Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Committee Papers

National Institute for Health and Care Excellence

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Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Merck Group**
   a. Company response
   b. Supplementary info

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Multiple Sclerosis Society
   b. Multiple Sclerosis Trust
   c. Association of British Neurologists
   d. Biogen

3. **Comments on the Draft Guidance from experts:**
   a. Dr Wallace Brownlee – clinical expert, nominated by Merck Group

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group (EAG) response following draft guidance**
   a. EAG critique of company response to the Draft Guidance
   b. EAG additional analyses

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

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NICE National Institute for Health and Care Excellence

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

Draft Guidance comments form

Consultation on the Draft Guidance document – deadline for comments 5pm on 9 January 2025. Please submit via NICE Docs.

Dear Appraisal Committee members,

Merck Serono Ltd welcome the opportunity to comment on the Draft Guidance for cladribine tablets in the treatment of adults with relapsing forms of multiple sclerosis (MS) with active disease as defined by clinical or imaging features. Merck are disappointed to receive the Committee's draft decision not to recommend cladribine tablets. However, we remain committed to working with NICE to achieve access to cladribine tablets for people with active relapsing-remitting multiple sclerosis (RRMS) in England and Wales. Expanding access to cladribine tablets from the current recommendation in highly active RRMS (TA616) to active RRMS can help address a high unmet need in underserved people with MS and women of child-bearing age given cladribine tablets' unique posology and low administrative burden. Below, we have summarised our comments on the Draft Guidance, and submitted revised and further analyses in response to the Draft Guidance:

- During the Committee meeting, we heard from the clinical and patient experts about the benefits of cladribine tablets, the unmet need this treatment would fulfil in a broader active RRMS population and issues around equality of access to MS therapy that it could address. They stated how cladribine tablets is an effective, long-acting, fixed course treatment that does not require continuous immunosuppression, with low burden to patients and the NHS which helps people who want to remain in work and makes it particularly beneficial for people who are planning a family, those who live a significant distance from a specialist centre, or disadvantaged groups who would find continuous disease modifying therapy (DMT) difficult to adhere to. We heard that the availability of cladribine tablets in the broader active RRMS population is highly anticipated by neurologists and patients alike and that more people could benefit from the advantages of cladribine tablets in this wider group. As such, due to these unique benefits of cladribine tablets and the underserved people with MS that it could especially help, there is a special urgency to secure access to cladribine tablets in active RRMS.

- Merck partially agree with the Committee's conclusion that the most appropriate comparators for cladribine tablets were dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod. In line with the opinion of clinical experts heard during the Committee meeting, Merck believe that the most relevant comparators to cladribine tablets are the three high efficacy DMTs (ofatumumab, ocrelizumab and ponesimod).

- Merck agree with the Committee's conclusion that the submitted network meta-analyses (NMA) were sufficient for decision-making.

- Merck disagree that the model has considerable structural uncertainty due to the lack of treatment switching or sequencing. Using a treatment sequencing model in the context of a single technology appraisal (STA) in MS is a very complex endeavour that will lead to higher uncertainty due to several reasons including: (i) the highly individualised treatment strategies for people with MS, (ii) the numerous lines of therapy people with MS usually receive in their lifetime, (iii) lack of evidence on comparative effectiveness of treatment sequences and associated treatment waning and discontinuation rates, (iv) potential overestimation of patients receiving subsequent therapies due to inconsistency in the definition of treatment discontinuation across relevant clinical studies and (v) confounding of the clinical benefit of first-line treatments due to risk of attributing the results to the totality of the sequence rather than specific individual therapies. Despite the above issues, in order to address the Committee's concerns and avoid issues with confounding of treatment effects from individual therapies in a sequence and the associated difficulties in attribution and interpretation of results, Merck have conducted two exploratory scenario analyses with a subsequent fixed treatment "basket" for both cladribine tablets and comparators to evaluate the potential impact on cost-effectiveness. Results from both "basket" scenarios showed that cladribine tablets remained cost-effective compared to relevant comparators.

- To address the Committee's feedback regarding validation of the natural history model and the existing British Columbia Multiple Sclerosis (BCMS) registry, Merck conducted a rapid literature review to identify whether more recent sources of data for untreated RRMS patients are available and/or validate the generalisability of the BCMS database to the NHS. Upon completion of this review, Merck believe that the BCMS dataset is still the most appropriate, and best available, source for informing natural history in MS models, including for this appraisal. To further demonstrate the robustness of the cost-effectiveness results

against variations in the natural history transition estimates, Merck have provided exploratory scenario analyses to address the Committee's concerns. However, Merck maintain their view that the original natural history estimates derived from the BCMS database provide the most appropriate source of natural history data for people with untreated MS and ensure consistency with previous NICE appraisals.

- Merck acknowledge the Committee's uncertainty regarding treatment discontinuation probabilities and will apply discontinuation for cladribine tablets post-year 2 in the economic model as per Committee feedback. However, based on the structure of the current economic model, Merck believe that the treatment discontinuation probabilities from the CLARITY study (for cladribine) and the NMA (for comparator DMTs) are the most appropriate due to the definition of discontinuation rates used (i.e., all cause discontinuation rather than time to next treatment). The Committee's suggestion to use the CLASSIC-MS study as a source for discontinuation probability for cladribine tablets can raise further uncertainties given the definition of discontinuation as 'time to next treatment', especially in the context of a single line economic model. This could introduce potential bias due to the lack of comparative evidence for other DMTs. However, in the absence of a clear alternative in terms of which source of discontinuation rates would be more appropriate to use, Merck are willing to accept the Committee's suggestion to use CLASSIC-MS as the source of discontinuation rates for cladribine tablets (and the NMA for comparator DMTs in the absence of comparator data from CLASSIC-MS), and have revised the base case, accordingly.

- The economic model has been further updated to reflect the Committee's preferences regarding (i) mortality rates by EDSS state using more recent data, when available; (ii) no costs for injection device training covered by company-sponsored nurses for injectable DMTs; (iii) monitoring costs for cladribine tablets including 1 MRI scan and 2 neurology appointments in total for the 2-year period of active cladribine tablets treatment, and; (iv) removal of beta interferons and glatiramer acetate as non-relevant comparators.

We acknowledge the broader MS modelling questions that were raised by the Committee. However, these are issues that have been considered at length in previous MS appraisals and ultimately all previous Committees have considered the established MS modelling (including model structure and natural history data source) as fit-for-purpose and appropriate for decision-making. A treatment sequencing approach would require numerous assumptions that will only contribute to a higher degree of uncertainty, making it more difficult to determine the most likely cost-effectiveness estimates or a maximum acceptable incremental cost-effectiveness ratio for cladribine tablets. Additionally, in the context of MS where people are likely to receive multiple lines of therapy over their lifetime, a treatment sequencing approach would not be appropriate as the aim is to assess a single technology for its relevant indication, rather than make recommendations on optimal treatment sequences for the management of the disease.

Based on the revised base case and various scenario analyses Merck conducted to test the robustness of our results, Merck have demonstrated that cladribine tablets remains a clinically- and cost-effective treatment against its relevant comparators for people with active RRMS.

We look forward to the opportunity to discuss these new analyses on 5th February 2025 at the second Appraisal Committee Meeting.

Yours sincerely,

[redacted]

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

Draft Guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck Serono Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1) Summary of revised base case and scenario analyses

Summary

In response to the Draft Guidance, Merck closely reviewed the Committee's preferred assumptions and made several changes to the cost-effectiveness base case, when considered appropriate, or in the absence of a clear alternative option, as summarised in Table 1.

The revised base case now includes (i) dimethyl fumarate, diroximel fumarate, teriflunomide, ocrelizumab, ofatumumab and ponesimod as comparators to cladribine tablets; (ii) discontinuation rates for cladribine tablets applied beyond year 2 from CLASSIC-MS, and from the NMA for the relevant comparators; (iii) mortality rates applied by EDSS state, using more recent data from Harding et al 2018, where available, and; (iv) 1 MRI scan and 2 neurology appointments in total for the 2-year period as cladribine tablets' monitoring costs. The revised base case now excludes iv) costs of self-injection training for injectable comparators. The base case does not include an alternative natural history data source nor include subsequent lines of treatment in the model. These are analysed in exploratory analyses presented in comments 6) and 7).

All the cost-effectiveness results presented throughout the responses to the Draft Guidance are based on the revised base case.

Table 1: Summary of Committee preferred assumptions and overview of revised base case

Committee preferred assumptions	Included in the revised base case?	Merck comments
1. Comparators The most appropriate comparators are dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod	Yes	In the Draft Guidance, the Committee did not specify if teriflunomide is considered as an appropriate comparator to cladribine tablets. Therefore, Merck have included teriflunomide, along with the other relevant DMTs, in the base case.
2. Model structure Subsequent treatment lines in the model to appropriately model time to next treatment	No	Merck have not updated the economic model to include subsequent treatment lines as this would further increase the uncertainty of the cost-effectiveness results. However, two exploratory scenario analyses were performed considering a fixed treatment "basket" for subsequent therapy following treatment with cladribine tablets and comparators to test the impact of this assumption and the robustness of our cost-effectiveness results. Please refer to Table 2 below and comment 6)) for further details.
3. **Source of natural history data** Use an updated data source for the natural history model to reflect the population with active RRMS in the NHS or validate the current British Columbia Multiple Sclerosis (BCMS) registry data	No	Merck believe that the BCMS registry data is still the most appropriate source of natural history data for people with untreated RRMS with detailed rationale provided in comment 7). Therefore, we have not revised the natural history model with more recent data. However, exploratory scenarios were conducted to assess the impact of alternative natural history transition probabilities and to test the robustness of the cost-effectiveness results. Please refer to Table 2 below and comment 7)) for further details.
4. Treatment discontinuation Use time to next treatment data from CLASSIC-MS for stopping cladribine tablets and comparator treatments or,	Yes	Based on the structure of the current economic model, Merck believe that the treatment discontinuation probabilities from the CLARITY study and the NMA are the most appropriate due to the consistent definition of

when not applicable, the company's NMA		discontinuation rates used between both sources. However, in the absence of a clear alternative on the best source of discontinuation rates, Merck have accepted the Committee's suggestion to use discontinuation rates for cladribine tablets from CLASSIC-MS. The base case has been revised accordingly.
5. Mortality rates Mortality rates by EDSS state should be applied to the economic model. More recent data should be used to inform the mortality rates for each EDSS state in the cost-effectiveness model.	Yes	Mortality rates by EDSS state have been applied to the revised base case. More recent data for standard mortality rates by EDSS were used from Harding et al 2018, where reported in the study (i.e., EDSS ≥4).
6. Self-injection training for comparator treatments Exclude nurse-led self-administration costs for injectables because the analysis ought to reflect NHS clinical practice	Yes	Nurse-led self-administration costs for injectables (i.e., ofatumumab) have been removed from the revised base case to reflect current NHS practice as per the Committee's preferred assumption.
7. Cladribine tablets monitoring costs Include 1 MRI scan and 2 neurology appointments in total for the 2-year period of active cladribine tablets treatment	Yes	Monitoring costs for cladribine tablets have been revised in the base case as per the Committee's preferred assumption.

BCMS: British Columbia multiple sclerosis; EDSS: Expanded Disability Status Scale; NMA: Network meta-analysis; NHS: National Health Service; MRI: magnetic resonance imaging

To further test the robustness of cost-effectiveness results using the revised base case (outlined above) and to address the Committee's concerns regarding uncertainties in the economic model, additional scenario analyses were performed as outlined in Table *2*. The corresponding comment number where the cost-effectiveness results of these scenario analyses are presented are listed in Table 2 below.

Table 2: Overview of the scenario analyses

Parameter	Base case	Scenario a	Scenario b	Scenario c	Scenario d	Relevant Comment
1. Model structure - subsequent treatment	Single-line DMT model structure (*i.e., patients transition to Best Supportive Care (BSC) after discontinuation*)	Subsequent treatment line with DMT ("basket" approach including mix of high-efficacy DMT comparators)	Subsequent treatment line with DMT ("basket" approach including mix of all relevant DMTs)	-	-	6)
2. Natural history EDSS source	British Columbia data for RRMS	An increase of 10% in the probability of remaining at the same EDSS score in natural history transition matrix	An increase of 20% in the probability of remaining at the same EDSS score in natural history transition matrix	An increase of 30% in the probability of remaining at the same EDSS score in natural history	London Ontario + British Columbia data for EDSS 0	7)

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					transition matrix		
	3. Treatment discontinuation	CLASSIC-MS discontinuation rate applied for cladribine tablets and NMA discontinuation rates for comparators (*both applied lifetime*)	CLARITY discontinuation rate applied for cladribine tablets and NMA discontinuation rates for comparators (*both applied lifetime*)	-	-	-	8)
	4. Mortality rates	Mortality rates by EDSS states from Harding et al. 2018	Mortality rates by EDSS states from Pokorski et al. 1997	Mortality rates by EDSS states from Eliasdottir et al. 2023	-	-	9)
	5. NMA data	ARR, CDP and all-cause discontinuation results from unadjusted NMA	ARR, CDP and all-cause discontinuation results from baseline risk-adjusted NMAs	-	-	-	5)
	ARR: annualised relapse rates; BSC: best supportive care; BCMS: British Columbia multiple sclerosis; CDP: confirmed disability progression; EDSS: Expanded Disability Status Scale; NMA: Network meta-analysis; RRMS: relapsing-remitting multiple sclerosis.						

2) Results of the revised base case

Merck performed the following revisions to the base case analysis to address and incorporate the Committee's preferred assumptions:

Detailed changes to the base case

Comparators

Beta interferons and glatiramer acetate were excluded from the relevant comparators along with best supportive care (BSC) as agreed by the Committee. In the Draft Guidance, the Committee did not specify if teriflunomide is considered as an appropriate comparator to cladribine tablets. Therefore, teriflunomide has been included in the base case.

Mortality

The base case has been updated by modelling mortality as a function of EDSS using standardised mortality ratios (SMRs) from a more recent study, Harding et al. 2018 (which reported SMRs for EDSS 4 to EDSS 9) as requested by the Committee. The data from the Harding et al. 2018 study was supplemented by Pokorski et al. 1997 data for initial EDSS stages SMRs (EDSS 0 to 3) which were not reported in Harding et al. 2018. A summary of the EDSS-related SMRs used in the new base case is shown in Table 3.

Table 3: Standardised mortality ratios by EDSS state

EDSS stage	Pokorski et al. 1997	Harding et al. 2018	Base case
EDSS 0	1.000	Not reported	**1.000**
EDSS 1	1.432	Not reported	**1.432**
EDSS 2	1.600	Not reported	**1.600**
EDSS 3	1.637	Not reported	**1.637**
EDSS 4	1.674	2.020	**2.020**
EDSS 5	1.842	2.020	**2.020**
EDSS 6	2.273	3.860	**3.860**
EDSS 7	3.097	4.760	**4.760**
EDSS 8	4.447	22.170	**22.170**
EDSS 9	6.454	60.740	**60.740**

Cost and healthcare resource use

Nurse-led self-administration costs for injectables (i.e., ofatumumab, as the other platform therapies and glatiramer acetate are not considered as relevant comparators) were excluded from the analysis based on Committee preference and to align with the provision of company-sponsored nurse training for some therapies in the NHS. Additionally, the number of neurology visits for cladribine tablets was updated from 2 to 1 in Year 1, while the MRI utilisation in the model remained the same as in the original submission (1 MRI in the first year in line with cladribine tablets SmPC),[1] thus complying with Committee's preferred assumption of using 1 MRI scan and 2 neurology appointments across the first 2 years of cladribine tablets.

Discontinuation rates

The model was updated following the Committee's preference to apply the CLASSIC-MS data to inform cladribine tablets treatment discontinuation. The median time to subsequent treatment for people treated with cladribine tablets as reported in the CLASSIC-MS study was 12 years,[2] which means that 50% of patients would move onto a subsequent treatment 12 years after having completed treatment with cladribine tablets. Using established modelling methods (as reported in Gidwani and Russell 2020),[3] the 12-year probability of subsequent treatment use was converted to an annual probability of 5.61% for inclusion in the model.

This 5.61% figure calculated from CLASSIC-MS was included in the model to inform treatment discontinuation for years 0-2, 2-10 and 10+ for cladribine tablets. For all other comparator DMTs in the model, the treatment discontinuation rates from the NMA were applied annually. The annualised discontinuation rates used in the new base case analysis are summarised in Table 4. In the base case model, all patients moved onto BSC after discontinuation.

Table 4: Annualised probability of discontinuation

Treatment	Annual discontinuation rate	Source
Cladribine tablets	5.61%	CLASSIC-MS
Dimethyl fumarate	[redacted]	Company's NMA
Teriflunomide	[redacted]	
Diroximel fumarate	[redacted]	
Ocrelizumab	[redacted]	
Ofatumumab	[redacted]	
Ponesimod	[redacted]	

EDSS data source and treatment sequencing

Merck have not updated the base case to reflect the Committee's preferred assumptions to use a natural history model with more recent data, due to (a) the need for a large and robust dataset of people with untreated MS for the economic model, (b) the applicability of the BCMS for the purposes of this economic model, (c) established use of the BCMS dataset in prior MS NICE appraisals, (d) the similarity of BCMS with more recent datasets in people with untreated MS (albeit based on limited evidence identified in the literature) and (e) the infeasibility of accessing and analysing an alternative robust data source in an untreated MS population within the timeframe of this consultation. In light of this, Merck believe that the BCMS registry data remains the most appropriate source of natural history data for the economic model. Merck have also not updated the base case analysis to include subsequent treatment lines, as this would further increase the uncertainty of the cost-effectiveness results given the complexity of modelling numerous treatment pathways due to individualised MS treatment strategies, the multiple lines of therapy associated with MS treatment and the lack of comparative evidence on subsequent therapies. Detailed explanation for Merck's preferred approach are outlined in comments 6)) and 7)).

Revised base case results

The deterministic cost-effectiveness results of the Committee preferred assumptions following the updates previously described are shown in Table 5.

Table 5: Deterministic results of the Committee preferred assumptions for patients with active RRMS at list price (cladribine tablets vs. comparator)

Treatment (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
Cladribine tablets	88,435	17.511	8.651	--	--	--	--
Teriflunomide	99,050	17.010	7.755	-10,615	0.501	0.896	Cladribine tablets dominant
Ponesimod	**99,567**	**17.127**	**7.984**	**-11,132**	**0.385**	**0.667**	**Cladribine tablets dominant**
Diroximel fumarate	126,806	17.176	8.070	-38,371	0.335	0.581	Cladribine tablets dominant
Dimethyl fumarate	130,582	17.188	8.092	-42,147	0.323	0.559	Cladribine tablets dominant
Ofatumumab	**136,051**	**17.313**	**8.333**	**-47,616**	**0.199**	**0.319**	**Cladribine tablets dominant**
Ocrelizumab	**138,591**	**17.367**	**8.453**	**-50,156**	**0.144**	**0.198**	**Cladribine tablets dominant**

ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to cladribine tablets.

Results from this analysis show that cladribine tablets is dominant over all other relevant comparators at list price.

Sensitivity analysis

Probabilistic sensitivity analysis

The probability that cladribine tablets are cost-effective versus all relevant DMTs in the active RRMS population was 97.9% at a threshold of £20,000 per QALY gained. The corresponding probability for cladribine tablets at £30,000 per QALY gained was 95.5%. At the same thresholds, the probability that dimethyl fumarate, diroximel fumarate, teriflunomide, ponesimod, ofatumumab or ocrelizumab is the optimal cost-effective strategy in the active RRMS population ranged from 0% to 3.5% (Table 6).

