconference, the approach was flagged and the ERG considered it appropriate (discussions of appropriateness from initial TC between NICE and ScHARR ERG [prior to the change to LiRIG]). Merck has gone to great lengths to validate this approach for this submission.	

Issue 5 Failure of ERG to acknowledge NICE precedent when assessing Merck's submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Application of annualised discontinuation rates On page 117 section 5.4.5 the ERG states: "The ERG and the AC for TA441 considered that it would be more appropriate to apply the	The company requests that the text is amended to include: "The ERG acknowledges that these data are not available to the company and so cannot be accommodated in the analysis."	The ERG fails to highlight that the company does not have access to yearly discontinuation rates for competitor trials, and is therefore unable to replicate the preferred analysis in TA441.	This is not a factual error and the ERG suggests an alternative approach not reliant on the data.

discontinuation rates that occurred during the last year, rather than the first year, of a trial over the whole model time horizon. The ERG accepts that it was inappropriate to apply all cause annualised discontinuation rates for natalizumab and daclizumab that were derived over the whole trial period."			
Approach to modelling discontinuation On page 115 of 166, the ERG states that: "However, in a scenario with only one line of treatment (as in this and previous MS submissions), with no alternative treatment to move onto, clinical advice to the ERG is that treatment would only stop when there was perceived to be no further clinical benefit to a patient even if a patient was still having relapses. The ERG considers that a more realistic approach to modelling discontinuation is, therefore, to use trial treatment discontinuation rates where available and then assume treatment would continue whilst the patient receives benefit, which, in the company model, is up until a	Merck suggests that the ERG's proposal requires qualification as there is no evidence to suggest that this change gives a more plausible prediction of time on treatment (as is being implied). We also propose that the ERG acknowledge that their suggestion is a departure from all previous appraisals of MS treatments (which assume non-zero discontinuation rates beyond trial follow-up).	Merck feels that it is important to recognise all models submitted previously to NICE used a non-zero discontinuation rate beyond the follow-up of clinical studies, and hence the ERG assumption is at odds with NICE precedent. Additionally, we wish to highlight that the ERG's adaptation to discontinuation rates was motivated by the desire to model discontinuation in a scenario where no further therapy is given. Merck and the ERG acknowledge that in practice further lines of therapy would be given and that there is currently insufficient information to conduct a sequencing analysis in the model. Merck argues that it would be more appropriate to include discontinuation rates as if a sequence of therapies is given,	This is not a factual error, no change made. The ERG is not bound by what has been done in previous appraisals. The ERG presents results with and without this amendment so the committee can decide not only on whether it should be incorporated but also on how important the amendment is.

patient reaches EDSS state 7."		e.g. as per the CS, to ensure that at least primary treatment (e.g. daclizumab, alemtuzumab, fingolimod and natalizumab) costs and QALYs reflect clinical practice. The current ERG preferred analysis, which assumes 0% discontinuation after year 2 unless transiting to EDSS 7.0 or greater, is likely to systematically overestimate the cost and QALYs for primary treatment in real practice. The company argues that this aspect of the ERG modification yields cost-effectiveness results that are less applicable to NICE decision-making than those generated using the company's assumptions.	
Inclusion of caregiver utilities in Merck model On page 87 of 166, the ERG acknowledge that prior appraisals have incorporated caregiver utilities however summarize this as 'inappropriate' and 'outside of the NICE Reference Case' (page 88 of 166).	Merck acknowledge that the approach may officially be 'outside of the NICE Reference Case' but propose that the ERG conclusion is modified to acknowledge that NICE precedent which conclusively establishes the acceptability of incorporating caregiver utilities deems it an appropriate (rather than an inappropriate) approach.	The impact of disability progression on the health utility of caregivers has been incorporated in all of the models submitted to NICE since TA127 and this has been accepted by Committees in all recent appraisals.	This is not a factual error, no change made. The ERG is not bound by the approaches taken in previous appraisals. The committee can decide whether or not caregivers disutility is appropriate to include and can verify the impact this has on the ICERs.

Issue 6 Omission of detail

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
No mention of lack of oral option for RES patients (Section 2.2)	Acknowledgement that Cladribine Tablets would be the only possible oral option in category 2 and for RES-RRMS patients.	We welcome the acknowledgment from the clinical community that Cladribine Tablets would be suitable as a category 2 option in the proposed ABN guidelines. This is consistent with the guidelines 'definition' of category 2 DMTs as those with an average relapse reduction more than 50%. As Cladribine Tablets would possibly be the only oral agent available in this category and the only oral agent that could be available as a treatment option for RES-RRMS patients we are proposing this additional detail is added.	Text has been added as follows: Cladribine tablets would be the only Category 2 drug that is administered orally and the only oral drug available as a treatment option for rapidly-evolving severe RRMS (RES-RRMS).

Issue 7 Inclusion of disability progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 2.2, the ERG states that "The aim of treatment with DMTs is to reduce the frequency and severity of relapses". The	Merck propose that the following sentence on page 20 of 166: "The aim of treatment with DMTs is to reduce the frequency and severity of	A key clinical aim of treatment with DMTs is to delay disease progression. This is not represented by the ERG's current	For clarity, text on page 20 has been reworded as suggested by the company.

statement is incomplete as it fails to acknowledge the other key aim of treatment, to delay disability progression.	relapses." Is replaced with: "The aim of treatment with DMTs is to reduce the frequency/ severity of relapses and delay progression of the disease."	phrasing.	The aim of treatment with DMTs is to reduce the frequency / severity of relapses and delay progression of the disease.

Issue 8 NICE Reference Case Checklist

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Table 36, NICE reference case, the ERG suggest that Merck have only partially addressed both the decision problem and the comparators for the reference case. Decision problem: "Partial. Cost effectiveness results were only generated for two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS)" when referring to whether the de novo evaluation matches the scope of the decision problem. Comparators: "Partial. Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost	Remove the term "partial" as the population and comparators included in the company submission were directly relevant to the anticipated licensed indication for Cladribine tablets, i.e. the scope was broader than the licence.	Merck would like to highlight that in the context of the licence for Cladribine Tablets, the use of 'partial' is misleading. The company request that the ERG clarify that "In line with its expected marketing authorization, results were generated for the two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS),", and remove the term "partial". Similarly, in Table 36, the ERG states: "Partial. Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS	The word partial has been removed as suggested by the company in Table 36.

effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS subgroups."		subgroups", implying that some relevant comparisons were omitted. The company suggests that the wording is amended to: "The comparators included in the company's cost effectiveness analyses were relevant to the licensed populations of RES-RRMS and SOT-RRMS. Comparators that were listed in the final scope for populations other than RES and SOT-RRMS were not considered".	

Issue 9 Typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 130 of ERG report states 17 patients in SOT-RRMS.	Please correct the number 17 to 19.		This has now been amended.