Figure 1: Multi-way cost-effectiveness acceptability curve for active RRMS at list price (all relevant DMTs)

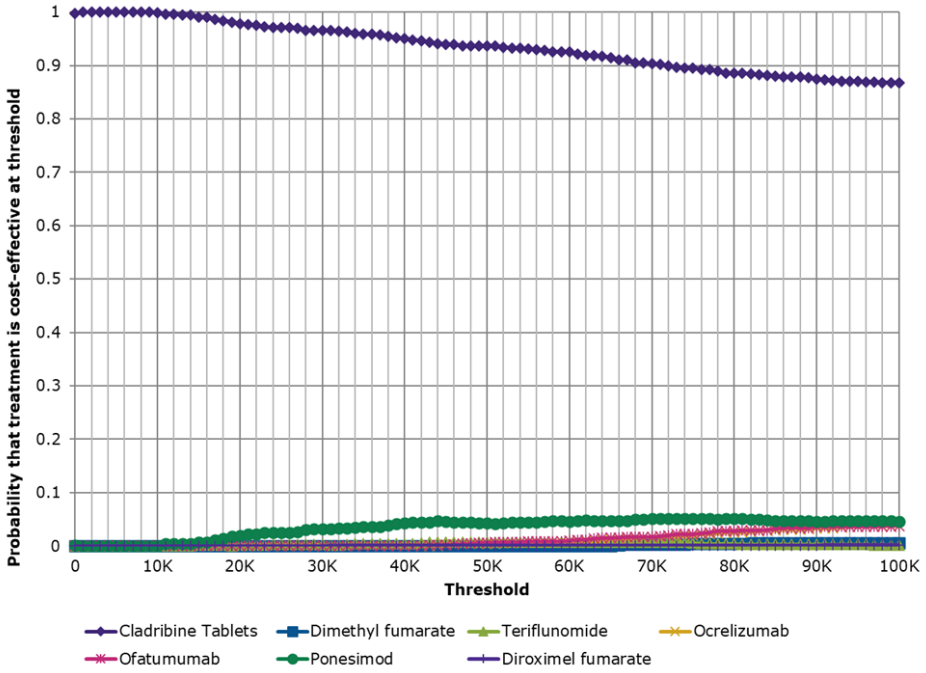

Table 6: Probabilistic results for active RRMS at list price (all relevant DMTs)

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Treatment (from least to most expensive)	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	Probability cost-effective at £30,000
Cladribine tablets	88,304	84,972	91,912	8.700	7.171	10.019	--	--	--	97.9%	95.5%
Teriflunomide	99,114	93,204	104,012	7.811	6.656	8.934	-10,811	0.890	Cladribine tablets dominant	0.7%	0.8%
Ponesimod	**99,545**	**91,701**	**107,401**	**8.030**	**6.713**	**9.297**	**-11,242**	**0.670**	**Cladribine tablets dominant**	**1.4%**	**3.5%**
Diroximel fumarate	127,242	114,916	141,848	8.113	7.038	9.290	-38,938	0.587	Cladribine tablets dominant	0.0%	0.1%
Dimethyl fumarate	130,799	122,521	139,485	8.136	7.018	9.320	-42,496	0.564	Cladribine tablets dominant	0.0%	0.0%
Ofatumumab	**135,999**	**125,910**	**145,334**	**8.386**	**7.165**	**9.549**	**-47,695**	**0.315**	**Cladribine tablets dominant**	**0.0%**	**0.0%**
Ocrelizumab	**138,579**	**128,075**	**149,163**	**8.496**	**7.350**	**9.675**	**-50,275**	**0.204**	**Cladribine tablets dominant**	**0.0%**	**0.1%**

ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

Compared to high-efficacy DMTs, the probability that cladribine tablets are cost-effective versus ponesimod, ocrelizumab and ofatumumab in the active RRMS population was 97.3% at a threshold of £20,000 per QALY gained. The corresponding probability for cladribine tablets at £30,000 per QALY gained was 95.4%. At the same thresholds, the probability that ponesimod, ofatumumab or ocrelizumab is the optimal cost-effective strategy in the active RRMS population ranged from 0% to 4.6% (

Table 7).

Table 7: Probabilistic results for active RRMS at list price (high-efficacy DMTs)

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	88,298	84,770	92,271	8.696	7.332	9.999	--	--	--	97.3%	95.4%
Ocrelizumab	**138,646**	**128,482**	**147,990**	**8.481**	**7.377**	**9.660**	**-50,348**	**0.215**	**Cladribine tablets dominant**	**0.0%**	**0.0%**
Ofatumumab	**136,339**	**127,162**	**146,222**	**8.376**	**7.184**	**9.618**	**-48,041**	**0.320**	**Cladribine tablets dominant**	**0.0%**	**0.0%**
Ponesimod	**99,533**	**91,564**	**106,970**	**8.023**	**6.744**	**9.286**	**-11,235**	**0.673**	**Cladribine tablets dominant**	**2.7%**	**4.6%**

ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

Deterministic sensitivity analysis

The results of the deterministic sensitivity analyses are summarised via a series of tornado diagrams. The analysis aimed to show the impact of variation in the values assigned to individual model parameters on the incremental net health effects of cladribine tablets versus DMT 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 were dominant versus all DMT 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-saving) 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. The results of the deterministic sensitivity analyses for active RRMS are summarised in the following tornado diagrams for comparisons versus dimethyl fumarate (Figure 2), teriflunomide (Figure 3), ocrelizumab (Figure 4), ofatumumab (Figure 5), ponesimod (Figure 6), and diroximel fumarate (Figure 7). The tornado diagrams show that the analyses were most sensitive to variation in the effect of DMT on 6-month CDP, discounting rate for costs and outcomes, and the discontinuation rate for comparator DMTs. Factors such as the effect of cladribine tablets on ARR and the discontinuation rate for cladribine tablets had a modest impact on results. The incremental net health effects comparing cladribine tablets versus dimethyl fumarate, teriflunomide, ocrelizumab, ofatumumab, and diroximel fumarate were positive in all scenarios. Cladribine tablets were therefore judged to be cost-effective versus all DMTs except ponesimod at a threshold of £30,000 per QALY gained. In the analysis comparing cladribine tablets versus ponesimod, the incremental net health effects were positive and in favor of cladribine tablets in all scenarios, except when varying the effect of DMT on disease progression where a negative net health effect was observed. This was observed due to the very conservative increase of the 6-month CDP HR of cladribine tablets at the higher bound of 95% CI (i.e., worsening 6-month CDP), which resulted in slightly more favorable results for ponesimod mainly due to ponesimod's lower treatment costs compared to other DMTs. **Figure 2: Tornado diagram for active RRMS, cladribine tablets versus dimethyl fumarate**

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

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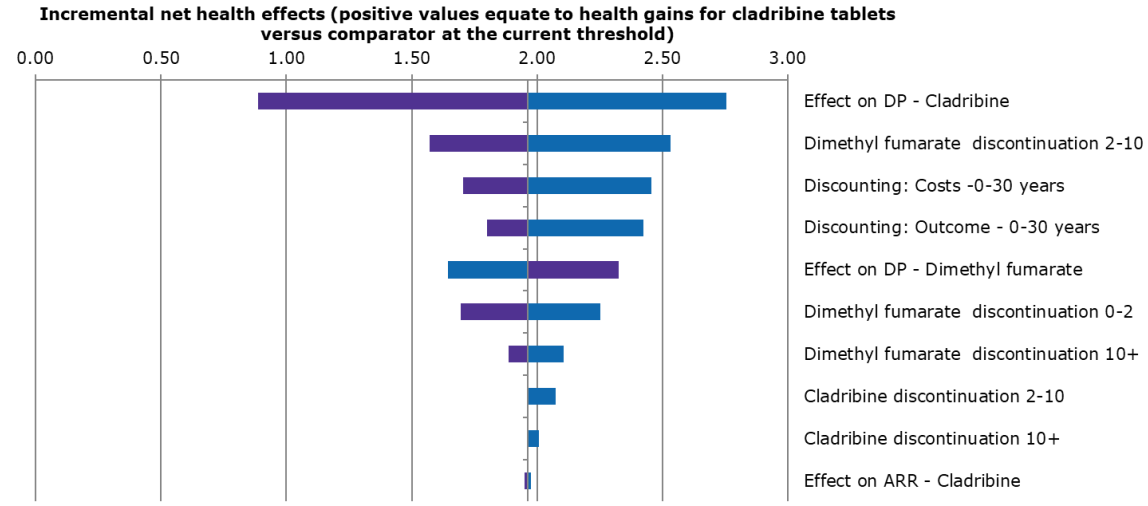

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 3: Tornado diagram for active RRMS, cladribine tablets versus teriflunomide

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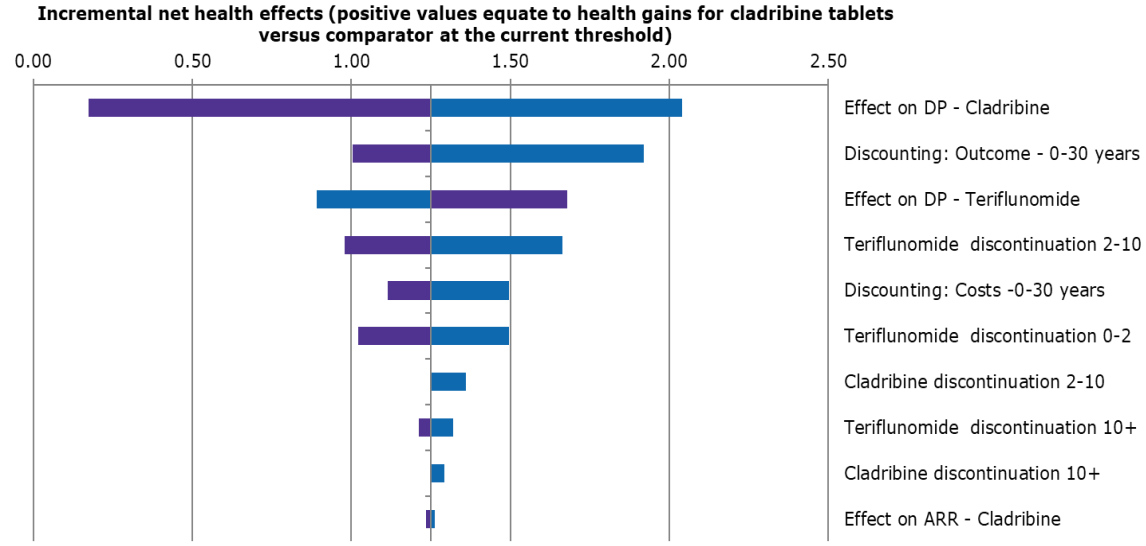

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 4: Tornado diagram for active RRMS, cladribine tablets versus ocrelizumab

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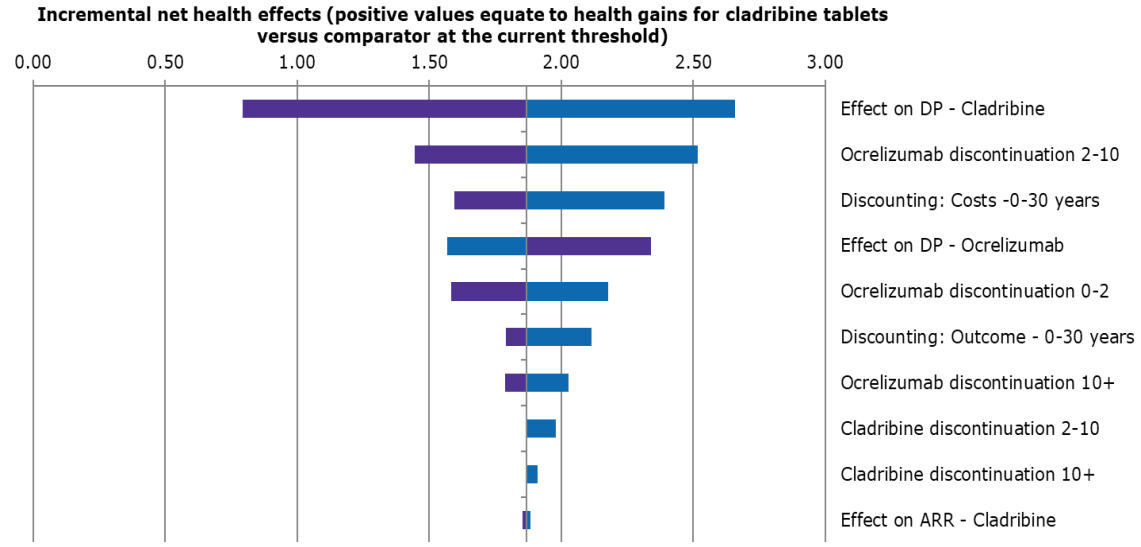

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 5: Tornado diagram for active RRMS, cladribine tablets versus ofatumumab

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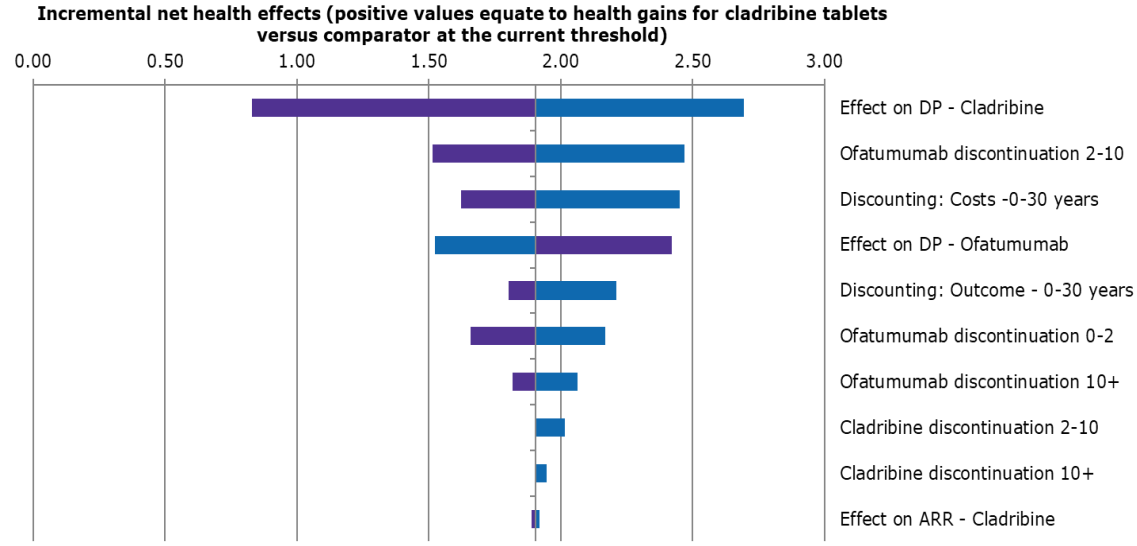

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 6: Tornado diagram for active RRMS, cladribine tablets versus ponesimod

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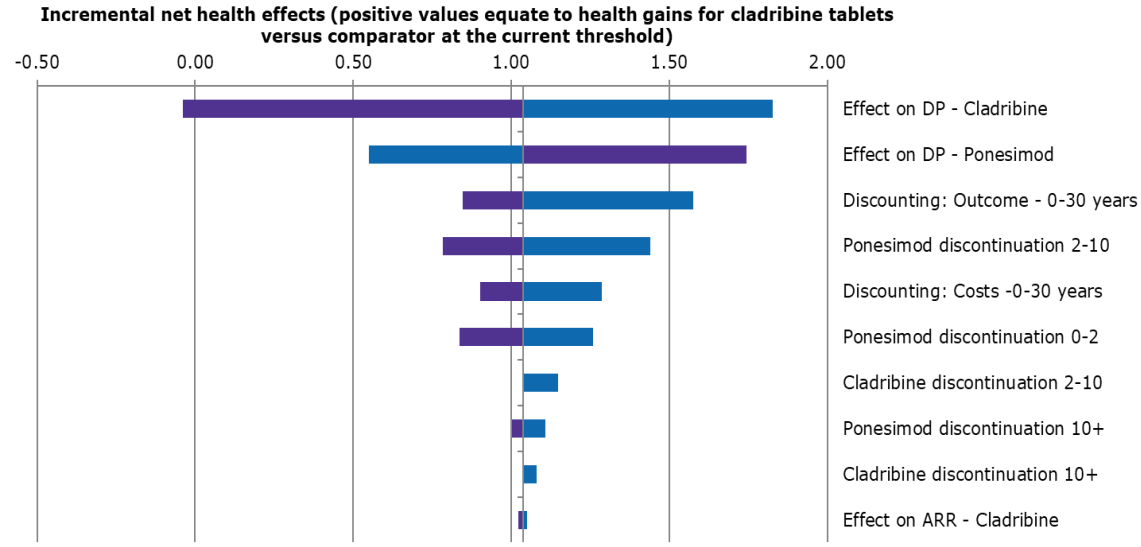

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 7: Tornado diagram for active RRMS, cladribine tablets versus diroximel fumarate

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

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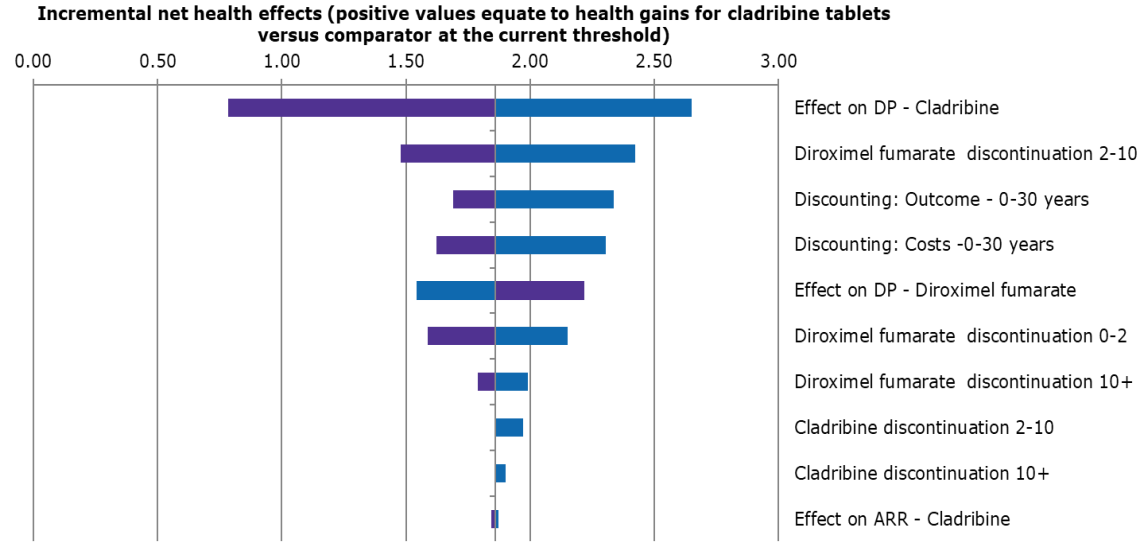

Purple bars show high variation and blue bars show low variation
ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

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3) Comparators	**<u>Draft Guidance Section 3.4, pages 6-7: Most appropriate comparators for cladribine tablets were dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod</u>** Merck partially agree with the Committee's conclusion that the most appropriate comparators for cladribine tablets were dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab and ponesimod. In line with the clinical experts' opinion heard during the first Committee meeting, Merck believe that the most relevant comparators to cladribine tablets for the treatment of active RRMS are the three high-efficacy DMTs (i.e., ofatumumab, ocrelizumab and ponesimod). However, in order to align with the Committee's preferred assumptions, cost-effectiveness results in the revised base case have been presented for dimethyl fumarate, diroximel fumarate, teriflunomide, ocrelizumab, ofatumumab and ponesimod. As such, beta interferons and glatiramer acetate have been excluded from the cost-effectiveness analysis results. In the Draft Guidance, the Committee did not specify if teriflunomide is considered as an appropriate comparator to cladribine tablets. Therefore, Merck have included teriflunomide along with the other relevant DMTs in the base case. A revised cost-effectiveness model including the Committee's preferred assumptions has been shared as part of the response. Revised results are presented in comment 1)).
4) Population	**<u>Draft Guidance Section 3.7, page 10, section 3.9, page 11, section 3.15, page 15</u>** The population of interest in this appraisal has been raised multiple times in the Draft Guidance (i.e., "The Committee acknowledged the uncertainty in the NMA results, ***noting that they were for the whole RRMS population",*** "such as from the UK MS registry, that: ***does not include data of people with highly active RRMS at baseline").*** To avoid any confusion and further clarify how this TA relates to TA616, Merck would like to clarify the population of interest. The marketing authorisation for cladribine tablets is for adults with relapsing multiple sclerosis (RMS). As outlined in the Decision Problem (Table 1 in company submission (CS) Document B), the population of focus in this appraisal is adults with active RRMS, as RRMS excludes patients with secondary progressive multiple sclerosis (SPMS). This reflects the target population for reimbursement and is aligned with the submitted evidence from CLARITY and CLARITY-EXT. In the final scope for this appraisal, it states that the population for whom cladribine tablets has already been approved by NICE in TA616 (adults with highly active relapsing-remitting multiple sclerosis [HA-RRMS]) will not be considered separately. This means that – unlike previous MS appraisals in active RRMS (TA533, TA699, TA767) – a separate sub-group analysis of the HA-RRMS subgroup was not explicitly requested by NICE, as cladribine tablets had previously been recommended by NICE in this subpopulation and demonstrated to be cost-effective. However, this does not mean that the HA-RRMS subgroup was excluded from our clinical evidence-base. Specifically, the dataset informing the network meta-analysis (NMA) and model (both cladribine tablets and comparator DMTs) are in the active RRMS population – which includes the highly active RRMS sub-group. Therefore, apart from previously demonstrating cost-effectiveness in the HA-RRMS subgroup in a separate appraisal process (TA616), this appraisal is, otherwise, identical to all other MS appraisal in active RRMS with respect to the overall target population – people with active RRMS (including HA-RRMS) – and the evidence base supporting this submission reflects this target population.

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5) Network meta-analyses

Draft Guidance Section 3.7, page 10: Committee's request to provide comparison and best-fit assessment of adjusted and unadjusted NMAs.

As part of the EAG's clarification questions, Merck carried out a baseline risk-adjusted NMA to understand the potential impact (if any) on the NMA results due to differences in the outcomes in the placebo arms across the trials. Along with this analysis, the model fit statistics were submitted. Results of baseline risk-adjusted NMAs were similar to conventional NMAs as shown in Table 8, Table 9 and

Table 10.

In terms of best-model fit, Merck tested the deviance information criterion (DIC), where a lower DIC value indicates a better fit. The DIC values for fixed effect and random effect NMAs were similar, with differences of less than 3. However, for the baseline risk-adjusted NMAs, the DIC values are significantly higher than the fixed effect and random effect NMAs which signifies a worse fit in the adjusted models (see Table 8, Table 9 and

Table 10). Therefore, it is not suggested to use the baseline risk adjusted NMA results in the base case.

Table 8: Comparison of results from fixed, random effects and baseline risk-adjusted NMAs for ARR

Treatment vs. placebo	Fixed effect	Random effect	Baseline risk-adjusted	Baseline risk-adjusted
	Median HR (95% CrI)			Mean (SD)
Cladribine tablets	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate*	[redacted]	[redacted]	[redacted]	[redacted]
DIC	144.8	145.51	657.44	

**Diroximel fumarate treatment effect was assumed the same as dimethyl fumarate in the absence of NMA results for this drug. ARR: Annualised relapse rate; DIC: deviance information criterion; DMT: Disease-modifying treatment; NMA: Network meta-analysis*

Please note that in the explanatory scenario using results of the baseline-risk adjusted NMA, ***mean*** values (Table 8 above) were used in the revised base case for ARR, as per the originally submitted economic model.

Table 9: Comparison of results from fixed, random effects and baseline risk-adjusted NMAs for 6-month CDP

Treatment vs. placebo	Fixed effect	Random effect	Baseline risk-adjusted
	Median HR (95% CrI)		
Cladribine tablets	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]

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Ofatumumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Diroximel fumarate*	[redacted]	[redacted]	[redacted]
DIC	68.12	68.82	267.001

**Diroximel fumarate treatment effect was assumed the same as dimethyl fumarate in the absence of NMA results for this drug. CDP: Confirmed disease progression; DIC: deviance information criterion; DMT: Disease-modifying treatment; NMA: Network meta-analysis*

Please note that in the explanatory scenario using results of the baseline-risk adjusted NMA, ***median*** values (Table 9 above) were used in the revised base case for 6-month CDP, as per the originally submitted economic model.

Table 10: Comparison of results from fixed, random effects and baseline risk-adjusted NMAs for probabilities of discontinuation

Treatment vs. placebo	Fixed effect	Random effect	Baseline risk-adjusted
	Median HR (95% CrI)		
Cladribine tablets	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]
DIC	116.02	110.38	388.669

CDP: Confirmed disease progression; DIC: deviance information criterion; DMT: Disease-modifying treatment; NMA: Network meta-analysis

Please note that in the explanatory scenario, ***absolute probabilities of discontinuation*** based on the random effects model from the baseline risk-adjusted NMA (Table 11 below) were used in the economic model, as per the originally submitted economic model.

Table 11: Absolute probabilities of discontinuation based on the random effects model from baseline risk-adjusted NMA

Treatment vs. placebo	Mean	Upper 95% credible interval value	Lower 95% credible interval value
Cladribine tablets*	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]

**Not applied in the base case analysis. NMA: Network meta-analysis*

Merck maintain their view that a more parsimonious model is preferred in light of the poorer-fit of the baseline risk-adjusted NMA. However, an additional exploratory scenario was undertaken, as requested by the Committee, using the baseline risk-adjusted NMA outcomes for ARR, 6-month CDP and all-cause discontinuation as shown in Table 8, Table 9 and

Table 10.

In this exploratory scenario, cladribine tablets remained dominant against the high-efficacy DMTs, diroximel fumarate, dimethyl fumarate and teriflunomide at list price. The results for this scenario are shown in Table 12.

Table 12: Cost-effectiveness results of the Committee preferred assumptions at list price – using baseline risk-adjusted NMA

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
Cladribine tablets	88,109	17.596	8.810	--	--	--	--
Teriflunomide	92,582	17.046	7.828	-4,473	0.550	0.982	Cladribine tablets dominant
Ponesimod	**92,842**	**17.145**	**8.026**	**-4,733**	**0.452**	**0.785**	**Cladribine tablets dominant**
Diroximel fumarate	119,287	17.187	8.098	-31,178	0.410	0.713	Cladribine tablets dominant
Dimethyl fumarate	122,915	17.200	8.122	-34,806	0.396	0.689	Cladribine tablets dominant
Ofatumumab	**126,154**	**17.323**	**8.365**	**-38,045**	**0.274**	**0.446**	**Cladribine tablets dominant**
Ocrelizumab	**136,459**	**17.247**	**8.214**	**-48,350**	**0.350**	**0.596**	**Cladribine tablets dominant**

ICER: Incremental cost-effectiveness ratio; EDSS: Expanded disability status scale; LY: Life years; LYG: Life years gained; MS: Multiple sclerosis; NMA: Network meta-analysis; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

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6) Model structure	**Draft Guidance Section 3.8, pages: 10-11: Subsequent treatment lines in the model to appropriately model time to next treatment**

Summary

- Merck acknowledges the Committee's concerns that in a disease area such as MS, having a single-line DMT model does not fully reflect clinical practice. However, unlike other disease areas, people with MS are younger and likely to receive multiple lines of treatment over their lifetime which are highly individualised with no clear established rule for sequencing of treatments.
- In the context of an STA in MS, NICE's remit is to evaluate the cost-effectiveness and make a recommendation for a specific treatment in comparison to standard of care, rather than make recommendations about complex treatment sequences or assess the cost-effectiveness of a specific treatment sequence. Therefore, adopting a treatment sequencing model would not be appropriate in this context and due to the complexity of treatment sequencing in MS, in particular.
- In terms of modelling, adopting a treatment sequencing is a very complicated endeavour which will lead to higher levels of uncertainty and add further complexity due to difficulties in attributing results to specific treatments. Specifically:
    - Treatment patterns of people with MS are highly individualised and treatment switching can occur due to various reasons, not only due to lack of treatment efficacy or associated adverse events. Therefore, there are no established or recommended treatment sequences routinely seen or followed in NHS clinical practice;
    - There is no direct evidence to inform the comparative effectiveness of subsequent treatments and different sequences;
    - Potential confounding of the clinical benefit of first-line treatments due to risk of attributing the results to the totality of the sequence rather than specific individual therapies, which can make it highly challenging to interpret the cost-effectiveness of cladribine tablets versus relevant comparators;
    - Definitions of treatment discontinuation vary across trials without necessarily capturing 'time to next treatment', which can result in overestimation of people receiving subsequent therapies. In addition, some medicines with higher discontinuation rates could disproportionately benefit from treatment sequencing in comparison to DMTs with lower discontinuation rates, and;
    - To most effectively model treatment waning across multiple lines of treatment, the sequencing model would need to be computationally complex and would likely require patient level simulation approaches (which is not feasible to implement within the timeframe of this Draft Guidance consultation).

All these uncertainties and challenges have been widely acknowledged by previous NICE Committees and EAGs. Despite the issues with modelling treatment sequences raised above, to address the Committee's concerns, Merck have conducted exploratory scenario analyses of treatment sequencing using two subsequent treatment "baskets", similar to the approach employed in the latest review of RRMS by the Institute for Clinical and Economic Review (ICER).[4] For both scenarios, simplified assumptions of fixed subsequent treatment "baskets" in terms of efficacy and costs were applied following treatment with cladribine tablets and comparators to capture treatment sequencing within the existing model structure. In both

scenarios, the same fixed "baskets" were applied as subsequent treatment following both cladribine tablets and comparator DMTs to emphasise potential differences in terms of treatment effect of the first line treatment, thus, minimise cofounding as much as possible.

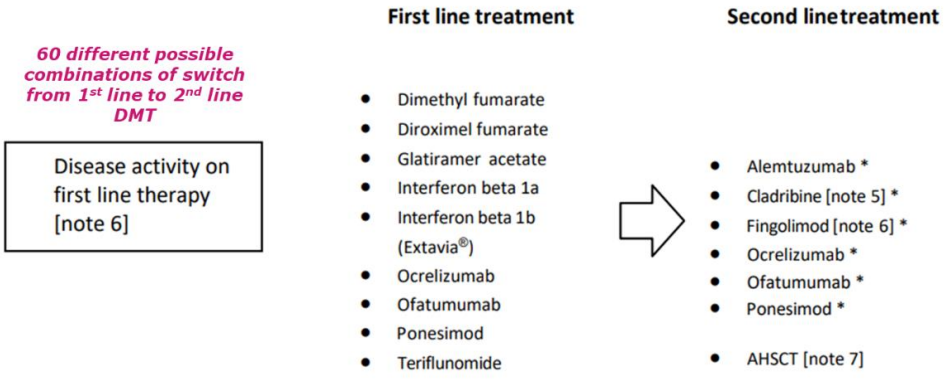
Despite the limitations of these exploratory scenarios and simplified assumptions, results showed that cladribine tablets remained dominant over most other relevant comparators at list price. Cladribine tablets were cost-effective in the SW quadrant versus ocrelizumab and ofatumumab, resulting in substantial cost savings but a small QALY loss.

Uncertainty with modelling multiple lines of therapy

Merck acknowledge that the current single-line DMT model structure for this appraisal (and all previous TAs in MS) is a simplified design and does not fully reflect what occurs in clinical practice, as people with MS are likely to be treated with multiple lines of DMTs over the course of their lifetime. However, modelling treatment sequencing in a condition like MS is expected to lead to considerable uncertainty and confounding issues due to the following:

- Unlike other therapy areas (for example, oncology), people with MS tend to be younger and are more likely to switch to more than one subsequent DMT in their lifetime (e.g. 2L, 3L, 4L+) which makes modelling of multiple DMT lines very challenging, with a lack of evidence from existing RCTs to inform the clinical effectiveness of DMTs in later lines of therapy.
- There are no established guidelines on specific treatment sequences in MS. The NHS England MS treatment algorithm provides guidance on the available DMTs for each specific line of therapy/sub-population. However, as treatment decisions are highly individualised and made on a case-by-case basis by the clinician and the patient, and decisions to switch treatments can be based on a number of different factors, multiple possible variations of treatment sequences would need to be modelled to reflect clinical practice, which introduces significant complexity. For instance, up to 60 possible treatment combinations/pathways could be possible from the treatments listed in Figure 8 below. Similarly, in previous TAs of MS, the Committee heard from clinical experts that there are no clear rules for sequencing of treatments (TA767, TA533, TA624).

Figure 8: Example of potential treatment sequence combinations based on the NHS England algorithm for disease activity on first-line therapy



- Incorporating multiples lines of DMT use would change the fundamental structure and outputs of the model, with results demonstrating the cost-effectiveness of *treatment sequences* rather than that of cladribine tablets vs. comparators. Adding further lines of treatment in the current model would confound the results by making it unclear whether any observed treatment effects are due to the first line treatment or later lines of treatment. Similarly, treatment sequencing could favour DMTs with higher discontinuation rates that would transition to higher efficacy treatments in subsequent treatment lines earlier, and demonstrate more favourable cost-effectiveness outcomes for these therapies. This could

lead to cost-effectiveness results that are largely being driven by the subsequent treatments' costs and efficacy, making it difficult to interpret the cost-effectiveness of cladribine tablets.

- In the context of an STA in MS, NICE's remit is to evaluate the cost-effectiveness and make a recommendation for a specific treatment in comparison to standard of care, rather than make recommendations about complex treatment sequences or assess the cost-effectiveness of a specific treatment sequence. Therefore, adopting a treatment sequencing model would not be appropriate in this context and due to the complexity of treatment sequencing in MS, in particular.
- In the previous appraisal of ponesimod in active RRMS (TA767), a scenario analysis using assumptions for treatment sequencing was explored but the Committee and the EAG concluded that it added uncertainty and complexity. The Committee also aligned with the ERG that a treatment sequencing model would be complex to construct and would be difficult to population with limited evidence. The Committee acknowledged the limitations of the single-line DMT model design but ultimately decided to accept it for decision-making and stated it was broadly aligned with previous models in MS. Please see excerpt from the ponesimod appraisal materials below:

  > *"The ERG considered conducting scenario analyses using assumptions for subsequent treatments suggested by clinical experts, however given that the choice and probability of subsequent treatment use will differ due to the reasons for discontinuing, the scenario was considered to introduce additional complexity and uncertainty. Furthermore, the ERG was unable to identify any prescribing data, which could inform subsequent treatment use in the model. This is a simplifying approach, given that, as noted above, the choice of subsequent treatment will depend on the rationale for stopping treatment. It should be noted that, for these scenarios, the company included the clinical effectiveness of subsequent treatments (based on the NMA results). Due to the limitations surrounding the clinical effectiveness estimates, the ERG considered that modelling subsequent treatment effects introduced additional uncertainty." (ponesimod ERG report, TA767)*
  >
  > *"The Committee noted that previous appraisals had criticised the lack of treatment switching or sequencing and the fixed treatment waning effect as major limitations of similar models. It considered that these oversimplify what would happen in NHS clinical practice. However, it acknowledged that a model that can simulate treatment sequencing and variable treatment waning would be complex to construct and difficult to populate because of limited data. The Committee considered that longer-term efficacy is difficult to establish and extrapolate from the short-term trials used in the network meta-analyses, the outputs of which have broad credible intervals. The Committee concluded that the model structure and inputs broadly aligned with previous models in the disease area, but it had limitations." (ponesimod FAD, TA767)*

Merck believe that restructuring the current economic model to incorporate treatment sequencing will not address the Committee's concerns. On the contrary, it will add significant uncertainty and complexity which will make subsequent interpretation of cost-effectiveness for cladribine tablets more challenging resulting in a lack of transparency for decision-making purposes.

Exploratory scenario

"Basket" treatment sequencing approach

Despite concerns around the uncertainty and complexity associated with treatment sequencing, to reassure the Committee on the potential impact of incorporating subsequent DMT use, we

have developed exploratory scenarios of two simplified subsequent treatment "baskets" similar to the approach adopted in the latest review of RRMS of the Institute for Clinical and Economic Review (ICER).[4] These exploratory scenarios aimed to more closely reflect clinical practice (i.e., patients being treated with another DMT after discontinuation) within the constraints of the current economic model structure, but also focus on the treatment effects of the initial treatment rather than allowing subsequent treatments to significantly drive the results.

The exploratory scenario analyses were performed using two different fixed subsequent treatment "baskets" which were applied equally following treatment with both cladribine tablets and comparator DMTs:

- ***Basket 1*** of subsequent treatments includes only the three high efficacy DMTs as treated patients will be more likely to switch to a high efficacy DMT rather than platform DMTs as per clinical expert opinion received by Merck.
- ***Basket 2*** of subsequent treatments includes all available and relevant DMTs including ocrelizumab, ofatumumab, ponesimod, dimethyl fumarate, diroximel fumarate and teriflunomide.

In both "baskets", cladribine tablets were not included as a potential subsequent therapy to avoid unnecessary uncertainty given that is not currently recommended for people with active RRMS.

In the exploratory model, when patients discontinue the initial DMT they switch to the fixed "basket" of subsequent DMTs (instead of switching to BSC as in the base case model) with a weighted annual drug acquisition cost and weighted treatment effect (i.e., 6 month-CDP hazard ratio versus placebo and ARR versus placebo estimates from the company NMA) based on estimated market shares of the DMTs in both Basket 1 and Basket 2. Therefore, by using the "basket" method approach, patients will incur the weighted cost and treatment effect (acting as a '"basket"' cost/effect for possible subsequent treatment) upon treatment discontinuation and this cost/effect will be incurred by the 'discontinued' population for the remainder of the model time horizon. The weighted treatment effects (i.e., 6 month-CDP and ARR) of Basket 1 and Basket 2 are applied to the natural history model in the same way as the treatment effects are applied to the initial DMT in the transition matrices of the base case model. Treatment waning is also applied for the subsequent DMT "baskets" at the same rates as applied for the initial DMT for the remainder of the model time horizon (i.e., 100% of treatment effect is assumed to apply to the '"basket"' DMT in the first 4 years, followed by 25% waning in Year 4-5, and 50% waning from Year 5 onwards). The weighted treatment cost includes the drug treatment acquisition, administration and monitoring cost drugs of the DMTs considered in the '"basket"'.

Table 13 provides an overview of the model characteristics that were revised for this "basket" (TA treatment sequencing scenario.

Table 13: Overview of the "basket" treatment sequencing scenario inputs

Model characteristics	Rationale
Treatment "basket" for the two scenario analyses	**Basket 1- High-efficacy DMTs:** Only high efficacy DMTs (excluding cladribine tablets): ponesimod, ofatumumab, ocrelizumab **Basket 2- All relevant DMTs:** All relevant available DMTs (excluding cladribine tablets): ocrelizumab, ofatumumab, ponesimod, dimethyl fumarate, diroximel fumarate, and teriflunomide

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Weighted efficacy

Weighted efficacy outcomes in terms of ARR and 6-month CDP were calculated for Baskets 1 and 2, based on re-distributed current market shares sourced from IQVIA Account Level Hospital Profiler (ALHP) data with additional internal forecasting projections that only include these DMTs, as seen in the two tables below. The weighted efficacy was calculated and added to the BSC arm of the model for both "baskets", respectively.

Table 14: Basket 1- High-efficacy DMTs

Treatment	Market share based on internal forecasting
Ocrelizumab	[redacted]
Ofatumumab	[redacted]
Ponesimod	[redacted]
Total	**100%**

Table 15: Basket 2- All relevant DMTs

Treatment	Market share based on internal forecasting
Ocrelizumab	[redacted]
Ofatumumab	[redacted]
Ponesimod	[redacted]
Dimethyl fumarate	[redacted]
Diroximel fumarate	[redacted]
Teriflunomide	[redacted]
Total	**100%**

When patients discontinue the first DMT treatment, they will incur this weighted efficacy (acting as a "basket" treatment effect for possible subsequent treatments) for the remainder of the model time horizon. This change was applied within the current model structure to best capture the additional benefit patients will incur when switching to a subsequent treatment after first-line DMT usage, while operating within the constraints of the original model design.

Table 16: Weighted treatment effect applied to the "basket" DMT by market share

Treatment	*Basket 1- High-efficacy DMTs*		*Basket 2-All relevant DMTs*	
	6 month-CDP (hazard ratio vs placebo)	ARR (rate ratio vs placebo)	6 month-CDP (hazard ratio vs placebo)	ARR (rate ratio vs placebo)
"Basket" DMT	[redacted]	[redacted]	[redacted]	[redacted]

ARR: Annualised relapse rate; CDP: Confirmed disease progression; DMT: Disease-modifying therapy

Weighted cost

A weighted annual drug acquisition, administration, and monitoring costs of both Baskets 1 and 2 on re-distributed current market shares (that only include these DMTs) was calculated and added to the BSC arm of the model in the two "basket" scenarios, respectively. When patients discontinue treatment, they will incur this weighted cost (acting as a '"basket"' cost for possible subsequent treatment) for the remainder of the model time horizon.

This change was applied within the current model structure to best capture the additional costs patients will incur when switching to a subsequent treatment after first-line DMT usage.

Table 17: Weighted average cost for the "basket" DMT by market share

	Treatment	*Basket 1- High-efficacy DMTs*			*Basket 2-All relevant DMTs*		
		Weighted drug acquisition cost	Weighted drug admin. cost	Weighted monitoring cost	Weighted drug acquisition cost	Weighted drug admin. cost	Weighted monitoring cost
	"Basket" DMT	£18,525	£800	£244	£18,044	£483	£263
	Admin: Administration; DMT: Disease-modifying therapy*						
Treatment discontinuation	For first-line treatment, as per the preferred Committee's preferred assumption, treatment discontinuation for cladribine tablets was applied from CLASSIC-MS to reflect time to next treatment. Due to lack of specific data on time to next treatment for the comparators, the discontinuation rates from the NMA were used. When patients move to second-line treatment (i.e., "basket" subsequent treatment), they do not discontinue treatment until death.						
Treatment waning	Treatment waning for the second-line (i.e., "basket" subsequent treatment) was assumed to be the same as treatment waning in first-line treatment and applied for the remainder of the time horizon. For instance, 100% of treatment effect is assumed to apply to the weighted "basket" treatment effect in the first 4 years, 25% waning in Year 4-5, and 50% waning from Year 5 onwards is applied (as per the company's base case and the Committee's preferred assumption).						

The results of both "basket" treatment sequencing scenarios are presented in Table 18.

Table 18: "Basket" treatment sequencing scenario results

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
Basket 1 – High-efficacy DMT comparators							
Cladribine tablets	283,147	18.194	9.511	--	--	--	--
Teriflunomide	366,361	18.007	9.118	-83,214	0.187	0.392	Cladribine tablets dominant
Ponesimod	**369,822**	**18.137**	**9.384**	**-86,675**	**0.056**	**0.126**	**Cladribine tablets dominant**
Dimethyl fumarate	385,032	18.125	9.363	-101,885	0.068	0.148	Cladribine tablets dominant
Diroximel fumarate	385,320	18.132	9.374	-102,173	0.062	0.137	Cladribine tablets dominant
Ofatumumab	**388,083**	**18.239**	**9.596**	**-104,936**	**-0.046**	**-0.085**	**1,228,492 (SW)†**
Ocrelizumab	**400,738**	**18.340**	**9.805**	**-117,591**	**-0.147**	**-0.295**	**398,826 (SW)†**
Basket 2- All relevant DMTs							
Cladribine tablets	273,558	18.085	9.369	--	--	--	--
Teriflunomide	353,078	17.849	8.893	-79,520	0.237	0.476	Cladribine dominant

Ponesimod	**356,388**	**17.977**	**9.153**	**-82,830**	**0.108**	**0.216**	**Cladribine dominant**
Dimethyl fumarate	372,412	17.977	9.153	-98,854	0.109	0.216	Cladribine dominant
Diroximel fumarate	372,491	17.980	9.159	-98,933	0.105	0.210	Cladribine dominant
Ofatumumab	**375,587**	**18.093**	**9.388**	**-102,029**	**-0.008**	**-0.019**	**5,467,026 (SW)†**
Ocrelizumab	**387,726**	**18.187**	**9.583**	**-114,168**	**-0.101**	**-0.213**	**534,787 (SW)†**

†*An ICER in the southwest (SW) is assessed via an inverted threshold, such that an ICER > £30,000 can be considered cost-effective.*
ICER: Incremental cost-effectiveness ratio; EDSS: Expanded disability status scale; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; SW: South-west; QALYs: Quality-adjusted life years
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

Results from both scenarios showed that cladribine tablets remained dominant over most other relevant comparators at list price. Cladribine tablets versus ocrelizumab and ofatumumab was cost-effective in the south-west (SW) quadrant, resulting in substantial cost savings but a small QALY loss compared to ocrelizumab an ofatumumab.

When net health benefits (NHB) are calculated [(total expected QALYs – (total expected costs / maximum acceptable incremental cost-effectiveness ratio value)] using values placed on a QALY gain of £20,000 and £30,000 for each DMT, cladribine had the highest NHB at £20,000 and £30,000, and was associated with positive incremental NHB versus all comparators.[5,6]

Table 19: Incremental net health effects results at list price (cladribine tablets vs. comparator)

Treatment	*Basket 1- High-efficacy DMTs*				*Basket 2- All relevant DMTs*			
	NHB at £20,000	Incr. NHB at £20,000 (QALY)	NHB at £30,000	Incr. NHB at £30,000 (QALY)	NHB at £20,000	Incr. NHB at £20,000 (QALY)	NHB at £30,000	Incr. NHB at £30,000 (QALY)
Cladribine tablets	-4.647	--	0.072	--	-4.309	--	0.251	--
Dimethyl fumarate	-9.889	5.242	-3.472	3.544	-9.467	5.159	-3.261	3.511
Teriflunomide	-9.200	4.553	-3.094	3.166	-8.761	4.452	-2.876	3.127
Ocrelizumab	**-10.232**	**5.585**	**-3.553**	**3.625**	**-9.803**	**5.495**	**-3.341**	**3.592**
Ofatumumab	**-9.808**	**5.161**	**-3.340**	**3.412**	**-9.391**	**5.083**	**-3.132**	**3.382**
Ponesimod	**-9.107**	**4.460**	**-2.943**	**3.016**	**-8.666**	**4.358**	**-2.727**	**2.977**
Diroximel fumarate	-9.892	5.245	-3.470	3.542	-9.466	5.157	-3.257	3.508

Inc.: Incremental; QALY: Quality-adjusted life year; NHB: Net health benefits
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

Limitations of the "basket" treatment sequencing approach

Due to the complexity and lack of clinical data informing treatment sequences, the exploratory treatment sequencing model has several key limitations. Firstly, the "basket" approach is still a simplification of treatment sequencing (with multiple DMT line combinations) that can occur in the real-world setting for people with MS given the likelihood of requiring multiple lines of therapy

	over their lifetime. Secondly, due to additional structural changes and time required, adverse events costs and disutilities were not included in the "basket" treatment sequencing approach (including adverse events rates would also require the assumption that the safety profile of a subsequent DMT is the same as for DMT for untreated patients, which may not be true). Thirdly, the clinical efficacy data to inform efficacy of the subsequent treatment "baskets" is not exclusively in second line treatment and therefore may not reflect the true efficacy of a previously treated population. Additionally, when patients switch to the subsequent treatment line, they remain on that subsequent treatment "basket" for the rest of the model time horizon and since there are no further treatment lines (including the transition to BSC) the EDSS 7 stopping rule cannot be applied to the "basket" DMTs (i.e., subsequent treatment patients will incur "basket" treatment costs and effects despite progression to EDSS 7). Adapting this would require significant structural changes to the model (e.g., including more treatment lines) which were not possible within the timeframe of this Draft Guidance consultation. However, to confirm, the EDSS 7 stopping rule is still applied for the initial DMT in this scenario. Even though these exploratory analyses can be informative when testing the robustness of cladribine tablets cost-effectiveness results, using these analyses for decision-making should be approached with great caution due to the use of simplifying assumptions which can further increase uncertainty. For the reasons outlined above and in line with the conclusions of previous MS appraisals, Merck believe that a single line model is more transparent and appropriate for decision-making in order to assess the cost-effectiveness of cladribine tablets vs. relevant comparators.

Consultation on the Draft Guidance document – deadline for comments 5pm on 9 January 2025. Please submit via NICE Docs.

7) Source of natural history data	**Draft Guidance Section 3.9, pages 11-12: Use an updated data source for the natural history model to reflect the population with active RRMS in the NHS or validate the current BCMS registry data**

Summary

- The BCMS database is a widely used source of natural history data of people with untreated MS and has been the preferred source of natural history data in all recent NICE appraisals, for various reasons including its large sample size, long study timespan (~10 years), inclusion of backward transitions to EDSS, and being one of the very few sources of MS clinical outcomes in a large population with MS that have not been previously treated with a DMT.
- To address the Committee's preferred assumptions of using a more recent source of natural history data to inform for EDSS transition probabilities and/or validate BCMS, Merck conducted a rapid review of the literature.
- Merck identified one study that compared untreated MS populations from the University of Wales Multiple Sclerosis (UoWMS) cohort in the UK and the BCMS cohort, published in 2016, which concluded that both cohorts had very similar disability EDSS progression over time. Merck identified only one recent study by Campbell et al (2024) that reported transition probabilities across EDSS states for untreated RRMS patients in Australia using the MSBase registry.[7] However, in this study, EDSS states are grouped into four categories (no, mild, moderate and severe disease) which does not align with the more granular categorisation of disability progression in our economic model (i.e., by 1-point increments of EDSS). Therefore, application of these transition probabilities to the current economic model was not possible without substantial structural changes to the model which was not feasible within the timeframe of this Draft Guidance consultation.
- The Committee recommended the validation of the natural history model with more recent data such as that from the UK MS Register. However, retrieving and analysing data from the UK MS Register for application in the natural history transition matrix would be a resource- and time-intensive exercise and therefore not feasible within the timeframe of the Draft Guidance consultation. Importantly, no existing publications using the UK MS Register have reported natural history data for untreated MS patients that Merck could potentially apply to/or use to validate the natural history model for this submission.
- Despite Merck's position that the BCMS database is the most comprehensive dataset and most appropriate source of natural history data for this economic model, to address the concerns of the Committee, Merck conducted exploratory scenarios to assess the impact of alternative natural history transition probabilities to test the impact on the cost-effectiveness results. Results from all exploratory scenarios showed that cladribine tablets remained dominant over all other relevant comparators at list price.

Suitability of BCMS dataset for application in the economic model

Below we outline in detail the reasons why the BCMS dataset is still the most appropriate, and best available, source for informing natural history in MS models, including for this appraisal.

Current economic model structure

The economic model structure requires a baseline set of EDSS transition probabilities upon which the treatment effect of cladribine tablets and comparator DMTs can be applied onto. In all previous MS appraisals (TA533, TA624, TA767, TA699), this natural history data set has been based on an untreated population to reflect a 'placebo' control.[8-11] In this way, the NMA results for each DMT vs. placebo (for ARR and CDP outcomes) can be applied to this 'placebo' control group to generate a new set of transition probabilities for each DMT to inform comparative

efficacy. As such, the application of baseline EDSS transition probabilities in an *untreated* population, rather than treated, is appropriate (and has been accepted in all previous TAs in MS).

Generalisability of BCMS

BCMS dataset remains the most reliable source of natural history data of untreated MS patients for the following reasons:

i. Prior analyses of the BCMS dataset looking at trends of disability progression in MS within 15 years from onset (Shirani et al study 2012) has shown that disability progression has not substantially changed over time.[12] Therefore, the risk of EDSS progression in an older dataset of an untreated population being significantly different to EDSS progression in a contemporary untreated population is likely to be very low.

ii. The use of a more recent dataset to generate EDSS transition probabilities for an untreated population — in other words, an untreated population that are potentially eligible for a DMT in a time when DMTs are readily available, but remain untreated— is associated with potential indication bias, as untreated patients are more likely to have milder disease and patients with more severe disease are more likely to be treated with a DMT given their availability.[13] As a result, a historical dataset, like BCMS, capturing disability progression in an untreated population prior to availability of DMTs, is likely to be more reflective of a broader untreated population, and less subject to bias.[14-16]

Established use of BCMS

The BCMS dataset has been used in many active RMS epidemiological studies that investigated the effects of DMTs in MS in terms of disease course before and after DMT introduction.[17] In addition, BCMS, has been used in the vast majority of previous NICE MS appraisals – including more recent appraisals such as TA533, TA624, TA767, TA699, and has been deemed acceptable for use in decision-making (please refer to Table 20 below). In fact, the validity of the BCMS dataset in RRMS has never been raised in previous TAs and based on TA624, the scientific advisory group (SAG) to the UK RSS scheme concluded that the BCMS dataset is the best natural history dataset in terms of the methodology used to capture EDSS score (EDSS prospectively captured) and registry completeness (an estimated 80% coverage of the BCMS population).[9]

Table 20: Natural history dataset used by other NICE TAs

TA	Company base case
Ocrelizumab (TA533)	BCMS
Peginterferon (TA624)	BCMS for transitions across EDSS for patients with RRMS London Ontario for transitions from RRMS to SPMS and during SPMS
Ponesimod (TA767)	BCMS for transitions across EDSS for patients with RRMS London Ontario for transitions from RRMS to SPMS
Ofatumumab (TA699)	BCMS for transitions across EDSS for patients with RRMS London Ontario and EXPAND for transitions from RRMS to SPMS and during SPMS

Validation of BCMS dataset compared to recent datasets

From a rapid review of the literature, and a review of previous NICE MS appraisals, we identified a study from Tilling et al in 2016 which compared untreated MS populations from the University of Wales Multiple Sclerosis (UoWMS) cohort in the UK, and the BCMS cohort (1980–1995).[18] This study did not report EDSS transition probabilities. However, it is a valuable validation of the BCMS dataset as despite including more recent data (up to 2011 in UoWMS vs. up to 1995 in the BCMS dataset), this study observed remarkably similar disability EDSS progression between the two datasets over time. [18,19]

Table 21 below summarises baseline characteristics of people with MS included in the BCMS and UoWMS databases to showcase similarities across the two cohorts.

Table 21: Baseline characteristics of the natural history cohorts

Natural History Dataset	Age	Sex	EDSS at baseline
BCMS (n=898)	Mean: 29.2 (8·7) Median: 28 (23–35)	Men: 232 (26%) Woman: 666 (74%)	Mean: 2.44 (1.70) Median: 2 (1–3.5)
UoWMS (n=404)	Mean: 31.1 (8.7)	Men: 98 (24.5%) Woman: 306 (75.7%)	Median: 3.5 (2, 4.5);

BCMS: British Columbia Multiple Sclerosis; UoWMS: University of Wales Multiple Sclerosis

Only one recent study with published EDSS transition probability data in an untreated active RRMS population (n=1,453) was identified in our rapid review.[7] This study by Campbell et al was published in 2024 and utilises data from the MSBase registry for an Australian population. An important limitation of this study, for the purposes of validation of the BCMS dataset, is that the authors categorised disability as: no disability (EDSS of 0), mild disability (EDSS of 1.0–3.5), moderate disability (EDSS of 4.0–6.0), and severe disability (EDSS of 6.5–9.5), instead of EDSS states by 1-point increments as reported for BCMS by Palace et al 2014[15]. Based on the structure of the current economic model, treatment effects are applied to adjust transition probabilities through each of the EDSS states, thus, application of transition probabilities from this study directly to our model was not feasible without significant structural changes to the economic model, that were not possible within the timeframe of this Draft Guidance consultation. Validation of the BCMS database through comparisons of the transition probabilities between EDSS 'groups' in the Campbell et al 2024 study vs. transition probabilities by individual EDSS states from the BCMS data was also not meaningful due to the different categorisation of the EDSS states between both sources. In Campbell et al, severe disability was defined by EDSS of 6.5–9.5, whereas in Palace et al, values of EDSS are reported by 1-point increments, therefore conversion of BCMS data into these 'groups' would not have been possible. It is also important to note that the MSBase registry has been criticised for its insufficient patient numbers for EDSS ≥ 7.0.[20]

In response to the Committee's recommendation to use the UK MS Register, Merck would like to highlight that retrieving and analysing data from the UK MS Register for application in the natural history transition matrix would be resource- and time-intensive exercise as well as not feasible within the timeframe of Draft Guidance consultation. The deadline for applications for data requests for the UK MS Register are every three months, and the UK MS Register Scientific Steering Committee, which review all applications, meet every three months. Importantly, no existing publications using the UK MS Register have reported natural history data that we could potentially apply in the economic model for this submission.

Merck have further submitted a supplementary file ', in response to the Committee's request for graphs showing health-state occupation that reflect EDSS state progression and mortality from the BCMS natural history dataset. In the supplementary file, graphs are provided for the natural history cohort as well as for people treated with cladribine tablets, both in the revised base case and the exploratory treatment sequencing scenario described earlier in comment 6)).

To conclude, based on the range of evidence provided above, Merck's position is that the BCMS still remains the most robust, comprehensive and appropriate source of natural history data for application in MS modelling, including in this appraisal.

Exploratory scenarios

Alternative EDSS transition matrices

Although Merck's case on the appropriateness of using the BCMS dataset has been made above, we have generated three exploratory scenario analyses to test the robustness of our results

against the potential impact of variation in natural history transition probabilities. To do this we generated three exploratory EDSS natural history transition matrices by taking the base case BCMS natural history transition matrix and reducing disease progression by 10%, 20% and 30%. Specifically, we did this by increasing the probability of patients remaining in the same EDSS score (e.g., transition probability from EDSS 5 to EDSS 5) by 10%, 20% and 30% as shown in Table 22, Table 23 and

Table ***24***.

Table 22: Annual transition probabilities (MS age of onset ≥28 years) from BCMS registry with a 10% increase of remaining in the same EDSS score

From/To	0	1	2	3	4	5	6	7	8	9
0	76.5%	15.7%	5.6%	1.7%	0.3%	0.1%	0.1%	0.0%	0.0%	0.0%
1	4.5%	76.5%	12.2%	4.7%	1.3%	0.4%	0.5%	0.0%	0.0%	0.0%
2	1.3%	10.3%	66.9%	14.2%	3.8%	1.6%	1.8%	0.1%	0.0%	0.0%
3	0.5%	4.3%	10.4%	59.9%	8.7%	5.0%	10.1%	0.9%	0.3%	0.0%
4	0.1%	2.0%	6.0%	10.4%	53.8%	9.4%	15.2%	2.3%	0.6%	0.1%
5	0.0%	0.5%	2.7%	5.3%	7.9%	53.6%	24.7%	3.5%	1.7%	0.1%
6	0.0%	0.1%	0.3%	1.8%	2.2%	2.9%	81.5%	7.8%	3.1%	0.3%
7	0.0%	0.0%	0.0%	0.2%	0.6%	0.3%	9.1%	76.2%	12.4%	1.2%
8	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.4%	99.4%	0.1%
9	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.3%	9.6%	90.0%

EDSS: Expanded disability status scale; MS: Multiple sclerosis

Table 23: Annual transition probabilities (MS age of onset ≥28 years) from BCMS registry with a 20% increase of remaining in the same EDSS score

From/To	0	1	2	3	4	5	6	7	8	9
0	83.4%	11.0%	3.9%	1.2%	0.2%	0.1%	0.1%	0.0%	0.0%	0.0%
1	3.2%	83.4%	8.6%	3.3%	0.9%	0.2%	0.3%	0.0%	0.0%	0.0%
2	1.1%	8.4%	72.9%	11.6%	3.1%	1.3%	1.5%	0.1%	0.0%	0.0%
3	0.5%	3.8%	9.1%	65.3%	6.9%	4.4%	8.9%	0.8%	0.3%	0.0%
4	0.1%	1.8%	5.4%	9.3%	58.7%	8.4%	13.6%	2.1%	0.5%	0.0%
5	0.0%	0.4%	2.4%	4.8%	7.1%	58.4%	22.1%	3.1%	1.5%	0.1%
6	0.0%	0.1%	0.2%	1.1%	1.3%	1.7%	88.9%	4.7%	1.9%	0.2%
7	0.0%	0.0%	0.0%	0.1%	0.4%	0.2%	6.4%	83.1%	8.8%	0.9%
8	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	1.9%	5.6%	90.3%	2.1%
9	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.6%	17.4%	81.8%

EDSS: Expanded disability status scale; MS: Multiple sclerosis

Table 24: Annual transition probabilities (MS age of onset ≥28 years) from BCMS registry with a 30% increase of remaining in the same EDSS score

From/To	0	1	2	3	4	5	6	7	8	9
0	90.4%	6.4%	2.3%	0.7%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%
1	1.8%	90.4%	5.0%	1.9%	0.5%	0.1%	0.2%	0.0%	0.0%	0.0%
2	0.8%	6.5%	79.0%	9.0%	2.4%	1.0%	1.2%	0.1%	0.0%	0.0%
3	0.4%	3.2%	7.7%	70.7%	5.8%	3.8%	7.5%	0.7%	0.2%	0.0%
4	0.1%	1.6%	4.7%	8.2%	63.6%	7.4%	12.0%	1.8%	0.5%	0.0%
5	0.0%	0.4%	2.1%	4.2%	6.2%	63.3%	19.5%	2.8%	1.3%	0.1%
6	0.0%	0.0%	0.1%	0.4%	0.4%	0.6%	96.3%	1.6%	0.6%	0.1%
7	0.0%	0.0%	0.0%	0.1%	0.2%	0.1%	3.8%	90.0%	5.2%	0.5%
8	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	1.9%	5.6%	90.3%	2.1%
9	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%	0.6%	17.4%	81.8%

EDSS: Expanded disability status scale; MS: Multiple sclerosis

EDSS transitions, values based on London Ontario dataset

Another explanatory scenario analysis was performed using a combination of data from London Ontario dataset and BCMS data for transition probabilities for EDSS 0.

The London Ontario, another widely known available MS dataset in an untreated population, was not used in the base case as it is subject to intrinsic flaws due to post-hoc data censoring, and because the matrix does not allow for improvements in EDSS as observed in clinical studies and as reported in the BCMS registry. Nevertheless, an additional scenario using this data set was also explored to test the impact on the cost-effectiveness results (Table 25).

Table 25: Annual transition probabilities from London Ontario registry

From/To	0	1	2	3	4	5	6	7	8	9
0*	[redacted]									
1	[redacted]									
2	[redacted]									
3	[redacted]									
4	[redacted]									
5	[redacted]									
6	[redacted]									
7	[redacted]									
8	[redacted]									
9	[redacted]									

Source: Academic in Confidence
**Transition probabilities from EDSS 0 to other scores from BCMS are applied due lack of data from London Ontario*

The cost-effectiveness results from all the exploratory scenarios varying the natural history transition probabilities are shown in Table 26 below. Results from all scenarios showed that cladribine tablets remained dominant over all other relevant comparators at list price. This demonstrates that the cost-effectiveness of cladribine is largely insensitive to change in baseline natural history transition probabilities.

Table 26: Results of sensitivity analyses using alternative EDSS transition probabilities and the London Ontario database

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Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
BCMS registry (MS age of onset ≥28 years) with a 10% increase in remaining in the same EDSS score							
Cladribine tablets	88,437	17.766	8.968	--	--	--	--
Teriflunomide	100,929	17.253	8.067	-12,492	0.513	0.901	Cladribine tablets dominant
Ponesimod	**101,061**	**17.372**	**8.296**	**-12,624**	**0.394**	**0.672**	**Cladribine tablets dominant**
Diroximel fumarate	129,330	17.423	8.384	-40,893	0.343	0.584	Cladribine tablets dominant
Dimethyl fumarate	133,354	17.436	8.405	-44,917	0.330	0.563	Cladribine tablets dominant
Ofatumumab	**138,561**	**17.562**	**8.645**	**-50,124**	**0.204**	**0.323**	**Cladribine tablets dominant**
Ocrelizumab	**140,536**	**17.617**	**8.762**	**-52,099**	**0.149**	**0.206**	**Cladribine tablets dominant**
BCMS registry (MS age of onset ≥28 years) with a 20% increase in remaining in the same EDSS score							
Cladribine tablets	87,391	18.596	9.801	--	--	--	--
Ponesimod	**101,384**	**18.299**	**9.225**	**-13,993**	**0.297**	**0.576**	**Cladribine tablets dominant**
Teriflunomide	101,607	18.211	9.029	-14,216	0.385	0.772	Cladribine tablets dominant
Diroximel fumarate	130,844	18.337	9.299	-43,452	0.259	0.502	Cladribine tablets dominant
Dimethyl fumarate	135,165	18.346	9.318	-47,774	0.250	0.483	Cladribine tablets dominant
Ofatumumab	**140,157**	**18.440**	**9.522**	**-52,766**	**0.156**	**0.279**	**Cladribine tablets dominant**
Ocrelizumab	**141,515**	**18.479**	**9.621**	**-54,123**	**0.117**	**0.180**	**Cladribine tablets dominant**
BCMS registry (MS age of onset ≥28 years) with a 30% increase in remaining in the same EDSS score							
Cladribine tablets	86,993	19.285	10.451	--	--	--	--
Ponesimod	**102,672**	**19.077**	**9.957**	**-15,679**	**0.208**	**0.494**	**Cladribine tablets dominant**

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Teriflunomide	103,402	19.015	9.783	-16,408	0.271	0.668	Cladribine tablets dominant
Diroximel fumarate	133,524	19.104	10.021	-46,531	0.181	0.430	Cladribine tablets dominant
Dimethyl fumarate	138,213	19.111	10.037	-51,220	0.175	0.414	Cladribine tablets dominant
Ofatumumab	**142,872**	**19.177**	**10.216**	**-55,879**	**0.108**	**0.235**	**Cladribine tablets dominant**
Ocrelizumab	**143,426**	**19.206**	**10.304**	**-56,433**	**0.079**	**0.146**	**Cladribine tablets dominant**
London Ontario registry							
Cladribine tablets	90,616	16.192	6.357	--	--	--	--
Teriflunomide	102,487	15.732	5.692	-11,871	0.460	0.666	Cladribine tablets dominant
Ponesimod	**102,618**	**15.838**	**5.867**	**-12,002**	**0.354**	**0.490**	**Cladribine tablets dominant**
Diroximel fumarate	130,047	15.883	5.933	-39,431	0.308	0.425	Cladribine tablets dominant
Dimethyl fumarate	133,800	15.895	5.949	-43,184	0.297	0.409	Cladribine tablets dominant
Ofatumumab	**138,742**	**16.008**	**6.130**	**-48,126**	**0.183**	**0.227**	**Cladribine tablets dominant**
Ocrelizumab	**141,108**	**16.057**	**6.221**	**-50,491**	**0.135**	**0.137**	**Cladribine tablets dominant**

BCMS: British Columbia Multiple Sclerosis; ICER: Incremental cost-effectiveness ratio; EDSS: Expanded disability status scale; LY: Life years; LYG: Life years gained; MS: Multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

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8)	**Economic model update: Treatment discontinuation probabilities**	**<u>Draft Guidance Section 3.10, pages 12-13: Use time to next treatment data from CLASSIC-MS for stopping cladribine tablets and comparator treatments or, when not applicable, the company's NMA</u>** We acknowledge the Committee's preferred assumptions that discontinuation should be applied to cladribine tablets post-year 2, despite its posology, to align more closely with what is observed in clinical practice. However, Merck do not fully agree with the Committee's preferred assumption to use discontinuation rates from CLASSIC-MS instead of the CLARITY trial for cladribine tablets for the following reasons: • Discontinuation rates from CLASSIC-MS are reported when patients were able to switch to subsequent DMT. Hence, this could contribute to uncertainties regarding the appropriateness of using this outcome in a single-line DMT model where patients do not move onto a subsequent DMT. • In terms of comparative effectiveness between cladribine tablets and other DMTs, we do not currently have similar estimates for other DMTs as the NMA captured all-cause discontinuations and not discontinuation defined as 'time to next treatment'. However, Merck are willing to accept the Committee's preferred assumption of using the CLASSIC-MS data to inform treatment discontinuation for cladribine tablets.[2] Therefore, the base case has been revised, accordingly. The median time to subsequent treatment for cladribine tablets-treated patients as reported in the CLASSIC-MS study was 12 years, which means that 50% of patients would move onto a subsequent treatment 12 years after having completed treatment with cladribine tablets. Using established modelling methods, as reported in Gidwani and Russell 2020, we converted the 12-year probability of subsequent treatment use to an annual probability of 5.6% for inclusion in the model. This 5.6% figure calculated from CLASSIC-MS was included in the model to inform treatment discontinuation for years 0-2, 2-10 and 10+ for cladribine tablets. As for all other comparator DMTs in the model, the treatment discontinuation was applied annually, and all patients moved onto BSC after discontinuation. This discontinuation rate for cladribine tablets was incorporated into the assumed Committee preferred assumptions and results are presented in comment 1) and Table 5. Cladribine tablets remained dominant over all other relevant comparators at the list price. **Exploratory scenario** **Discontinuation rates from CLARITY beyond year 2+: Merck preferred assumption** An exploratory scenario analysis was performed by using the CLARITY trial discontinuation rate applied for cladribine tablets beyond year 2+ and NMA discontinuation rates for comparators, as presented in Table 27. The results of this scenario analysis are presented in Table 28. Cladribine tablets remained dominant over all other relevant comparators at the list price. **Table 27: Discontinuation rates for the scenario analysis (applied over lifetime)** | Treatment	Scenario 1	Source | |---|---|---| | Cladribine tablets | [redacted] | CLARITY | | Dimethyl fumarate | [redacted] | Company's NMA | | Teriflunomide | [redacted] | | | Diroximel fumarate | [redacted] | | | Ocrelizumab | [redacted] | | | Ofatumumab | [redacted] | |

Ponesimod	[redacted]	

Table 28: Discontinuation rates scenario results of Merck's preferred assumption

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
Cladribine tablets	88,506	17.546	8.706	--	--	--	--
Teriflunomide	99,050	17.010	7.755	-10,544	0.536	0.950	Cladribine tablets dominant
Ponesimod	**99,567**	**17.127**	**7.984**	**-11,061**	**0.420**	**0.722**	**Cladribine tablets dominant**
Diroximel fumarate	126,806	17.176	8.070	-38,300	0.370	0.635	Cladribine tablets dominant
Dimethyl fumarate	130,582	17.188	8.092	-42,076	0.358	0.614	Cladribine tablets dominant
Ofatumumab	**136,051**	**17.313**	**8.333**	**-47,545**	**0.234**	**0.373**	**Cladribine tablets dominant**
Ocrelizumab	**138,591**	**17.367**	**8.453**	**-50,085**	**0.179**	**0.252**	**Cladribine tablets dominant**

ICER: Incremental cost-effectiveness ratio; EDSS: Expanded disability status scale; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years.
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

9) Economic model update: Mortality rates

Draft Guidance Section 3.11, pages 13-14: Mortality rates by EDSS state should be applied to the economic model. More recent data should be used to inform the mortality rates used for each EDSS state in the cost-effectiveness model. Justification and validation of mortality data should be provided to improve the generalisability of the model outputs to the NHS population

Merck acknowledge that the study by Harding et al published in 2018 provides more recent SMRs by EDSS score in a relevant population from the southeast Wales MS registry (n=2,604).[21] This source was also applied in the most recent MS TA (TA767), which further reinforces the validity of this study.[11] As such, the base case has been revised to include SMR by EDSS from Harding et al, where data is available. However, a limitation of the Harding et al study is that authors only reported SMRs for EDSS 4 and above. As such, the SMRs for EDSS 4 and below in the base case model are still based on the SMR by EDSS state modelled using the data reported in Pokorski et al. (1997) and re-analysed in Sadovnick et al. (1992).

In a more recent study which expanded upon the work of Harding et al. (2018), authors used an SMR of 1 (i.e., no excess mortality risk) for EDSS <4.0 to calculate life expectancies for patients with MS according to EDSS score.[22] However, the authors highlighted that the assumption of no excess mortality in EDSS 0-3.5 may overestimate life expectancy by neglecting the increased risk of suicide recognised in young MS patients (Cutter et al., 2015).[23] Therefore, the data from Pokorski et al. (1997) for EDSS<4.0 are the most appropriate to use in the revised base case, in light of evidence paucity.

To validate the mortality data, Merck conducted a rapid review of the literature. A more recent study reporting mortality of MS patients in Iceland (N=526), published in 2023, using the Icelandic national registry was identified. The SMR by EDSS across different studies are reported in Table 29.

Table 29: SMR by EDSS in people with MS across different studies

EDSS	Standardised mortality ratio (95% CIs)		
	Pokorski et al. 1997	Harding et al. 2018	Eliasdottir et al. 2023[24]
0	1.0	Not reported	1.1 (0.7–1.6)
1.0	1.4	Not reported	1.1(0.7–1.6)
2.0	1.6	Not reported	1.1(0.7–1.6)
3.0	1.6	Not reported	1.2 (0.6–2.3)
4.0	1.7	2.02 (0.98-3.71)	1.2 (0.6–2.3)
5.0	1.9	2.02 (0.98-3.71)	1.2 (0.6–2.3)
6.0	2.3	3.86 (2.63-5.47)	2.3 (1.7–3.0)
7.0	3.1	4.76 (2.82-7.56)	2.3 (1.7–3.0)
8.0	4.5	22.17 (18.20-26.75)	2.3 (1.7–3.0)
9.0	6.5	60.74 (47.62-76.41)	2.3 (1.7–3.0)

To note, SMRs from the Harding et al study are considerably higher than those reported by Pokorski et al and Eliasdottir et al for EDSS states ≥8.

Exploratory scenarios

To test the robustness of our results, scenario analyses using the SMRs by EDSS from Pokorski et al and Eliasdottir et al were conducted and results are presented in Table 30. Cladribine tablets remained dominant over all other relevant comparators at list price.

Table 30: SMR by EDSS scenarios results

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine tablets vs. comparator (£/QALY)
SMR by EDSS from Pokorski et al. 1997							
Cladribine Tablets	97,848	19.872	8.793	--	--	--	--
Teriflunomide	110,000	19.709	7.906	-12,152	0.163	0.887	Cladribine dominant
Ponesimod	**110,167**	**19.744**	**8.132**	**-12,319**	**0.127**	**0.661**	**Cladribine dominant**
Diroximel fumarate	137,333	19.760	8.218	-39,485	0.112	0.575	Cladribine dominant
Dimethyl fumarate	141,091	19.764	8.239	-43,243	0.108	0.554	Cladribine dominant
Ofatumumab	**146,208**	**19.803**	**8.477**	**-48,360**	**0.069**	**0.316**	**Cladribine dominant**
Ocrelizumab	**148,562**	**19.819**	**8.596**	**-50,714**	**0.052**	**0.197**	**Cladribine dominant**
SMR by EDSS from Eliasdottir et al. 2023							
Cladribine Tablets	101,549	20.871	8.910	--	--	--	--
Teriflunomide	114,198	20.781	8.009	-12,650	0.090	0.901	Cladribine dominant
Ponesimod	**114,285**	**20.800**	**8.238**	**-12,736**	**0.071**	**0.673**	**Cladribine dominant**
Diroximel fumarate	141,510	20.809	8.324	-39,961	0.062	0.586	Cladribine dominant
Dimethyl fumarate	145,283	20.811	8.346	-43,734	0.060	0.564	Cladribine dominant
Ofatumumab	**150,341**	**20.832**	**8.587**	**-48,792**	**0.039**	**0.323**	**Cladribine dominant**
Ocrelizumab	**152,643**	**20.842**	**8.707**	**-51,094**	**0.029**	**0.203**	**Cladribine dominant**

ICER: Incremental cost-effectiveness ratio; EDSS: Expanded disability status scale; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years.
Note: The bold text and blue rows present results against the high-efficacy DMTs, which the company believes are the most relevant comparators to Cladribine tablets.

10) Economic model update: Self-injection training for comparator treatments

Draft Guidance Section 3.13, pages 14-15: Exclude nurse-led self-administration costs for injectables because the analysis ought to reflect NHS clinical practice

Merck disagree with the Committee's preferred assumptions to not include nurse-led training for injectables. Merck agreed with the clinical experts that support provided by company-funded nurses may stop in the future. In addition, this service might not apply to all patients.

However, in order to align with the Committee's preference, Merck have revised the base case and have not included nurse training costs which are covered by pharmaceutical companies for injectable therapies. Specifically, nurse training costs for ofatumumab were excluded given that the other platform therapies and glatiramer acetate are not considered as relevant comparators). Please see results of the revised-base case in comment 1)), which demonstrated that the impact on the ICERs was minimal and cladribine remained dominant over all other relevant comparators at list price.

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

Draft Guidance comments form

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11)	**Economic model update: Cladribine tablets monitoring costs**	**Draft Guidance Section 3.14, page 15: Include 1 MRI scan and 2 neurology appointments in total for the 2-year period of active cladribine tablets treatment.** Based on the Committee's preference, the base case has been revised to include 1 neurologist visit per year (i.e., 1 neurology visit in Y1 and 1 neurology visit in Y2) and 1 MRI scan in the first year in line with the SmPC for cladribine tablets.[1] Please see results of the revised-base case in comment 1), which demonstrated that the impact on the ICERs was minimal.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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- Do not use abbreviations.
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Consultation on the Draft Guidance document – deadline for comments 5pm on 9 January 2025. Please submit via NICE Docs.

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Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

Draft Guidance comments form - *Supplementary information*

1 Health State Occupancy

This section presents the health state occupancy for BSC, cladribine tablets, and DMTs.

1.1 Natural History Cohort (BSC)

Figure 1: EDSS distribution – BSC (base case)

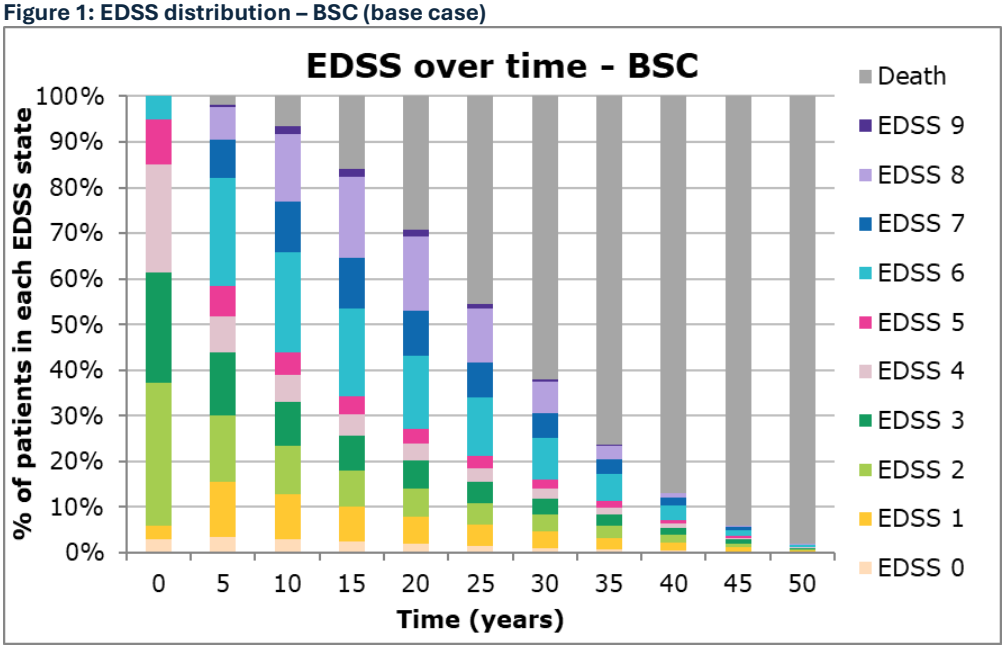

Table 1: Health state occupancy (numerical values) – BSC (base case)

Time	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Death
0	3%	3%	31%	24%	24%	10%	5%	0%	0%	0%	0%
5	3%	12%	15%	14%	8%	7%	24%	8%	7%	1%	2%
10	3%	10%	10%	10%	6%	5%	22%	11%	15%	2%	7%
15	2%	8%	8%	8%	5%	4%	19%	11%	18%	2%	16%
20	2%	6%	6%	6%	4%	3%	16%	10%	16%	2%	29%
25	1%	5%	5%	5%	3%	3%	13%	8%	12%	1%	45%
30	1%	3%	4%	4%	2%	2%	9%	5%	7%	0%	62%
35	1%	3%	3%	2%	2%	1%	6%	3%	3%	0%	76%
40	1%	2%	2%	2%	1%	1%	3%	2%	1%	0%	87%
45	0%	1%	1%	1%	0%	0%	1%	1%	0%	0%	94%
50	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	98%

1.2 Cladribine Tablets in the revised base-case model

Figure 2: EDSS distribution – Cladribine Tablets (base case)

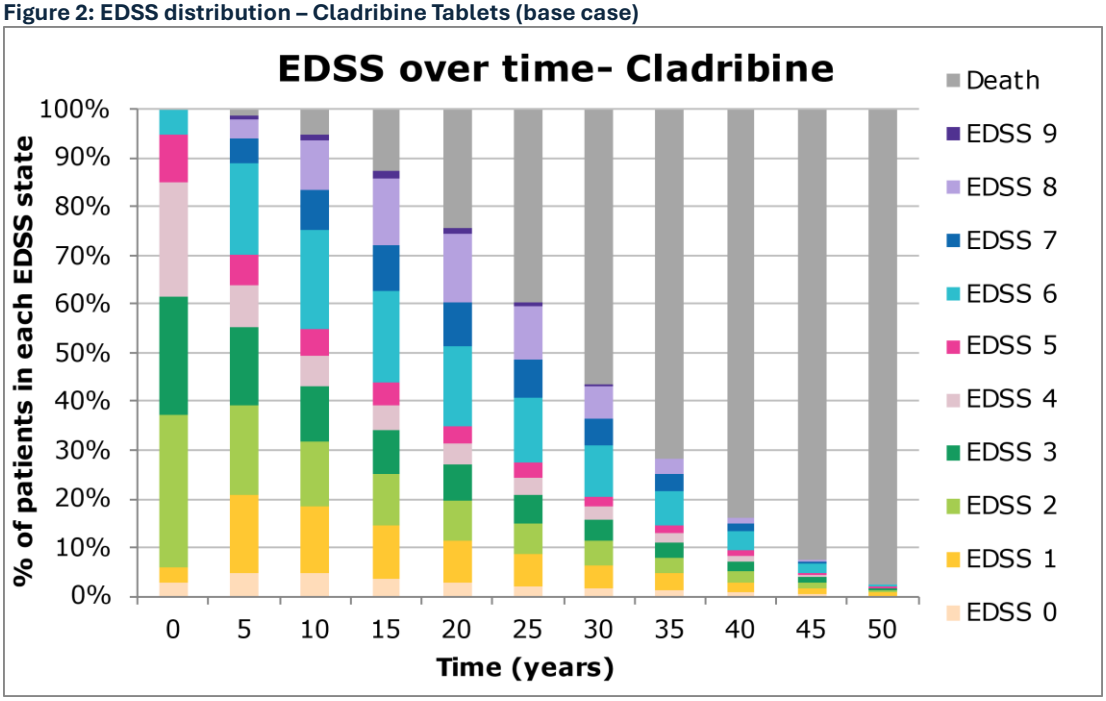

Table 2: Health state occupancy (numerical values) – Cladribine Tablets (base case)

Time	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Death
0	3%	3%	31%	24%	24%	10%	5%	0%	0%	0%	0%
5	5%	16%	19%	16%	9%	6%	19%	5%	4%	0%	1%
10	5%	14%	13%	11%	6%	5%	20%	8%	10%	1%	5%
15	4%	11%	10%	9%	5%	4%	19%	9%	14%	1%	13%
20	3%	8%	8%	7%	4%	4%	17%	9%	14%	1%	24%
25	2%	6%	6%	6%	3%	3%	14%	8%	11%	1%	40%
30	2%	5%	5%	4%	3%	2%	10%	6%	7%	0%	56%
35	1%	3%	3%	3%	2%	2%	7%	4%	3%	0%	72%
40	1%	2%	2%	2%	1%	1%	4%	2%	1%	0%	84%
45	0%	1%	1%	1%	1%	0%	2%	1%	0%	0%	93%
50	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	98%

1.3 Cladribine Tablets in the exploratory basket treatment sequencing scenario: Basket 1 - High-efficacy DMTs

Figure 3: EDSS distribution – Cladribine Tablets (Basket 1)

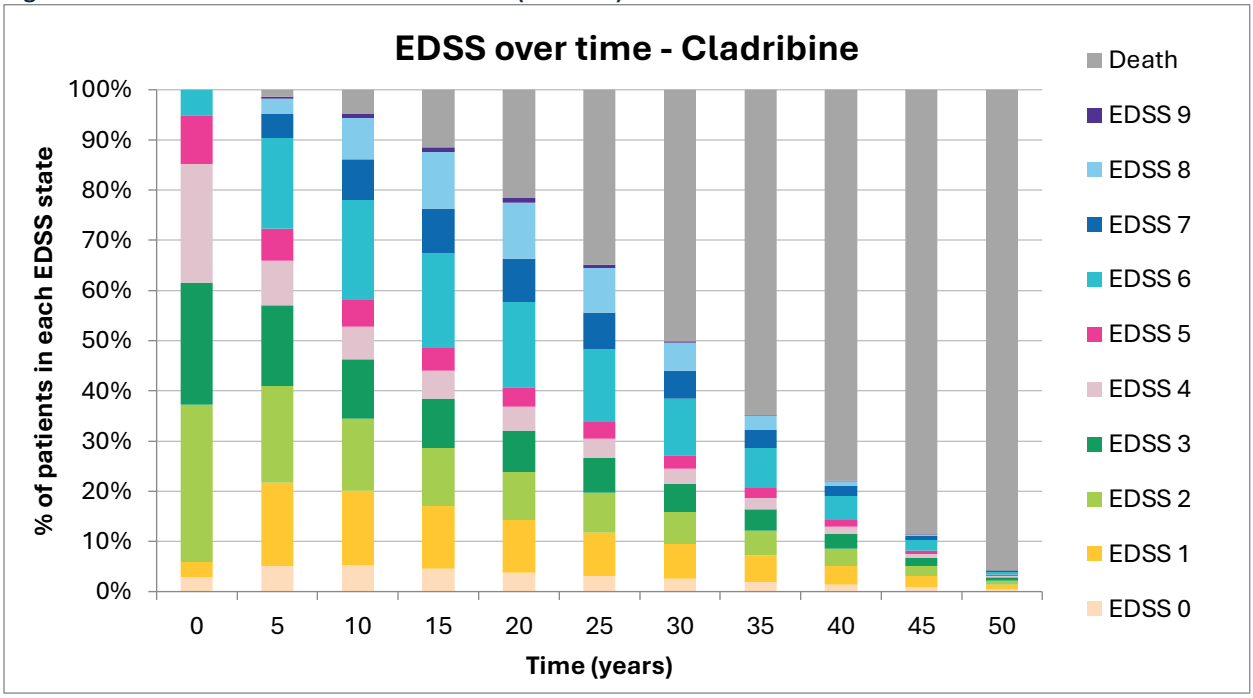

Table 3: Health state occupancy (numerical values) – Cladribine Tablets (Basket 1)

Time	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Death
0	3%	3%	31%	24%	24%	10%	5%	0%	0%	0%	0%
5	5%	17%	19%	16%	9%	6%	18%	5%	3%	0%	1%
10	5%	15%	14%	12%	7%	5%	20%	8%	8%	1%	5%
15	5%	13%	12%	10%	6%	5%	19%	9%	11%	1%	11%
20	4%	11%	10%	8%	5%	4%	17%	8%	11%	1%	21%
25	3%	9%	8%	7%	4%	3%	14%	7%	9%	1%	34%
30	3%	7%	7%	6%	3%	3%	11%	5%	5%	0%	49%
35	2%	6%	5%	4%	2%	2%	8%	4%	3%	0%	64%
40	2%	4%	4%	3%	2%	1%	5%	2%	1%	0%	77%
45	1%	2%	2%	2%	1%	1%	2%	1%	0%	0%	88%
50	0%	1%	1%	1%	0%	0%	1%	0%	0%	0%	95%

1.4 Cladribine Tablets in the exploratory basket treatment sequencing scenario: Basket 2 – All relevant DMTs

Figure 4: EDSS distribution – Cladribine Tablets (Basket 2)

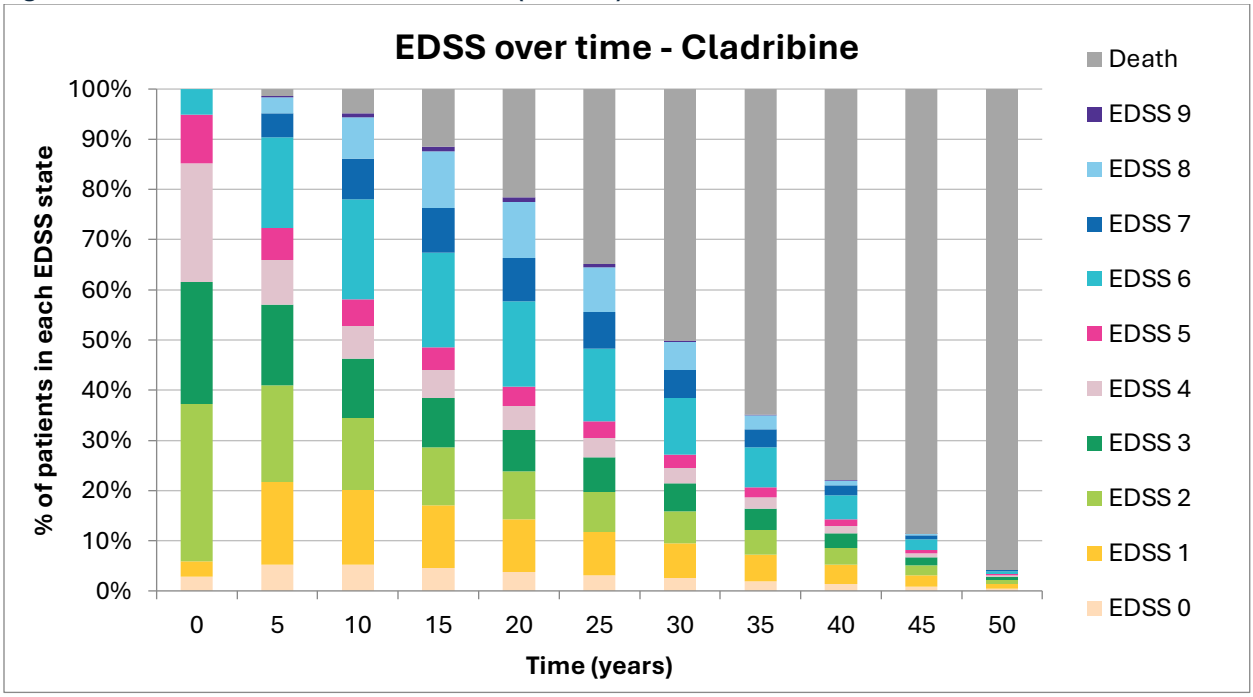

Table 4: Health state occupancy (numerical values) – Cladribine Tablets (Basket 2)

Time	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Death
0	3%	3%	31%	24%	24%	10%	5%	0%	0%	0%	0%
5	5%	17%	19%	16%	9%	6%	18%	5%	3%	0%	1%
10	5%	15%	14%	12%	7%	5%	20%	8%	8%	1%	5%
15	5%	13%	12%	10%	5%	5%	19%	9%	11%	1%	11%
20	4%	10%	10%	8%	5%	4%	17%	9%	11%	1%	22%
25	3%	9%	8%	7%	4%	3%	14%	7%	9%	1%	35%
30	3%	7%	6%	6%	3%	3%	11%	6%	6%	0%	50%
35	2%	5%	5%	4%	2%	2%	8%	4%	3%	0%	65%
40	1%	4%	3%	3%	2%	1%	5%	2%	1%	0%	78%
45	1%	2%	2%	2%	1%	1%	2%	1%	0%	0%	89%
50	0%	1%	1%	1%	0%	0%	1%	0%	0%	0%	96%

2 Mortality

This section details the mortality rates included in the CEM and the deaths by EDSS for BSC, cladribine tablets, and all DMTs.

2.1 Deaths by EDSS

Given that the cost-effectiveness model does not track individual patients who have died and only considers cumulative totals after each model cycle, it is not possible to calculate deaths by EDSS using the current model engines. Therefore, additional structural changes were implemented in the model engines for BSC, cladribine tablets, and DMTs to calculate cumulative death by EDSS at 5-years cycles. The estimated results were validated against the total cumulative death by 5-years cycles reported in the model.

2.1.1 Natural History Cohort (BSC)

Table 5: Cumulative deaths by EDSS at 5-year cycles – BSC (base case)

Time (yrs)	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Total Death
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.0%
5	0.02%	0.09%	0.22%	0.20%	0.17%	0.11%	0.41%	0.12%	0.33%	0.08%	1.7%
10	0.05%	0.24%	0.40%	0.38%	0.31%	0.22%	1.25%	0.56%	2.53%	0.69%	6.6%
15	0.09%	0.42%	0.62%	0.58%	0.46%	0.35%	2.39%	1.33%	7.61%	2.08%	15.9%
20	0.14%	0.62%	0.86%	0.82%	0.64%	0.51%	3.83%	2.38%	15.39%	4.02%	29.2%
25	0.19%	0.87%	1.15%	1.10%	0.86%	0.70%	5.63%	3.73%	25.07%	6.11%	45.4%
30	0.26%	1.17%	1.50%	1.45%	1.12%	0.93%	7.79%	5.31%	34.76%	7.80%	62.1%
35	0.33%	1.51%	1.91%	1.84%	1.43%	1.20%	10.13%	6.93%	42.17%	8.84%	76.3%
40	0.42%	1.90%	2.37%	2.28%	1.75%	1.47%	12.43%	8.36%	46.57%	9.34%	86.9%
45	0.52%	2.33%	2.85%	2.73%	2.07%	1.74%	14.42%	9.45%	48.49%	9.53%	94.1%
50	0.61%	2.70%	3.26%	3.09%	2.30%	1.93%	15.61%	10.00%	49.05%	9.58%	98.1%

2.1.2 Cladribine Tablets

Table 6: Cumulative deaths by EDSS at 5-year cycles – Cladribine Tablets (base case)

Time (yrs)	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	Total Death
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.0%
5	0.02%	0.10%	0.25%	0.21%	0.19%	0.10%	0.31%	0.07%	0.19%	0.05%	1.5%
10	0.07%	0.30%	0.49%	0.42%	0.33%	0.21%	1.04%	0.37%	1.58%	0.43%	5.2%
15	0.13%	0.56%	0.76%	0.66%	0.50%	0.35%	2.13%	0.98%	5.30%	1.43%	12.8%
20	0.20%	0.85%	1.08%	0.95%	0.70%	0.53%	3.57%	1.91%	11.61%	3.00%	24.4%
25	0.28%	1.19%	1.46%	1.30%	0.96%	0.74%	5.45%	3.19%	20.17%	4.84%	39.6%
30	0.38%	1.60%	1.92%	1.73%	1.27%	1.01%	7.80%	4.78%	29.37%	6.46%	56.3%
35	0.49%	2.07%	2.46%	2.22%	1.64%	1.33%	10.43%	6.49%	36.93%	7.52%	71.6%
40	0.61%	2.60%	3.05%	2.77%	2.03%	1.66%	13.12%	8.09%	41.72%	8.08%	83.7%
45	0.75%	3.17%	3.69%	3.35%	2.43%	1.99%	15.51%	9.36%	43.95%	8.30%	92.5%
50	0.88%	3.67%	4.22%	3.82%	2.73%	2.24%	16.99%	10.03%	44.62%	8.36%	97.6%

NICE National Institute for Health and Care Excellence

Cladribine for treating relapsing multiple sclerosis [ID6263]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 9 January 2025. Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MS Society

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Cladribine for treating relapsing multiple sclerosis [ID6263]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Merck/Merck Serono** May 2024 Grant towards Helpline Specialist Nurses service £20,000 **Roche** Feb 2024 Sponsorship of MS Frontiers £10,000 May 2024 Grant towards the MS Helpline £35,000 **Sanofi Genzyme** June 2024 Sponsorship of MS Frontiers conference £10,000
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……
1	We are disappointed by the initial decision not to recommend cladribine for use in people with active relapsing remitting MS (RRMS). Recommending cladribine for this group would increase patient choice for people with active RRMS, and there are groups that could particularly benefit from it being available.

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	Our evidence from speaking with patients mirrors the MS Trust's, as outlined in their submission. Within the currently available DMT treatment range, oral options are still limited. The wider population of people with active relapsing MS would benefit from a further safe and highly effective oral treatment. People with MS tell us that the practicality and convenience of DMTs that can be self-administered, as opposed to requiring frequent visits to the hospital, is a significant advantage, particularly for those of working age. Because cladribine is taken in two short courses over two years it allows people to be treated with minimal disruption to their lives. As one person on cladribine put it, *'I love that I can completely forget about taking any medication for most of the year. It has made me feel much more relaxed about my treatment. And the fact it's a stronger medication helps me feel more in control and positive about my future with MS.'*
2	We have identified that not recommending cladribine could have a different impact on people protected by the equality legislation than on the wider population, in particular on women considering pregnancy, marginalised and minoritised racial and ethnic groups with lower trust or poorer access to health services, and on disabled people, including those with a learning disability or who are neurodiverse, who may need a wider option of treatments to facilitate equitable health outcomes. We expand on these points for each protected group in comments 3, 4 and 5.
3	A decision not to recommend cladribine may have a disproportionate impact on younger people, particularly women, who are more likely to consider family planning and pregnancy in their treatment decisions. Cladribine offers fewer restrictions on family planning compared to some other DMTs, as it involves treatment in years one and two with no further treatment in years three and four. Both women and men can safely consider trying for a family after the six-month washout period following treatment. This means that women who have completed two courses of cladribine may benefit from the effects of DMT treatment during pregnancy and breastfeeding without any exposure to disease modifying drugs. Alternative options for safe pregnancy and breastfeeding are taking less effective DMTs or pausing all treatment, which both risk relapses and irreversible disability progression.
4	A decision not to recommend cladribine may have a disproportionate impact on marginalised groups and minoritised racial and ethnic groups. As cladribine has low administration and monitoring burden, and can be self-administered, recommending cladribine for use in a wider population could particularly benefit people who have poor access to health services, low trust in hospital administered treatment, or reluctance to spend periods of time in hospital because of risk of losing precarious employment or due to additional caring responsibilities. In particular, cladribine may benefit several health inclusion groups, including homeless people, Gypsy, Roma and Traveller communities and Black and Minority Ethnic communities. It would also benefit those who cannot travel frequently to hospital due to cost or work commitments, as well as those who live in more rural or isolated communities far away from major centres for treatment.
5	A decision not to recommend cladribine may have a disproportionate impact on disabled people, including those with a learning disability or those who are neurodiverse, and who may find hospital treatment stressful or injections and infusions particularly difficult. As cladribine requires fewer hospital visits and can be taken orally, it offers an additional, effective treatment option for this protected population group, who we know have poorer health outcomes than the general population and find access to health services and treatment inequitable.
6	

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Cladribine for treating relapsing multiple sclerosis [ID6263]

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	We have no comments on the clinical and cost effectiveness evidence but would like to highlight that cladribine is one of three DMTs for MS added to the World Health Organization (WHO) Essential Medicine List in 2023. This followed a submission from MS International Federation (MSIF). WHO selects essential medicines based on disease prevalence and public health relevance, cost-effectiveness, and evidence of efficacy and safety. According to WHO, essential medicines should always be available in functioning health systems.[1] [1] WHO, 2023 (https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.02)

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Multiple Sclerosis Trust

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Funding received from August 2023 to August 2024. Biogen £18640 conference sponsor Merck £32300 conference platinum sponsor Merck £1163.45 funding for honorarium Novartis £32548.33 conference platinum sponsor Novartis £50000 specialist nurse funding Roche £33814.17 conference platinum sponsor Roche £30000 education bursaries Roche £1312.50 advisory board and expenses Sanofi Genzyme £32000 conference sponsor Teva £4370 conference sponsor Sandoz £32129.98 platinum conference sponsor Janssen £32140 platinum conference sponsor
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The report outlines several issues with the clinical and cost effectiveness evidence that we agree with. We look forward to seeing a more realistic analysis that reflects clinical practice more closely.
2	The distinction between active and highly active RRMS is somewhat irrelevant to the person living with MS. Basically, inflammatory activity is either controlled or it isn't. Neurologists need to be able to try different disease modifying treatments to find a solution that works for the person living with

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	MS. When breakthrough activity is seen either radiologically or in a clinical relapse, the treatment would be reviewed, no matter how active your MS supposedly is. And how do you decide on MS activity level in a person who has been treated with disease modifying drugs all that time? If you're lucky enough to get the right treatment first, you can potentially avoid many relapses, any of which could be the one to steal your sight, your mobility, your continence, marriage or career. If you're not lucky enough to get a good fit first, you will have to 'fail' on that one and then go through a switch to find something else, accumulating relapse damage as you go. It's a race to preserve nerve function. There is evidence that different MS prescribing centres have preferred options for reasons that are not evidence-based. And let's not forget that the UK has fewer neurologists per head than anywhere in Europe and prescribes effective DMDs at a lower level overall. Until we know why some people respond well to some DMDs but not others, there is no benefit in restricting access. Neurologists need to be free to work with patients to find the best treatment fit to control relapsing MS, enabling people to work and live well for as long as possible, and to minimise the accumulation of disability and reduce further health and social care needs. (Cameron et al., 2019. Factors influencing multiple sclerosis disease-modifying treatment prescribing decisions in the UK, MS and Related Disorders, Volume 27, pages 378-382)
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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NICE TA 6263 – Cladribine for treating relapsing remitting multiple sclerosis – ABN response

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

We note that the negative TA is based primarily on uncertainties around the cost effectiveness data. We would like to highlight that the cost effectiveness uncertainty was primarily based around how discontinuations were modelled, and hope that with improved modelling data provided this obstacle can be overcome. This is an important consideration - cladribine is given over a short time with efficacy extending beyond the treatment period, introducing complexity into the modelling of discontinuations and switching. We also noted that the models did not account for the order in which treatments are given, a further limitation in how the available evidence was interpreted.

• Are the recommendations sound and a suitable basis for guidance to the NHS?

In our view, the potential positive impact of oral cladribine on service delivery within the NHS has not been considered. The full impact of infusion costs, staffing requirements to facilitate scheduling of day case admissions, days of work lost for patients and carers, and long term cumulative risks associated with other MS treatments have not been fully included in the costing comparator populations.

• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

We disagree with the statement that the potential equality issues were based on the disease, multiple sclerosis, rather than the technology. Inequitable access to the technology within the disease population (who are, by nature of the disease and/or associated demographic characteristics, more likely to have protected characteristics) is an equality issue. In the context of the proposed negative decision, women with MS considering pregnancy continue to have inequitable access to highly effective treatments. Oral cladribine may be a useful alternative treatment for ageing people with MS who often bear a burden of multiple comorbidities and polypharmacy and who are more exposed to the adverse effects of continuous immunosuppressive therapy and risk of continuous drug interactions. The negative TA will also adversely impact people with MS who are homeless or vulnerable, and hence unable to take daily long term treatments; protected characteristics are over-represented in this group. This TA offers an opportunity to overcome inequity, which is specific to the drug being evaluated, and this has been ignored.

Further, we disagree with the response to statement 5 in the EIA. The preliminary negative recommendation will have an adverse impact on people with disabilities who are unable to travel to neuroscience centres on a regular basis; as they remain unable to access more than one effective treatment first line (the only treatment available to

them would be ofatumumab, which requires self-injection and may not be suitable for some). Those with lesser disability who are able to travel will be able to access a range of effective treatments (ublituximab, ocrelizumab, ofatumumab). This negative TA therefore has a direct effect on treatment access for more disabled people with MS.

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Cladribine for treating relapsing multiple sclerosis [ID6263]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Biogen Idec Ltd

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Should the committee have a preference to model treatment sequencing, consideration should be given to the ongoing technology appraisal of natalizumab in HARRMS and the economic model developed by Bristol EAG (ID6369) to ensure consistency in decision making. This appraisal could also be used to validate the BCMS natural history dataset as it includes analyses of the UK MS Registry in a population with RRMS..

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Cladribine for treating relapsing multiple sclerosis [ID6263]

Draft guidance comments form

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2	Biogen agree with the committee's preferred assumptions to use of EDSS specific mortality rates which is consistent with prior RRMS technology appraisals.
3	Biogen are concerned that use of health state costs from Hawton et al, in the base case cost-effectiveness analysis by the manufacturer significantly underestimate the cost of managing RRMS. Hawton et al appears to have been chosen based on being a recent study despite acknowledgment that this study omits a range of medical costs including inpatient and outpatient services (CS document B p 140). This selection is also inconsistent with recent and ongoing MS appraisals. Little commentary is provided by the EAG to understand these differences (EAG report p122).
4	
5	
6	

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Clinical Expert

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	I have received honoraria for participation in educational activities and/or consulting from Biogen, Merck, Neuraxpharm, Novartis, Roche, Sanofi, Sandoz and Viatris
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Wallace Brownlee

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The clinical effectiveness data is reasonable. It is therefore unclear why the committee concluded there was uncertainty over the clinical effectiveness stated in 3.18 in the conclusion. The uncertainty appears to be largely related to the cost effectiveness and challenges over how to model a medicine that is given as two short courses, rather than on a continuous basis and semantics over whether it is possible to “discontinue” a medicine of this nature. It seems unsatisfactory that this treatment with so many unique attributes (as

Cladribine for treating relapsing multiple sclerosis [ID6263]

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	noted by the patient representative, Professor Dobson and myself) with much wider benefits to the NHS might not be deemed cost-effective because of a failure of statistical modelling. I would urge the committee to revisit this and use the CLASSIC-MS data as the basis for estimating treatment discontinuation for cladribine given this is the most robust long-term estimate.
2	I am concerned about the interpretation of the clinical experts comments during the meeting around the natural history data and summary presented in section 3.9. The data from the British Columbia Multiple Sclerosis (BCMS) registry was not presented during the committee meeting and it is unreasonable to expect Professor Dobson or myself to comment on this in detail. As the clinical experts noted, in recent years, treatment and care for people with MS has improved prognosis, so progression to higher EDSS states happens less frequently. The BCMS registry is an older dataset, however, if the purpose of the natural history reference model is to reflect a population that is untreated, the BCMS registry data is an appropriate source. The UK MS register is not an appropriate source of this information since most patients now receive disease-modifying therapy, and those who don't take treatment may have mild disease, or their illness has progressed to the extent that treatment is not needed. Furthermore, my understanding of the NICE process historically is that all approved MS medicines have used the BCMS registry as a natural history comparator. If NICE want to introduce a new way to evaluate MS medicines this should be done in a prospective way, and not part of the way through evaluation of this drug.
3	Section 3.4 the most relevant comparators are ocrelizumab, ofatumumab and ponesimod as stated in this section. I would not categorise dimethyl fumarate and diroximel fumarate as relevant comparators, as they are now seldom started in treatment naïve patients because there are much more effective and better tolerated medicined available.
4	I would like to reiterate my disagreement with the committee's conclusion in section 3.10 about treatment waning. Treatment response in MS is binary, not ordinal in nature. If a patient has a relapse or progression on a treatment we would usually switch to another therapy within a treatment target of no evidence of disease activity.
4	I am concerned that the recommendations downplay the potential benefits of cladribine treatment within the wider NHS context. Cladribine has the lowest burden of administration and monitoring of any of the available high efficacy MS treatments. The most recent audit of UK MS services in 2021 found that no service is currently able to cope well with their current workload, and that caseloads are increasing by 10%/year at a time where there is no funding available to expand services. Furthermore MS drugs represent a huge financial burden to the wider NHS. Cladribine tablets, a small molecule drug, will become generic in the next few years and more widespread use of the drug in an active RRMS population could lead to enormous cost savings for the NHS.
5	Section 3.17 should highlight that access to cladribine for a broader active MS population would help address equality issues associated with MS. Restricting access to cladribine, which is a high efficacy DMT, with durable benefits and high persistence rates, from this broader active RRMS population could disproportionally negatively impact young women with MS considering pregnancy, people with MS who want minimum disruption in their everyday lives and work, and people with MS who are homeless or vulnerable or live far from a specialist centre – all of whom would benefit from cladribine give it is a short-course, effective, low burden treatment.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	[redacted]
Comments on the DG:	

Has all of the relevant evidence been taken into account?

Diagnostic criteria and understanding of MS have changed significantly over the years, and the sub classifications of RRMS used in clinical trials (and therefore commissioning) are not necessarily reflective of current clinical experience in practice. Therefore we support the company proposal of expanding the recommendations of using cladribine also for RRMS and not only highly active RRMS.

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

Looking at the evidence presented, the side effect profile (which seems mild compared to other DMT), the advantage of being able to have the benefit without exposure to the drug for 2 more years, and the convenience of a tablet formulation, we are in favour of the additional indication.

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

We think all evidence have been taken into account and interpretations are reasonable.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

"Cladribine has a low monitoring and administration burden making it the ideal choice for some underserved population groups whose lifestyle make other therapies less than ideal due to administration or monitoring burden (eg homeless, those with high travel needs). The reduced burden on MS teams and supporting services (eg phlebotomoty, labortatory services, homecare pharmacy

and OPD pharmacy) to deliver ongoing therapies and monitoring is a benefit to the limited NHS resources that are caring for an increased patient population. Olga Tanda on behalf of UKCPA Neuroscience committee"

Name	[redacted]
Other role	[redacted]
Organisation	[redacted]
Comments on the DG:	

Comment on section 1.1 ‘relapsing’

"Relapsing-remitting is consistent with other TAs.

I also think the title of the TA needs amending to clearly distinguish it from the other cladribine TA."

Comment on section 1.1 ‘active disease’

"There is no clear definition of active/highly active in clinical practice. By saying this is not recommended in active will people immediately know it's still an option in highly active?

I also think 'active' implies it can be used anywhere in the treatment pathway. For example, see ponesimod, which is has similar rec wording and is positioned throughout the NHS treatment pathway: Ponesimod is recommended for treating relapsing–remitting multiple sclerosis with active disease defined by clinical or imaging features in adults.
So this contradicts our highly active TA"

Comment on section 1.2 ‘This does not include everyone it is licensed for.’

"See comment above. I think this does include everyone it is licensed for:

MAVENCLAD is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease as defined by clinical or imaging features."

Cladribine tablets for treating relapsing multiple sclerosis [ID6263]

External Assessment Group (EAG) Comments on Company's Responses to NICE Draft Guidance

Comparators for Cladribine

The EAG agrees with the company that the most appropriate comparators for cladribine are the high-efficacy disease-modifying therapies (DMTs), including ofatumumab, ocrelizumab, and ponesimod. These align with the treatment pathways for patients requiring high-efficacy options. However, the EAG also emphasises the importance of considering other DMTs, such as dimethyl fumarate and diroximel fumarate, as comparators. Including these treatments broadens choice, ensuring accessibility for patients whose clinical needs or preferences may preclude high-efficacy DMTs. These additional comparators are particularly relevant for patients who prioritize oral administration or have contraindications to other therapies.

Company NMAs

The EAG agrees with the company that the submitted network meta-analyses (NMAs) for annualized relapse rates (ARR), 6-month confirmed disability progression (CDP), and all-cause discontinuation provide an appropriate basis for decision-making. However, the EAG notes that there is some uncertainty surrounding the probabilities of treatment discontinuation generated by the company's NMAs. As detailed in the EAG report (Section 3.5.1.1), the EAG was unable to replicate the probabilities of treatment discontinuation from the company's NMA, although the hazard ratios were successfully replicated. This discrepancy suggests potential methodological or data-related issues within the company's analyses that could affect the reliability of the discontinuation estimates.

Company's Model Structure

The EAG concurs with the Committee's assessment that the model demonstrates considerable structural uncertainty, primarily due to the lack of treatment switching or sequencing. This represents a significant limitation, as treatment switching is a common feature of the care pathways for patients with multiple sclerosis (MS). The company's model assumes that patients who discontinue disease-modifying therapies (DMTs) transition directly to best supportive care (BSC), a scenario that does not align with NHS clinical practice. In reality, patients who discontinue a DMT typically switch to an alternative DMT rather than transitioning to BSC.

This limitation is particularly concerning given cladribine's unique posology, where treatment is administered only during the first two years, yet the model assumes lifetime benefits. By failing to account for treatment sequencing, the model likely underestimates the probability of discontinuation for cladribine, which unfairly favours it compared to other DMTs. Although the company conducted exploratory analyses using a fixed treatment "basket," this approach does not fully resolve the structural uncertainties inherent in the single-line model.

The EAG maintains that a more comprehensive approach to modelling treatment sequencing and switching would provide a better reflection of real-world clinical practice and address these structural uncertainties in cost-effectiveness analyses. However, the EAG also acknowledges the company's view that modelling treatment switching in the context of this appraisal could overly complicate things and potentially introduce further uncertainties. This is particularly relevant given that the scope of this appraisal focuses on individual DMTs rather than sequences of DMTs, the large number of possible DMTs that could be included in such a model, and the lack of clear guidance on treatment switching in MS. Therefore, while recognising the limitations of the current model, the EAG agrees that attempting to incorporate sequence of treatments at this stage may not be feasible or practical.

Treatment Discontinuation

The EAG supports the Committee's preference to base the probability of treatment discontinuation for cladribine on CLASSIC-MS data. Data provides information on long-term use of cladribine with a median time on treatment of 12 years. However, to ensure consistency across treatments, the EAG recommends applying hazard ratios for comparator DMTs (from the NMA) to the discontinuation probabilities for cladribine derived from CLASSIC-MS. This approach ensures internal consistency within the economic model by preserving the within-trial randomised comparisons generated by the NMA while addressing uncertainties related to treatment discontinuation rates. This method allows the model to appropriately reflect differences in discontinuation rates while maintaining alignment with the Committee's preference for data sources. Table 1 presents the annual probability of treatment discontinuation, calculated by applying the hazard ratios for comparator DMTs (relative to cladribine) to the annual probability of treatment discontinuation for cladribine, as derived from the CLASSIC-MS data.

Table 1: Probability of treatment discontinuation generated by applying hazard ratios from the CS NMA to probability of treatment discontinuation for cladribine generated from CLASSIC-MS data

Treatment versus Cladribine	Median HR from CS NMA	Annual probability of treatment discontinuation
Cladribine tablets	[redacted]	0.056
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer Acetate	[redacted]	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]
IFNβ-1b (Betaferon/Extavia)	[redacted]	[redacted]
IFNβ-1a (Peginterferon beta-1a)	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]

Ponesimod	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]

IFNβ-1a (Peginterferon beta-1a) assume same probability as IFNβ-1a (Rebif 22µg)

The results of applying the probabilities in Table 1 to the company's revised base case, which incorporates the Committee's preferred assumptions where possible, are presented in Table 2. Cladribine dominated the high-efficacy DMTs except ocrelizumab. For ocrelizumab, cladribine was less expensive, with incremental costs of [redacted], but also produced fewer health benefits, with incremental QALYs of -[redacted]. This resulted in an ICER of [redacted] per QALY lost when compared with ocrelizumab. This ICER lies in the South-West quadrant when plotted on the cost-effectiveness plane.

Table 2: ICERs generated from applying EAG's estimates of probability of treatment discontinuation to the company's revised base-case that takes into account committees preferred assumptions

Intervention	Total Cost	Total QALY	Incremental cost	Incremental QALY	ICER vs. Cladribine (QALY)
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Glatiramer Acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b (Betaferon/Extavia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Peginterferon beta-1a)	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant

Other Issues Raised in the DG

The EAG reviewed the updates made to the economic model to reflect the Committee's preferences and verified their accuracy. Specifically, the EAG confirms that the model was updated to include (i) mortality rates by EDSS state based on more recent data (Harding 2018 study), (ii) the removal of costs for injection device training provided by company-sponsored nurses for injectable DMTs, (iii) monitoring costs for cladribine tablets, including one MRI scan and two neurology appointments over the two-year active treatment period, and (iv) the exclusion of beta interferons and glatiramer acetate as non-relevant comparators.

Title: ID6263 Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis- additional analyses

Produced by	Warwick Evidence
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Date completed	30/01/2025

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Declared competing interests of the authors
None

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IG: led the clinical section.
FA: led the cost-effectiveness section and the statistical analysis.
AT: senior clinical reviewer and led the ITC.
RC: Information Specialist conducted the searches and referencing.
XA: supported the clinical section and review of this report.
LAK: led this appraisal.

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1 Introduction

Below is commentary, critique and additional analyses the EAG undertook on the evidence and revised economic model submitted by the Merck Serono in response to the draft guidance (DG) on cladribine. The company's revisions addressed issues identified in the DG and tested the robustness of their revised base-case against alternative assumptions and data sources. The EAG's assessment encompasses a critique of key updates, including the "basket" treatment sequencing approach and the application of EDSS variations by mortality. Additionally, the EAG has tested the company's scenario analyses, incorporating further scenarios based on the EAG's revised base-case assumptions. Due to time constraints, external data sources to validate the natural history data were not identified; however, the EAG has provided commentary on this aspect. Furthermore, the EAG evaluated treatment discontinuation methods, employing alternative approaches to derive probabilities for competitor DMTs and conducting scenario analyses using probabilities from the company's network meta-analysis. A confidential appendix utilising cPAS prices for cladribine and competitor DMTs is provided as a separate document.

2 Model structure and treatment switching sequencing

To address the committee’s concerns about the inability of the model structure to reflect treatment switching, which is common in clinical practice for patients with MS, the company argued that explicitly modelling treatment switching or sequencing in the current appraisal of cladribine would introduce additional uncertainty into the cost-effectiveness analysis without resolving the committee’s concerns. Instead, the company proposed two scenarios where a “basket” of treatments is used. In this approach, patients who discontinue a DMT transition to a basket of other treatments instead of moving to Best Supportive Care (BSC).

The basket approach calculates the treatment effect on ARR and 6-month CDP and the acquisition cost of the basket DMTs weighted by their respective market shares. Two baskets were defined in the company’s revisions:

Basket 1 includes only the high-efficacy DMTs: Ocrelizumab, Ofatumumab, and Ponesimod.

Basket 2 includes all DMTs considered by the AC1 Committee as relevant comparators to cladribine in this appraisal: Ocrelizumab, Ofatumumab, Ponesimod, Teriflunomide, Dimethyl Fumarate (DMF), and Diroximel Fumarate (DRF).
Of the two baskets, the EAG clinical advisors indicated that, in contemporary practice across UK multiple sclerosis (MS) centres, transitioning to Basket 1 after treatment discontinuation aligns more with practice and is to be preferred, as dimethyl fumarate (DMF), teriflunomide, and diroximel fumarate (DRF) are used less frequently.
Further EAG clinical advice suggests that RRMS patients who experience a relapse or new MRI activity after completing full treatment with cladribine (i.e., two courses) would typically transition to a high-efficacy DMT, such as anti-CD20 therapies or natalizumab. Patients where cladribine is used as a downstream DMT (i.e., not in treatment-naïve patients), hematopoietic stem cell transplantation (HSCT) may be considered as the next step.
Therefore, the EAG concludes that while the basket approach does not fully replicate treatment sequencing, it can be regarded as an approximation that addresses some of the committee's concerns about the model's lack of realism. The EAG has identified several limitations of the basket approach:

1. **Lack of side-effect consideration**: The model does not account for the side-effect profiles of the competitor DMTs in the basket, which can significantly influence tolerability, switching behaviour, and the cost of managing side effects in real-world practice.
2. **Asymmetry in basket application:** The baskets are applied asymmetrically. For patients on cladribine, discontinuation leads to transition into the basket of competitor DMTs. However, there is no reciprocal scenario where patients on competitor DMTs transition to a basket containing cladribine. This asymmetry creates a scenario where patients on competitor DMTs may theoretically remain on the same treatment after moving to the basket, which is unrealistic in practice.
3. **Assumption on treatment waning**: The assumption that treatment waning for the second-line (basket) treatments is identical to first-line treatments is problematic. This could misrepresent long-term outcomes and cost-effectiveness, as treatment waning is likely to vary based on treatment type, duration, and line of therapy.

Despite these limitations, the EAG believes that the basket approach is a closer representation of clinical practice compared to the assumption that patients transition directly to BSC upon discontinuation. The EAG recognises the potential value of conducting additional sensitivity analyses to assess whether the absence of a reciprocal basket containing cladribine introduces bias against cladribine in the model. However, due to time constraints, the EAG was unable to implement these analyses. Such evaluations could determine whether adjustments are necessary to ensure a more balanced application of the basket approach.

3 Pokorski (1997) for modelling mortality in EDSS 0–3 states and Harding (2018) for EDSS 4-9.

The company's revised base-case sourced data from Pokorski et al. 1997 to model mortality in EDSS 0–3 states and Harding (2018) for EDSS state 4-9. Pokorski provides a widely used historical dataset that offers a consistent foundation for modelling mortality rates in RRMS population in the absence of more contemporary data. Its inclusion ensures continuity with previous models and avoids abrupt methodological changes between lower and higher EDSS states. However, there are significant drawbacks to relying on this dataset. Being over 25 years old, Pokorski's data may not reflect substantial advancements in MS treatment and care since its publication. These improvements, including the widespread use of DMTs noted by clinicians during AC1, have led to better health outcomes and reduced mortality, particularly in earlier stages of the disease. Furthermore, the static mortality rates from Pokorski fail to account for evolving survival trends over time, especially among individuals in lower EDSS states who are less likely to experience severe disability or MS-related mortality.

In contrast, Harding et al. 2018 provides more recent mortality data, and may therefore be seen to better aligns with modern MS care practices, though it only covers EDSS states 4 and above. While Harding captures the increased mortality risks associated with severe disability and reflects current treatment practices, its lack of data for EDSS 0–3 necessitates continued reliance on Pokorski for these states, which introduces potential inconsistencies in the model.

Considering the strengths and weaknesses of both datasets, the EAG agrees with the committee's preference for mortality rates informed by Harding, given that it is based on a more recent cohort of UK RRMS patients and is likely to better reflect the

mortality experience of the NHS population. However, the absence of Harding data for EDSS 0–3 creates uncertainties when combined with Pokorski data, due to the lack of continuity and the potential for inconsistencies in the model. While these uncertainties are acknowledged, the EAG is unable to determine their impact on the overall cost-effectiveness of cladribine.

4 EAG Comment on the updated base case

The EAG has concerns about the updated base case, particularly regarding treatment sequencing and switching, as well as the handling of treatment discontinuation probabilities for cladribine. Additionally, the EAG notes uncertainties arising from the combination of mortality data from Pokorski and Harding. It was unable to quantify the impact on these uncertainties on the cost-effectiveness of cladribine and recognises the lack of an alternative mortality data source that covers all EDSS states.

4.1 Treatment Sequencing and Switching

The EAG is concerned about the company's inability to fully incorporate treatment sequencing and switching into the model. Despite the limitations of the proposed approach, the EAG considers moving patients to a basket of treatments scenario, rather than switching to best supportive care (BSC), to be a more accurate reflection of NHS patient experience. As a result, the EAG has revised its base case to include the company's scenario analysis that incorporates Basket 1 of the treatment sequencing model. While this approach is not without its challenges and uncertainties, the EAG thinks it better aligns with real-world treatment pathways in the NHS.

4.2 Treatment Discontinuation Probabilities

The EAG also raises concerns about the company's approach to estimating the probability of treatment discontinuation for cladribine. In the original submission, the company's network meta-analysis (NMA) estimated the probability of treatment discontinuation for cladribine with a mean value of [redacted] (median [redacted]). However, the company chose not to use this NMA-derived estimate and instead used a lower value of 4.85%, derived from the pooled probabilities in the CLARITY study. The company justified this decision by arguing that using the NMA estimate would

overstate discontinuation for cladribine because tolerability events are assumed to occur only between the first and second treatment courses.
The EAG does not accept this rationale. Since cladribine is administered over a two-year period, using probabilities derived from a mean placebo anchor probability over 2–3 years is not considered inappropriate or an overestimate. Relying on data from CLARITY for cladribine while using NMA-derived estimates for other disease-modifying therapies (DMTs) undermines the advantages of randomised comparisons within the NMA. This inconsistency introduces biases typically associated with observational studies, compromising the robustness of the model.

4.3 Annualization of the discontinuation probability based on CLASSIC-MS data

In the revised base case, the company accepted the committee's preference for the treatment discontinuation probability to be sourced from the CLASSIC-MS study. CLASSIC-MS is an extension of the CLARITY and CLARITY Extension studies. It included 435 participants from CLARITY, with or without participation in the CLARITY Extension, who received at least one course of cladribine tablets or placebo. According to the CLASSIC-MS study (Figure 6), the median time to subsequent treatment for patients treated with cladribine tablets was 12 years. This indicates that 50% of patients transitioned to a subsequent treatment 12 years after completing cladribine therapy.
The annual probability of treatment discontinuation was derived from this 12-year probability using established methods for converting median survival to annual probabilities. The company cited Gidwani and Russell (2020) as the basis for this conversion, resulting in an estimated annual probability of 5.61% for cladribine. The EAG verified that this method assumes an exponential distribution when converting median survival to annual probabilities. Consequently, the accuracy of the calculation depends on how well the exponential model fits the data. If an alternative survival distribution, such as the Weibull distribution, provided a better fit to the data, additional information would be required to estimate the annual probability.

4.4 EAG Preference for Discontinuation Probabilities

The EAG prefers to maintain the randomised comparisons between DMTs within the discontinuation NMA. Given the committees preference for the CLASSIC-MS data,

the EAG suggests using the probability of treatment discontinuation for cladribine from the CLASSIC-MS estimated to be 5.6% per annum for cladribine as baseline. Hazard ratios of treatment discontinuation for competitor DMTs, relative to cladribine, could then be applied to this probability to estimate discontinuation rates for other DMTs. This approach would preserve the relative randomised comparisons between all DMTs, including cladribine. Alternatively, the company's NMA-derived annual absolute probability of treatment discontinuation for cladribine ([redacted]), consistent with the methodology applied to competitor DMTs. This ensures consistency and preserves the validity of the randomised NMA comparisons. The EAG believes that either of these approaches would provide a more consistent and robust framework for modelling treatment discontinuation, addressing the concerns raised around the company's updated base case.

5 Baseline risk adjusted and unadjusted NMAs

The company presented adjusted network meta-analyses (NMAs) to account for baseline risk differences in the networks for ARR, 3- and 6-month CDP, and all-cause treatment discontinuation. While baseline risk adjustment can help control variability in control group event rates across studies and account for treatment effect modifiers in meta-analyses, its application in NMAs introduces significant challenges.

A major issue arises when a substantial proportion of studies in the network lack a placebo control arm, as is the case in all three networks of interest in the cladribine appraisal (ARR, 6-months CDP and All-cause treatment discontinuation). For the ARR network, 38% of studies lacked a placebo arm, with even higher proportions in the 6-month CDP (50%) and treatment discontinuation (43.5%) networks. These high proportions of non-placebo-controlled studies create challenges.

Including studies without placebo arms requires imputing control group response rates under a missing at random (MAR) assumption. This process adds numerous hyperparameters to the Bayesian model, increasing its complexity and potentially degrading model fit. When a large number of studies require imputation, as seen in these networks, the reliability of the adjusted models is undermined due to inflated DIC values and reduced robustness. On the other hand, excluding non-placebo-controlled studies entirely to avoid imputation fundamentally alters the evidence base, introducing selection bias and compromising the validity of the NMA results.

The EAG cannot ascertain whether the company applied the MAR assumption or

excluded these studies when fitting their baseline risk models. The EAG considers the exclusion of non-placebo-controlled studies to be the more problematic approach due to the significant bias it could introduce.

The company reported DIC values to justify their modelling approach. DIC values for the baseline risk-adjusted models were high, suggesting poor model fit. Furthermore, the differences in DIC between fixed- and random-effects unadjusted models were minimal, falling below the threshold of 3 points required to indicate a meaningful improvement in fit. Thus, based on DIC statistics, baseline risk-adjusted models did not provide significant advantages over unadjusted models and may even yielded less reliable results due to their reliance on a large number of imputed parameters in this application. Overall, the company assertion that the model with the lowest DIC offers the best fit should be interpreted with caution. Small differences in DIC (<3 points) do not represent a meaningful improvement in fit and should not be used as the sole criterion for selecting between fixed- and random-effects models.

Given the limitations of the baseline risk-adjusted models, the EAG suggests that unadjusted NMAs provide a more reliable framework for analysing treatment effects in this appraisal. Baseline risk adjustment appears to be introduced uncertainties in the cost-effectiveness, particularly when applied to networks with high proportions of non-placebo-controlled studies, and does not appear to offer meaningful improvements in model performance based on the companies reported DIC values.

5.1 BCMS Registry Data as the Most Appropriate Source of Natural History Evidence

The EAG acknowledges the company's position that the BCMS registry remains the most appropriate source of natural history data for RRMS and broadly agrees for the following reasons.

Natural history data requires a cohort that accurately captures the progression of RRMS over a patient's lifetime in the absence of effective treatment. The BCMS cohort meets this requirement, as it includes untreated patients and was collected before 1995, prior to the widespread availability of DMTs in the NHS. This ensures that the data reflects the natural progression of RRMS without the confounding influence of treatment.

Additionally, the company referenced a study published in 2016 comparing the BCMS cohort with the University of Wales Multiple Sclerosis (UoWMS) cohort. This study found that disability progression in untreated MS populations was very similar

across both cohorts, providing external validation for the BCMS data. The consistency between these two independent cohorts supports the reliability of the BCMS data in representing the natural history of untreated RRMS.
The company also conducted exploratory scenarios that increased the EDSS transition probabilities by 10%, 20%, and 30%, which substantially altered the revised base-case ICER.
While the EAG agrees that the BCMS data is the most appropriate source for this appraisal, certain limitations should be acknowledged. The BCMS cohort reflects data collected before the introduction of DMTs and may not fully represent the natural history of RRMS under modern diagnostic criteria or clinical practices. Furthermore, while validation with the UoWMS cohort lends support to the BCMS findings, more recent data sources, such as the UK MS Register, could provide additional reassurance regarding the validity of the natural history model. To address this, the EAG conducted a rapid review of the evidence to identify alternative studies; however, no relevant studies were found.

5.2 EAG revised base-case

The EAG has revised its base-case model, retaining the company's modifications submitted in response to the draft guidance, with two key adjustments:

1. **Treatment discontinuation probabilities:** For cladribine, the EAG utilized discontinuation probabilities from the CLASSIC-MS study. For competitor disease-modifying therapies (DMTs), hazard ratios relative to cladribine were applied to the CLASSIC-MS probability to estimate corresponding discontinuation probabilities.
2. **Basket Treatment Sequencing Approach:** Upon discontinuation of a DMT, patients transition to a basket of treatments (Basket 1) rather than moving to best supportive care (BSC), as was the case in the company's original and revised base-cases. Table 1 presents the results from the revised EAG base-case.

Table 1: EAG revised base-case at list price for all DMTs

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)

Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained							

6 Scenario analyses

The EAG conducted scenario analyses based on its revised base-case model, with results presented in Table 2. Due to constraints within the provided treatment sequencing models and limited time, the EAG was unable to implement a 10%, 20% and 30% increase in disease progression by adjusting EDSS transition rates. The scenarios explored include:

1. **Treatment Discontinuation Probabilities**: Utilising probabilities for all DMTs, including cladribine, as derived from the company's network meta-analysis (NMA) on treatment discontinuation.
2. **Baseline Risk-Adjusted NMA Results**: Applying baseline risk-adjusted NMA outcomes for annualized relapse rate (ARR), 6-month confirmed disability progression (CDP), and treatment discontinuation probabilities for competitor DMTs.

Table 2 details the outcomes of these scenario analyses, particularly focusing on the treatment discontinuation probabilities sourced from the company's NMA.

Table 2: EAG revised base-case scenario analyses

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Scenario: BRNMA							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: NMA probability of treatment discontinuation for cladribine and competitor DMTs							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained							

7 Additional analyses

In this section we present the pairwise results for the additional analyses as requested by NICE. Results are reported based on the list prices for cladribine and the committee's preferred comparators and the following assumptions:

- Use the CLASSIC-MS probability of treatment discontinuation for cladribine as the baseline.
- Apply the hazard ratio for competitor DMTs relative to cladribine to calculate the treatment discontinuation probabilities for the competitor DMTs.
- Source treatment discontinuation probabilities all DMTs, including cladribine, from the company's network meta-analysis (NMA) on all-cause treatment discontinuation.

In Table 3 and Table 4, we present the results based on the following:

Base-case

- Probability of treatment discontinuation based on the EAG preferred estimates

Scenario analyses

- BRNMA
- The probability of disease progression increased by 10%, 20%, and 30%
- Basket 1
- Basket 2

7.1 Company's cost-effectiveness results, using list prices

Table 3: Company's deterministic base-case results, using list prices: Apply the hazard ratio for competitor DMTs relative to cladribine to CLASSIC-MS probability to calculate the treatment discontinuation probabilities for the competitor DMTs.

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Base-case							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: BRNMA							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 10% increase in disease progression							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 20% increase in disease progression							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 30% increase in disease progression							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Treatment sequencing (Basket 1)							
Cladribine tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Scenario: Treatment sequencing (Basket 2)							
Cladribine tablet	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained							

Table 4: Company's deterministic base-case results, using list prices. Probability of treatment discontinuation sourced from company's all-cause treatment discontinuation NMA for cladribine and competitor DMTs.

Technologies	Total costs (£)	Total LY	Total QALY	Incremental costs (£)	Incremental LYG	Incremental QALY	ICER (£/QALY)
Base case							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario: BRNMA							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 10% increase in disease progression							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 20% increase in disease progression							
Cladribine Tablets	[redacted]	[redacted]	[redacted]				

Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: EDSS transitions 30% increase in disease progression							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Treatment sequencing (Basket 1)							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Treatment sequencing (Basket 2)							
Cladribine Tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained							