Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Merck Group:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Multiple Sclerosis Trust – *endorsed by patient expert Claire Winchester*
   b. Association of British Neurologists

4. **Expert personal perspectives** from:
   a. Professor Ruth Dobson, Professor of Clinical Neurology & Consultant Neurologist – clinical expert nominated by Association of British Neurologists
   b. Dr Wallace Brownlee, Consultant Neurologist – clinical expert nominated by Merck
   c. Carla King – patient expert nominated by Multiple Sclerosis Trust

5. **External Assessment Report** prepared by Warwick Evidence

6. **External Assessment Report – factual accuracy check**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID6263]

Document B

Company evidence submission

June 2024

File name	Version	Contains confidential information	Date
ID6263_CladribineRRMS_Document B_25Jun24_redacted	Version 1	Yes	25 June 2024
ID6263_CladribineRRMS_Document B_02Aug24_redacted_resubmission	Version 2	Yes	02 August 2024

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List of Abbreviations

Abbreviation	Definition
AAC	Accelerated Access Collaborative
ABN	Association of British Neurologists
AE	Adverse event
ARR	Annualised relapse rate
BCMS	British Columbia Multiple Sclerosis
BID	Two times a day
BNF	British National Formulary
BSC	Best supportive care
CC	Complication and comorbidity
CDMS	Clinically defined multiple sclerosis
CDP	Confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Clinically isolated syndrome
CMA	Cost-minimisation analysis
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disorder
CPI	Consumer Price Index
CRPD	Clinical Practice Research Datalink
CSR	Clinical study report
CU	Combined unique
DCE	Discrete Choice Experiment
DES	Discrete-event simulation
DIC	Deviance information criterion
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DP	Disease progression
DRF	Diroximel fumarate
DSU	Decision Support Unit
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	Food and Drug Administration
FEM	Fixed-effect model
GA	Glatiramer acetate
GCP	Good clinical practice
GI	Gastrointestinal
HA	Highly active
HCP	Healthcare professional
HDA	High disease activity

HL	Cladribine tablets 3.5 mg/kg in Year 1 followed by cladribine tablets 1.75 mg/kg in Year 2 (cumulative dose of 5.25 mg/kg)
HLLL	Cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4
HLPP	Cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4
HPV	Human papilloma virus
HR	Haraz ratio
HRG	Healthcare Resource Group
HRU	Healthcare resource utilisation
HSE	Health Survey for England
HSU	Health state utility
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IJSR	Injection site reaction
IL	Interleukin
ILS	Influenza like symptoms
IM	Intramuscular
IPE	Iterative parameter estimation
IRT	Immune reconstitution therapy
ISR	Infusion site reaction
ITC	Indirect treatment comparison
ITT	Intention-to-treat
JCV	John Cunningham's virus
KFS	Kurtzke Functional Systems
LL	Cladribine tablets 1.75 mg/kg in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg)
LLLL	Cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4
LLPP	Cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4
LTBI	Latent tuberculosis infection
LY	Life year
LYG	Life year gained
ME	Macular oedema
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIS-8D-P	Multiple Sclerosis Impact Scale-Eight Dimensions-Patient Index
NEDA	No evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported

ONS	Office of National Statistics
PAS	Patient Access Scheme
PDDS	Patient Determined Disease Steps
PICOS	Population, interventions, comparators, outcomes, study design
PML	Progressive multifocal leukoencephalopathy
PO	Oral administration
PP	Placebo in Year 1 and Year 2
PPLL	Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4
PPMS	Primary progressive multiple sclerosis
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PY	Patient year
QALY	Quality-adjusted life year
QD	Once daily
QOD	Every other day
QOW	Every other week
QW	Once a week
RCT	Randomised controlled trial
RD	Residual deviance
REM	Random effects model
RES	Rapidly evolving severe
RMS	Relapsing multiple sclerosis
RPSFTM	Rank preserving structural failure time model
RRMS	Relapsing-remitting multiple sclerosis
RSS	Risk Sharing Scheme
RW	Real-world
RWE	Real-world evidence
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMPC	Summary of product characteristics
SOT	Sub-optimally treated
SPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
SUPF	Supplemental follow-up
SW	South-west
TA	Technology appraisal
TEAE	Treatment-emergent adverse events

TIW	Three times weekly
TNF	Tumour necrosis factor
TRE	Thyroid related event
TSD	Technical Support Document
UK	United Kingdom
VAS	Visual Analogue Scale
WTP	Willingness-to-pay

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

Executive summary

On the 22nd March 2024, cladribine tablets received approval from the Medicines and Healthcare products Regulatory Agency (MHRA) for an expanded indication, in active relapsing multiple sclerosis (RMS) in Great Britain. The MHRA approval in this broader population will enable more patients to receive treatment with cladribine tablets, a highly effective, short-course, oral disease modifying therapy (DMT), which can address the unmet need for an efficacious treatment option that is convenient to use, and further reduces the healthcare resource burden of the National Health Service (NHS) and treatment burden for patients. The objective of this submission is to demonstrate the clinical and cost-effectiveness of cladribine tablets in the updated MHRA indication and to secure a positive National Institute for Health and Care Excellence (NICE) recommendation in the broader active relapsing-remitting MS (RRMS) patient population.

- MS is a debilitating autoimmune disease of the central nervous system resulting in inflammation, demyelination, and progressive disability [1]. Due to its chronic nature, patients with MS require long-term treatment. There are a range of oral, injectable and infusion DMTs authorised for use in the UK and recommended by NICE in active RRMS, including low-to-moderate-efficacy DMTs (interferon-based therapies, glatiramer acetate, dimethyl fumarate, teriflunomide, diroximel fumarate) and high-efficacy DMTs (ponesimod, ofatumumab, ocrelizumab) [2].
- Cladribine is considered a high-efficacy DMT [2]. In line with the previously approved indication [3], NICE currently recommends cladribine tablets for the treatment of adult patients with highly active RRMS as defined by clinical or imaging features [4].
- The recent MHRA approval of the expanded indication for cladribine tablets to the active RMS population was based on robust clinical and safety data including (i) the pivotal studies (CLARITY and CLARITY-EXT) in patients with active RRMS [5-8], (ii) extensive post-marketing authorisation clinical and safety data for cladribine tablets, and (iii) real-world data, proving the benefit-risk profile of oral cladribine tablets in active RRMS, as well as high rates of treatment persistence and low treatment switching demonstrated in the UK RWE study in a high active RRMS patients (CLARENCE) [9, 10].

- Despite the number of treatments available within NHS England for active RRMS, most high-efficacy DMTs deliver their effect by continuous immunosuppression which requires regular administration and close monitoring [11]. More specifically, ponesimod, the only approved oral high-efficacy DMT requires daily administration, and ofatumumab and ocrelizumab (alternative infusion/injectable DMTs for active RRMS) may contribute to higher healthcare resource use as they require frequent administration, monitoring and management of side effects [12-17].The unique posology of cladribine tablets, which belong to the 'immune reconstitution therapies' drug class, allows patients to take oral medication for only two weeks per year in Years 1 and 2 to achieve a sustained efficacy lasting over four years (with no further treatment required in Years 3 and 4), thus delivering robust and durable clinical benefit without continuous immunosuppression (vs. other high-efficacy DMTs).
- Expanding the NICE recommendation for cladribine tablets to include all patients with active RRMS would fulfil an unmet medical need for a broader population of patients, who are seeking a convenient and highly efficacious treatment, with the potential to:
    - **Improve treatment adherence:** infrequent dosing of cladribine tablets provides advantages over maintenance therapies by reducing the treatment burden and treatment fatigue for patients [18-21].
    - **Provide an alternative treatment option for women of childbearing potential:** sustained efficacy and no retreatment in Years 3 and 4 offered by cladribine tables provides a treatment option allowing patients not to be on continued immunosuppression during pregnancy, which is important as the majority of newly diagnosed MS patients are women of childbearing age [22].
    - **Reduce healthcare resource use:** oral administration resulting in minimal administration costs and reduced need for monitoring (vs. other high-efficacy DMTs) may translate into benefits for NHS England by alleviating the healthcare resource use [17].
    - **Improve patient outcomes with reduced burden:** Improve short- and long-term clinical outcomes of patients in a minimally disruptive way due to the short-course oral treatment
    - **Address inequality of access:** Allow access to a preferred MS treatment option by both clinicians and patients [2, 23, 24], as well as expand access to patients impacted by socio-economic inequalities, who may have limited access to full services offered by NHS England [24]

- Overall, cladribine tablets are a high-efficacy DMT with an established clinical and safety profile, which have been in use for the treatment of some MS patients in NHS England since 2017 (TA493/TA616) [4, 25]. Together with its differentiating attributes (novel mechanism of action, unique posology, short-course oral treatment) and extended MHRA indication [26], cladribine tablets are well positioned to address the overarching treatment goals from the perspective of clinicians (i.e., early intensive treatment), the unmet needs faced by patients (i.e., efficacious and safe treatment option that is convenient to use) and are aligned with NHS England effective use of resources.

B.1.1 Decision problem

Table 1 presents the final NICE scope and the decision problem addressed in this submission.

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adult patients with relapsing forms of multiple sclerosis (RMS). The population for whom cladribine tablets has already been evaluated in TA493/TA616 (adults with highly active relapsing multiple sclerosis) will not be considered.	Adults with active relapsing-remitting multiple sclerosis (RRMS)	The decision problem is focused on adults with active RRMS rather than adults with active RMS, as RRMS excludes patients with secondary progressive multiple sclerosis (SPMS). This reflects the target population for reimbursement and is aligned with the submitted evidence. The evidence presented in the submission is based on a phase III RCTs (CLARITY and CLARITY-EXT) that evaluated cladribine tablets compared to placebo in people with RRMS. The submitted evidence does not include data on people with SPMS.
Intervention	Cladribine tablets	As per scope	n/a
Comparator(s)	For people with active RMS: • optimised standard care with no DMT • beta interferon • peginterferon beta-1a • dimethyl fumarate • diroximel fumarate • glatiramer acetate • teriflunomide • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab • ponesimod For people with SPMS with evidence of active disease: • siponimod • beta-interferon	For people with active RRMS: • optimised standard care with no DMT • beta interferon • peginterferon beta-1a • dimethyl fumarate • diroximel fumarate • glatiramer acetate • teriflunomide • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab • ponesimod	As the company submission does not include evidence on the SPMS population and focuses on patients with RRMS (see above), the comparators for the SPMS subgroup are not considered in this submission. Autologous haematopoietic stem cell is not included as a comparator in this submission as it does not address the decision problem: • It is not licenced by the MHRA, the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) for the treatment of RRMS • It is not used routinely in clinical practice in the UK • While it is funded by the NHS, there is currently no NICE recommendation for its use in RRMS

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	For people that progress on previous lines of treatment and after discussion with specialist multidisciplinary team: • autologous haematopoietic stem cell transplantation		• Autologous haematopoietic stem cell is typically reserved for a more severe or progressive population, based on clinical expert opinion.
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • disease progression • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom from disease activity • mortality • adverse effects of treatment • HRQoL	As per scope	n/a
Subgroups to be considered	If the evidence allows, the following subgroup of people will be considered: • people who could not tolerate previous treatment	No additional subgroups are suggested.	Merck is not aware of any available data that indicates the relative effectiveness of DMTs will vary between patients who tolerate treatment and those who switch due to intolerance and therefore will not be presenting evidence for this subgroup in this submission. Additionally, the efficacy data in this subgroup is not publicly available for competitor DMTs to be able to assess comparative effectiveness. TA533, TA699, TA767 also did not consider this subgroup due to lack of evidence.

SOURCE: [27]

DMT: Disease-modifying therapies; EDSS: Expanded Disability Status Scale; FDA: Food and Drug Administration; HRQoL: Health related quality of life; NHS: National Health Service; RCT: Randomised control trials; RES: Rapidly evolving severe; RMS: Relapsing multiple sclerosis; RRMS: Relapse-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; TA: Technology appraisal

B.1.1.1. History of previous NICE recommendations TA493/TA616

Cladribine tablets were approved by the EMA in August 2017 for the treatment of adult patients with highly active RMS, as defined by clinical or imaging features (see section 5.1 of the SmPC) [3].

The pivotal Phase 3 randomised control trial, CLARITY, demonstrated clinical efficacy in the broader active RRMS patient population, however, the EMA recommendation in highly active RMS patients was a result of Scientific Advice from the Committee for Medicinal Products for Human Use (CHMP). Due to initial safety concerns (namely lymphopenia, infection risk and malignancy risk), the company was advised to focus on the patient population with the greatest overall risk-benefit profile. Consequently, in the 2016 EMA submission, the company demonstrated a post-hoc analysis of the CLARITY trial data set on the highly active population (in CLARITY, highly active RMS was defined as (i) patients with one relapse in the previous year and at least one T1 gadolinium (Gd) enhanced lesion or ≥9 T2 lesions, while on therapy with other DMTs, or (ii) patients with two or more relapses in the previous year, whether on DMT treatment or not), as well as results from three additional RCTs and a prospective observational safety registry, all focusing on RRMS with high disease activity (HDA-RRMS), therefore increasing patient experience from 2,000 patient-years (PYs) in 2009 to over 10,000 PYs at the time of the 2016 submission. This additional data and the introduction of a risk management plan proposed by Merck have substantiated the positive clinical efficacy of cladribine tablets while also mitigating safety concerns previously identified by the CHMP, resulting in 2017 EMA approval authorising the use of cladribine tablets for treatment of highly active RMS as defined by clinical or imaging features [3].

Later in 2017, cladribine tablets were recommended by NICE for the treatment of highly active RRMS (TA493) [25]. In 2018, cladribine tablets were selected as a Rapid Uptake Product by the Accelerated Access Collaborative (AAC) [28, 29] leading to fast tracked 2019 NICE guidance update (TA616), which removed some barriers to accessing cladribine tablets, namely, the requirement for gadolinium-enhancing magnetic resonance imaging (MRI) before treatment [30, 31].

Since 2017, when the EMA approval was granted and the original NICE guidance was issued, additional evidence has become available to support the benefit-risk profile for the use of cladribine tablets in the active RRMS population. In addition to the ITT population trial data from the pivotal studies, CLARITY and its extension study CLARITY-EXT, there is now extensive post-marketing authorisation clinical and safety data, and real-world data available [10, 17, 23, 32, 33]. The experience with oral cladribine tablets in approximately 78,613 treated patients globally as of July 2023 (providing 161,999 PYs of exposure) throughout the

marketing period has helped to better understand the benefit-risk profile of oral cladribine tablets in active RRMS under real-life conditions, where the clinical efficacy benefits offered by treatment with cladribine tablets outweighed the potential safety risks. Additionally, as demonstrated by the CLARENCE study – a UK RWE study, which assessed treatment persistence and switching based on Blueteq® forms for 1,934 MS patients treated with cladribine tablets in line with the existing NICE recommendation in highly active RRMS – rates of persistence were high (91%) and few patients (4%) switched treatments while on cladribine tablets [9, 10].

As such, an expanded indication application was submitted to the UK MHRA in February 2023 and approved on 22nd March 2024 for the treatment of adult patients with active RMS as defined by clinical or imaging features [26].

Currently, the National Institute of Health and Care Excellence (NICE) recommends treatment with cladribine tablets in two subgroups of highly active RRMS (TA493/TA616) [34]:

- Rapidly evolving severe relapsing–remitting multiple sclerosis (RES-RRMS) defined as two or more relapses in the previous year, and baseline MRI evidence of disease activity, or
- RRMS that has responded inadequately to treatment with DMT, defined as one relapse in the previous year and MRI evidence of disease activity, referred to as patients who are sub-optimally treated (SOT) in the initial submission to NICE for cladribine tablets

This submission is based on the active RRMS indication to align with the new indication approved by the MHRA and the ITT population trial data from the pivotal studies of cladribine tablets, CLARITY and CLARITY-EXT [26]. The final NICE scope for this technology appraisal submission identifies the relevant patient population as adult patients with RRMS with active disease as defined by clinical or imaging features.

B.1.2 Description of the technology being evaluated

A summary of the technology is presented in Table 2. In addition, in support of this appraisal, the MHRA Summary of Product Characteristics (SPC) is included in the Appendix C. The UK public assessment report (PAR) is not available; this is because the original regulatory procedure was performed by EMA and the MHRA has not provided an updated PAR for the indication extension.

Table 2: Technology being evaluated

UK approved name and brand name	"Cladribine tablets" (MAVENCLAD®)

Mechanism of action	• Cladribine tablets are a deaminase-resistant nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells • The mechanism by which cladribine tablets exert its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS [35] • A distinguishing feature of cladribine tablets is discontinuous immunosuppression. Periods of lymphocyte depletion around treatment are followed by repopulation resulting in durable efficacy well beyond the period of treatment
Marketing authorisation/CE mark status	• Cladribine tablets have marketing authorisation in the UK o An application for marketing authorisation for highly active RMS was submitted to the European Medicines Agency in June 2016, and was approved in August 2017 o An application for variation of the marketing authorisation to expand the indication to active RMS was submitted to the MHRA in February 2023 and approved on 22 March 2024 [26]
Indications and any restriction(s) as described in the SmPC	• The indication approved by the MHRA in March 2024 is for the treatment of adult patients with RMS with active disease as defined by clinical or imaging features. This technology appraisal submission is for people with active RRMS to align with the MHRA indication expansion • Prior to the updated MHRA approval in March 2024, cladribine tablets were indicated for the treatment of adult patients with highly active RMS as defined by clinical or imaging features
Method of administration and dosage	• Cladribine tablets are administered orally. The recommended cumulative dose is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year o Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year o Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight o No further treatment is required in Years 3 and 4
Additional tests or investigations	• The introduction of cladribine tablets in the active RRMS population would not require additional tests, investigations or administration beyond those that are currently required for all patients with MS
List price and average cost of a course of treatment	Confirmed list price [36]: • Cladribine tablets 10 mg x 1 tablet £2,047.24 • Cladribine tablets 10 mg x 4 tablets £8,188.97 • Cladribine tablets 10 mg x 6 tablets £12,283.46 Annual cost: approximately £13,000 per annum when the complete treatment cost of approximately £52,000[a] is spread over a 4-year period. For further details on treatment costs, see Section B.3.5.
Patient access scheme (if applicable)	A Patient Access Scheme has not been included in the submission

Note: [a]the approximate treatment cost of £52,000 was calculated based on the average of 12.7 tablets per patient per year, based on the results of the CLARITY trial. The number of tablets per patient, and therefore total annual cost, may vary depending on patient's weight, as cladribine tablets are an oral medication where the recommended cumulative dose is 3.5 mg/kg body weight over 2 years.
EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency; MS: Multiple sclerosis; NHS: National Health Service; RMS: Relapsing multiple sclerosis; SmPC: Summary of product characteristics; UK: United Kingdom

B.1.2.1. Mechanism of Action

Cladribine tablets are a nucleoside analogue of deoxyadenosine that is activated by intracellular phosphorylation in lymphocytes, resulting in preferential and sustained reduction of dividing and non-dividing T and B lymphocytes, with less effect on other immune cells. The selective targeting of CD4+ and CD8+ T cells, and CD19+ B cells leads to their subsequent apoptosis resulting in a reduction in absolute lymphocyte count and an overall reduction in pro-inflammatory activities (e.g., fibroblast growth factor, TGF-β1, TNF-α) accompanied with enhanced anti-inflammatory activity (e.g., IL-4, IL- 5 and IL-10) [3, 35, 37, 38].

Further, in addition to the impact of MS on the peripheral nervous system, there also is an important central nervous system (CNS) component contributing to the MS pathophysiology (local inflammation and/or degradation), which is theorised to particularly be dominant later in the disease process. Therefore, targeting the CNS may be of therapeutic benefit [39]. Cladribine tablets can target the CNS by penetrating the blood-brain barrier. Together with its sustained effects on circulating lymphocytes, cladribine tablets may affect the recruitment of inflammatory cells into nascent inflammatory foci in the CNS in MS patients [35].

Although cladribine tablets have a short half-life, the observed effect is due to the immediate selective depletion of both T and B cell lymphocytes, followed by repopulation to normal levels over time, thereby giving this treatment a unique posology that consists of a short treatment course followed by a prolonged period of sustained drug efficacy for at least 4 years, without continuous immunosuppression (Section B.2). This posology allows patients who have active RRMS the opportunity to maintain a low impact treatment regimen and continue with normal daily activities, with minimal treatment burden.

Such therapies are classified as an immune reconstitution therapy (IRT) [40]. IRTs provide long-term qualitative changes in adaptive immune function following short courses of therapy, with clinical efficacy extending beyond the period of active treatment [41]. The reduction in absolute lymphocyte count following administration of cladribine tablets is considered to be a prerequisite for the long-term clinical effects attributed to cladribine tablets.

B.1.2.2. Method of administration and dosage

Cladribine tablets are an oral medication where the recommended cumulative dose is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year [3]. Each treatment course consists of two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight (Table 3) [3]. Cladribine tablets are recommended to be administered at approximately 24-hour intervals. If one of the daily doses consists of two tablets, both tablets are taken together as a single dose [3].

Table 3: Dose distribution of cladribine tablets per treatment week in each treatment year

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

Source: [3]

Lymphocyte counts must be normal before initiation of cladribine tablets in Year 1, and patients should have at least 800 cells/mm^3 before initiation of cladribine tablets in Year 2. In the absence of this, a treatment course could be delayed for up to 6 months to allow lymphocyte counts to recover [3].

Following completion of the two treatment courses, no further treatment with cladribine tablets is required in Years 3 and 4 [3]. This can provide patients with minimal treatment burden through to Year 4, whilst also supporting hospitals to relieve capacity and reduce the burden of frequent infusions (see Section B.1.3.4 and Section B.2). Figure 1 illustrates the full 4-year treatment course for cladribine tablets.

Figure 1: Dosing regimen for cladribine tablets

Note: The blue dots represent the number of days on which treatment should be administered in the month

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

B.1.3.1. Disease overview

Multiple sclerosis is a chronic autoimmune disease of the central nervous system resulting in inflammation, demyelination, and progressive disability [1]. Disability caused by MS is characterised by the impairment of mobility, cognition, eye sight, and the presence of comorbidities such as depression and anxiety [42]. There are over 130,000 people with MS in the UK (1 in 500 people) and nearly 7,000 people are newly diagnosed each year [22]. MS affects twice as many women as it does men, and the average age of disease onset is typically 32 years [22]. Among young adults, MS is the most common debilitating neurological disease and the leading cause of non-traumatic disability in many countries (including the UK) [22].

MS can be categorised into four disease phenotypes: clinically isolated syndrome (CIS), RRMS, primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS). Additionally, RMS encompasses RRMS and SPMS. The majority of patients with MS (85%) initially present with RRMS [22], which is characterised by intermittent disease exacerbations (relapses) followed by periods of partial or complete recovery (remission) [22, 43]. Over the course of 20 years, more than 50% of patients with RRMS will progress to SPMS, characterised by progressive disability [1, 44]. In addition, patients with RRMS who experience frequent clinical relapses and/or MRI activity either when untreated or while on a DMT are considered to present with a more aggressive form of RRMS, referred to as high disease activity RRMS (HDA-RRMS), leading to disability progression and a faster onset of SPMS [45].

The progressive aspect of MS is most closely associated with a decline in neurological function over time and disability progression. Disability progression most adversely affects a patient's quality of life and the ability to perform routine daily activities. Therefore, preventing or delaying

sustained disability progression is considered one of the most important outcomes for any DMT indicated in MS.

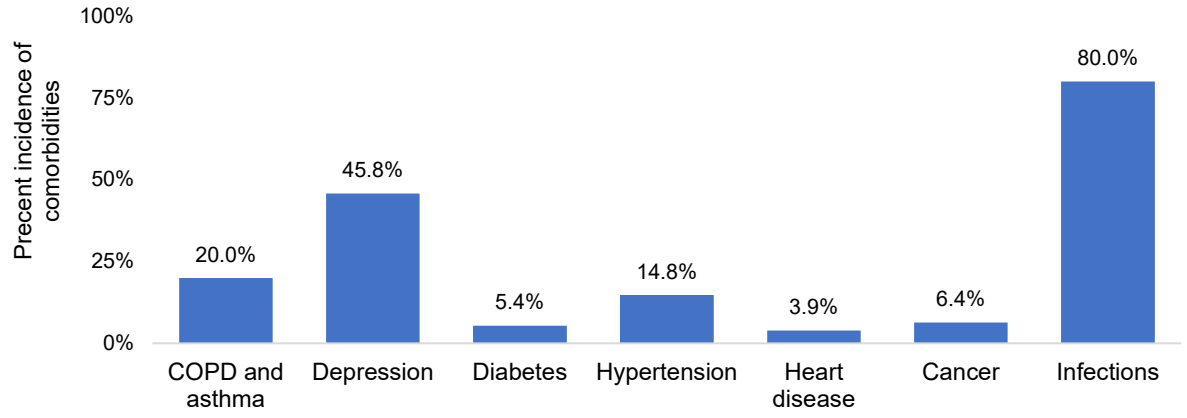
B.1.3.2. Disease burden and unmet need

Clinical burden of MS

Patients with MS experience a number of emotional, cognitive, and physiological comorbidities at a greater prevalence than the general population. Compared with the general population, the life expectancy of patients with MS is reduced by approximately 10 years and they are more likely to die of a comorbid condition [46-48]. Specifically in the UK, patients with MS experience cardiovascular comorbidities, psychological conditions (e.g., depression, anxiety, bipolar disorder), epilepsy, restless leg syndrome, migraines, pulmonary diseases (e.g., asthma), autoimmune conditions, cancer, and metabolic disorders (e.g., dyslipidaemia, diabetes) [49].

A UK-based observational study assessed comorbidities in 1,713 patients with MS between 1993-2006 using data from the Clinical Practice Research Datalink (CRPD) (77% presented with RRMS at baseline). Common comorbidities experienced by patients with MS include chronic lung disease, depression, and cardiovascular conditions (Figure 2) [50].

Figure 2: Incidence of comorbid conditions in patients with MS in the UK



Source: [50]

COPD: Chronic obstructive pulmonary disorder; MS: Multiple sclerosis, UK: United Kingdom

Note: Heart conditions include ischemic heart disease, angina, myocardial infraction and heart failure

The presence of comorbidities in patients with MS is associated with an increased relapse rate and can negatively impact treatment persistence as well as disease progression [51-53].

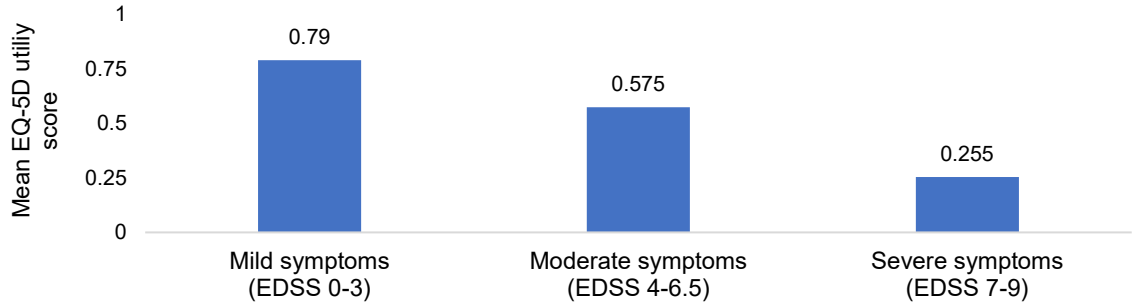
Humanistic burden of MS

The burden of disability and comorbidities experienced by patients with MS has a detrimental effect on patients' quality of life (QoL). Fatigue and pain are common symptoms affecting the majority of patients with MS that can have a considerable impact on the QoL [54, 55]. Patients

with MS have a lower QoL than patients with many other chronic conditions including ischaemic heart disease, Type 2 diabetes, and Crohn's disease [56].

Patient's QoL is further exacerbated by increased relapse frequency and progression of disease [57, 58]. A study conducted across the UK, Germany, France, Italy and Spain suggests that activities of daily living, measured using the PRIMUS questionnaire, is negatively impacted with increasing disease severity (Figure 3) [42].

Figure 3: Patient QoL by MS disease severity across UK, Germany, France, Italy, and Spain



Source: [42]

EDSS: Expanded Disability Status Scale; EQ-5D: EuroQoL five dimensions questionnaire; MS: Multiple sclerosis; QoL: Quality of life; UK: United Kingdom

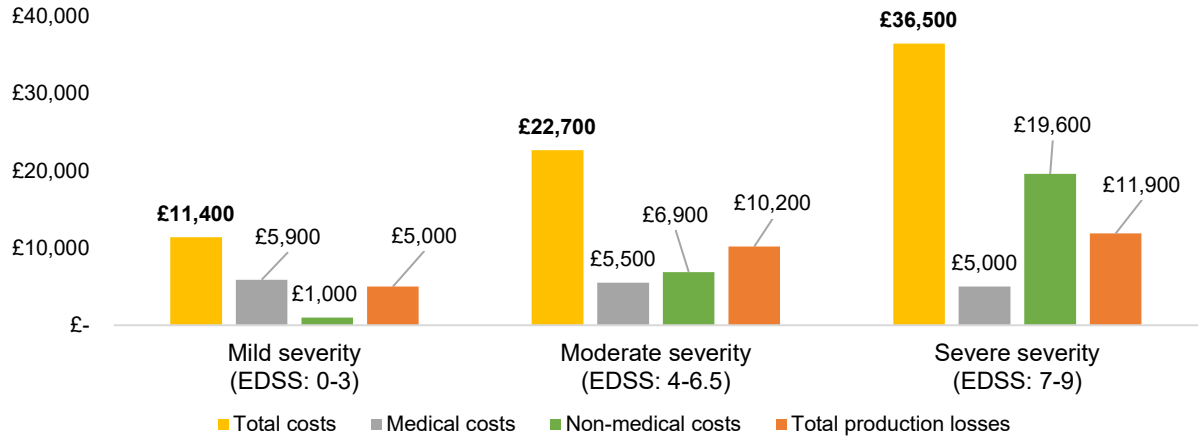
Note: n=248 France, n=324 Spain, n=251 Italy, n=244 Germany, n=194 UK

Economic burden of MS

Medical costs, such as treatment costs, contribute significantly to the healthcare costs associated with MS. A cross-sectional, retrospective study by Kobelt at al. assessed the economic burden of MS associated with the level of disability across 16 countries from the societal perspective in 2015. For the UK study sample (n=779; 36.7% with RRMS diagnosis), the total average cost per year ranged from £11,400 to £36,500 (Figure 4). The study reported that the total cost of MS was dominated by the cost of DMTs, particularly in patients with EDSS scores of 0-6.5 [59].

In addition, due to the young age of onset and progressively incapacitating nature of the disease, the cost of MS to patients, their families, and society is also high [60, 61]. Considering the prognosis of MS, over time disability can worsen as the disease progresses, reducing the ability for patients to work which is usually during prime employment years. The study by Kobelt et al. found that the costs of informal care and productivity losses increased substantially with disease severity, which was largely attributed to relapses (Figure 4) [59].

Figure 4: Total mean annual cost (£) per patient in the UK by disease severity (2015)



Source: Adapted from [59]

EDSS: Expanded Disability Status Scale; UK: United Kingdom

Note: Total UK study sample=779, cost values are denoted in the British pound (2015); Total production losses includes short- and long-term absence and early retirement

Treatment and monitoring burden for patients

Many DMTs, although efficacious, are often burdensome for patients and can be difficult to adhere to. Most DMTs available for the treatment of active RRMS deliver their effect by continuous immunosuppression (i.e., ponesimod, ofatumumab and ocrelizumab all require continuous, uninterrupted daily, monthly or 6-montly dosing to maintain their therapeutic effect) and in turn, patients receiving these treatments require close monitoring. The implications can be considerable; many patients travel significant distances to reach services for regular treatment administration and/or for monitoring that, due to its frequency, can interfere with daily life.

The burden of frequent and lengthy infusions required by many DMTs (e.g., ocrelizumab) or subcutaneous injections required by many DMTs (e. g., ofatumumab) and their subsequent monitoring can be demanding for patients. For example, the average time required to administer maintenance ocrelizumab (including infusion, post-infusion observational period, premedication and aseptic pharmacy preparation) is approximately 5.5 hours per infusion and administered every 6 months. In addition, patients may also be exposed to infusion-related reactions (e.g., pruritus, rash, throat irritation) [12, 13]. Therefore, factors such as distance from the hospital, employment status, level of disability, or childcare requirements are important parameters that patients will consider, especially when undergoing infusible DMT treatment [62].

Consequently, inclusion of patient preferences is a critical component in determining an appropriate treatment strategy and improve DMT compliance. A Discrete Choice Experiment (DCE) conducted in 2017 assessed the DMT preferences between patients with RRMS in the

UK and Germany. The study reported that the patients in the UK (n=799) and in Germany (n=363) prefer orally administered (42%) compared to injectable (16%) or infusion administered (38%) DMTs, where treatment with cladribine tablets was the most preferred oral treatment [23].

More than 25% of patients with active RRMS have shown to discontinue treatment within one year of its initiation [63]. Limiting factors such as a demanding dosing schedule can trigger poor adherence, which in turn results in reduced effectiveness and is associated with disease progression [64, 65]. The most common reasons for non-compliance include forgetting to take medication, a perceived lack of efficacy, adverse events, and the treatment fatigue that results from daily or intermittent dosing schedules [18-21].

Most NICE-approved DMTs for the treatment of active RMS require an extensive treatment schedule (e.g., frequent infusions, prolonged time at the hospital), impacting daily life activities for patients. Therefore, a short course oral therapy with durable efficacy and good tolerability would offer a desirable alternative for the treatment of active RRMS, helping patients to avoid treatment fatigue and, thus, enhance their treatment experience and adherence.

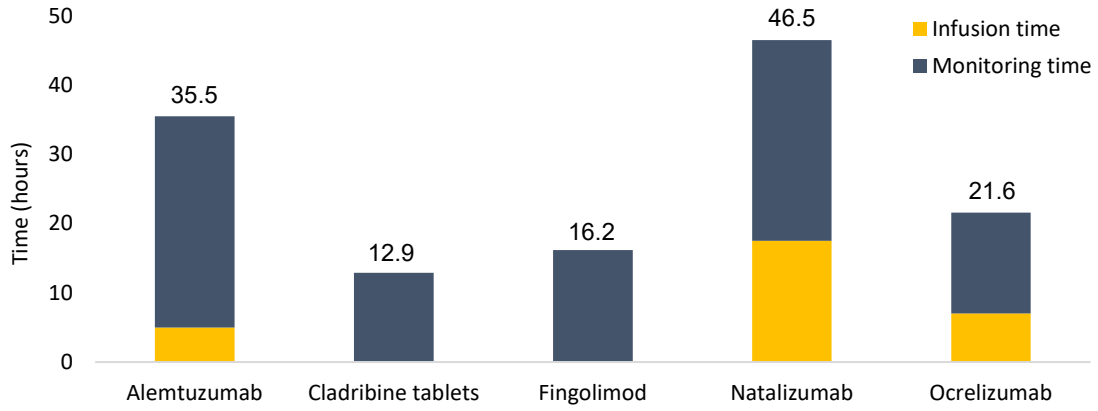
The majority of the available DMTs are considered maintenance therapies, and patients receiving these treatments require close monitoring. As such, in addition to the already mentioned disease and treatment burden for patients, there is substantial administrative and monitoring time burden for the healthcare service associated with the high-efficacy DMTs currently available for active RRMS (ponesimod, ofatumumab and ocrelizumab).

MS specialist nurses are key health professionals managing the provision and monitoring of DMTs, and they are under mounting pressure to deliver complex monitoring regimes for the DMTs in an increasingly resource-constrained NHS. MS Trust highlighted these concerns, which were supported by expert nurse feedback received by Merck [14-16]. The MS Trust reported that 64% of patients with MS in the UK live in areas where MS specialist nurses have unsustainable caseloads; although this is based on a report from 2016, it may still be representative of practice in 2024. Compounded with the shortage of MS specialist nurses in the UK and increased prevalence of MS, the demands of managing DMT treatment and lack of multidisciplinary MS services throughout the UK limit hospitals and MS clinics to deliver appropriate care. The MS Trust report highlights that there is a substantive need for treatments with reduced administration and monitoring burden than the currently available DMTs provide, which would help relieve healthcare capacity [14].

To demonstrate this, Merck completed a retrospective time and motion study from 2019 to 2021 in the currently NICE-approved highly active RRMS population to quantify the administration and monitoring burden commonly associated with high-efficacy DMTs. The UK-

based study reported that high-efficacy infusion DMTs: alemtuzumab (35.5 hours), natalizumab (46.5 hours), and ocrelizumab (21.6 hours) required the greatest amount of healthcare provider time associated with administration and monitoring over 4 years compared to high efficacy oral DMTs: cladribine tablets (12.9 hours) and fingolimod (16.2 hours), where treatment with cladribine tablets required the lowest amount of time overall (Figure 5).

Figure 5: Estimated total active HCP time per patient over 4 years, by DMT



Source: [17]
DMT: Disease-modifying treatment; HCP: Healthcare professional

Family planning

MS affects twice as many women as it does men, of which many are young women with active RRMS who want to start or extend their family while controlling their MS. Delaying treatment so that patients can complete their families is often not an option as it can lead to disease progression and potential irreversible disability [66]. However, the options for treatments that can be continued during pregnancy are limited and exhibit only modest efficacy. In contrast, high-efficacy DMTs, most of which require continuous uninterrupted dosing, are contraindicated or should be avoided in pregnancy [66]. This creates a dilemma for patients who require or request high efficacy therapies yet wish to prioritise their family life. As such, patient preferences play a critical role in the clinical decision-making process with their healthcare delivery team.

Unmet need

As MS is a life-long disease requiring chronic treatment; therefore, therapies that are convenient, easy to self-administer, non-invasive, and well tolerated are important to patients. Availability of a therapy which is easy to adhere to is also highly important (e.g., a drug regimen with a reduced risk of treatment fatigue, typically associated with frequent injections or once or twice daily oral medications). Therefore, regimens that enhance patient compliance would offer an advantage over many of the currently used treatments.

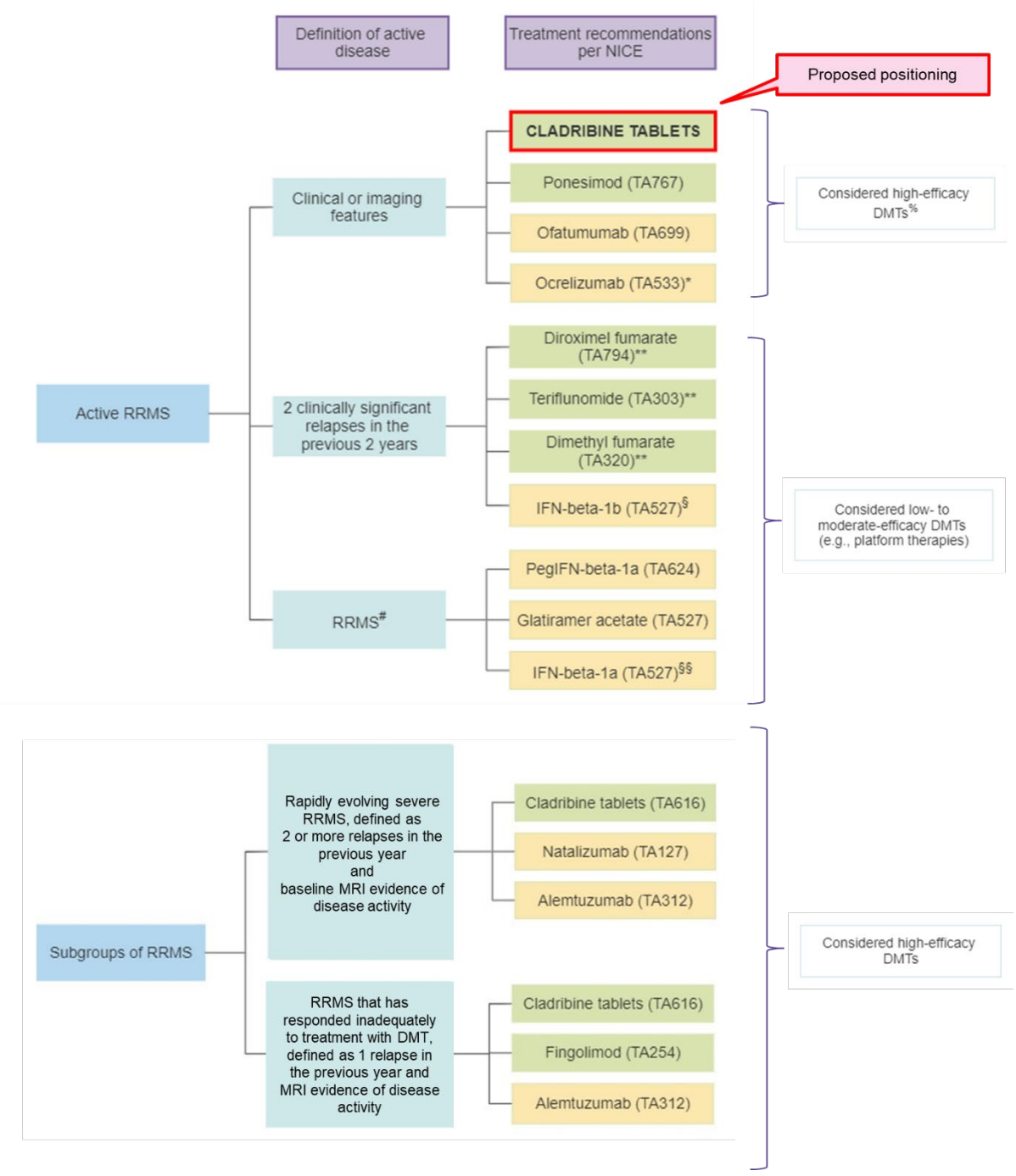
Furthermore, across the active RRMS treatment landscape, ponesimod is the only DMT currently approved by NICE for active RRMS that is considered a high-efficacy DMT and administered orally. Considering that this oral treatment option is an S1P receptor modulator and requires daily administration, there is a lack of diversity in providing an alternative oral, high-efficacy DMT for patients and healthcare providers, with minimal treatment and tablet burden and proven long-term efficacy.

Overall, the broader availability of an increasingly diverse range of treatment options provides opportunities for better management of patients with RRMS.

B.1.3.3. Clinical treatment pathway

There are no curative agents available for the treatment of MS; however, there are a range of oral, injectable and infusion therapies authorised for use in active RRMS in the UK. Figure 6 below shows the treatment algorithm for patients with RRMS based on NICE recommendations [67], including the potential positioning of cladribine tablets.

Figure 6: DMT treatment algorithm for the treatment of RRMS based on NICE recommendations, including the potential positioning of cladribine tablets



Source: Adapted from the NHS England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies [67]

DMT: Disease modifying therapy; IFN: Interferon; NICE: National Institute for Health and Care Excellence; RRMS: Relapse-remitting multiple sclerosis; TA: Technology appraisal

Note: Green indicates DMTs offered as oral administration; yellow indicates DMTs offered as injectable/infusion administration; potential position of cladribine tablets is marked by a red box

#Active disease not specified. Recommendation for patients with RRMS

*Ocrelizumab is recommended only if alemtuzumab is contraindicated or otherwise unsuitable

**Recommended only if patients do not have highly active or RES-RRMS

§IFN beta-1b refers to branded product Extavia®

§§IFN beta-1a refers to branded products Rebif® and Avonex®

%All high-efficacy DMT recommendations for the broad RRMS population includes the HDA-RRMS sub-populations

In addition to the treatment pathway based on NICE recommendations, real-world practice demonstrates varying pharmacological treatment approaches. Historically, the treatment pathway for most patients has been based on an escalation strategy; treatment typically begins with moderately efficacious therapies (i.e., platform therapies) that are perceived to have low toxicity and escalating to more potent therapies (i.e., high-efficacy DMTs) in the face of continued disease activity. However, there is growing evidence that early intensive treatment with high-efficacy DMTs is associated with more favourable long-term clinical benefits. This treatment approach could be an appropriate strategy for many patients in order to avoid irreversible disability, early disease progression and conversion to a secondary progressive course [2, 68-72].

In a recent retrospective study of data obtained from the MSBase registry and the Swedish MS registry, high efficacy DMTs were associated with less disability after 6 to 10 years when commenced within 2 years of disease onset compared to when started later (4 to 6 years after disease onset in patients with RRMS [73]. Similar findings were observed in other studies, including a UK cohort study, which showed that patients receiving early intervention with high-efficacy therapies had more favourable long-term outcomes compared with patients receiving platform therapies as part of an escalation strategy [69-72].

The approach of using less efficacious platform therapies earlier in the treatment paradigm is to mitigate the perceived safety concerns with high-efficacy DMTs [11, 69, 74]. However, the long-term safety of many high-efficacy DMTs (including cladribine tablets; Section B.2.10) has been favourable. Therefore, the traditional escalation approach may be an inadequate strategy for many patients, where growing evidence demonstrates that high-efficacy DMTs are most effective at preventing disease progression and future disability at the early stages of the disease [68, 72, 74].

Of the 12 DMTs recommended by NICE for the treatment of the active RRMS population, only three treatments (ponesimod, ofatumumab, and ocrelizumab) are considered high-efficacy DMTs (i.e., agents that have a greater impact on inflammation) alongside older platform therapies [2]. Of these three DMTs, there is only one oral treatment, ponesimod, which requires daily administration.

B.1.3.4. Position of cladribine tablets in RRMS

Based on clinical trial evidence supporting the benefit-risk profile of cladribine tablets in the active RRMS population, and in line with the extended MHRA indication, cladribine tablets should be considered as a high-efficacy DMT option for all patients with active RRMS, including early, first-line use in treatment-naïve patients and as a switch treatment in treatment-experienced patients. The proposed use of cladribine tablets is also supported by extensive post-marketing authorisation clinical and safety data both globally and in the UK.

Finally, expanding the NICE recommendation for cladribine tablets to align with the extended MHRA indication will fulfil several unmet needs from both the patients' and NHS England's perspectives. Due to the unique posology and mechanism of action, cladribine tablets (belonging to the 'immune reconstitution therapy' drug class) offer a highly efficacious, short-course, oral DMT, which:

- Delivers **robust and durable efficacy** across the spectrum of RRMS **without continuous immunosuppression;** the unique posology of cladribine tablets allows for patients to take oral medication for **only two weeks per year in Years 1 and 2** to achieve a **sustained efficacy lasting over four years**, with no re-treatment required in Years 3 and 4
- Offers a **convenient treatment option with infrequent oral dosing** that translates into **reduced treatment burden and treatment fatigue for patients**, as well as **alleviates healthcare resource utilisation** for NHS England due to reduced treatment and monitoring burden
- Has the potential to **maximise the efficacy** offered by cladribine tablets through initiation of **early intensive treatment**, which as demonstrated by a growing number of studies, is **associated with better long-term health outcomes**

B.1.4 Equality considerations

Historically, MS has been most common in the white population, though recent evidence suggests that MS occurrence in ethnic minorities is more frequent than previously thought [75]. Across multiple diseases, including MS, systemic differences in healthcare access, socioeconomic inequalities, cognitive biases and racism within healthcare systems have been shown to have a role in poorer disease-related outcomes among patients from ethnic minorities. Additionally, populations with low education levels and low employment status face obstacles in accessing quality healthcare, which subsequently affects disease-related or clinical outcomes [75].

There are equality considerations for current DMTs recommended by NICE which may apply to patients impacted by socio-economic inequalities. High-efficacy DMTs currently available within NHS, are associated with high treatment burden (e.g., need for regular appointments for administration and/or monitoring purposes). In particular, as mentioned by the MS Trust during consultations for the scope of this appraisal, factors such as requirement for regular travel to infusion centres or prescribing hubs, need for time off work or assistance from carers are often cited by people with low incomes and/or disability as reasons for refusal of high-efficacy DMTs in favour of low-to-moderate-efficacy DMTs that can be self-administered at home [24]. Increasing access to home-delivered, high-efficacy DMTs could reduce the risks of worsening disability (as a result of sub-optimal disease management with more convenient but less efficacious treatments), as well as offer patients the choice of their preferred treatment option. The MS Trust also commented that expanded access to an effective treatment for RRMS, which offers infrequent administration and minimal monitoring can be especially beneficial for people who are insecurely housed or homeless, and members of travelling communities such as Roma or Irish Travellers [24]. Additionally, younger MS patients, who are more likely to consider family planning, may be disproportionately impacted by restricted choice of treatment options, as continuous immunosuppression associated with most of high-efficacy DMTs may be contraindicated for some women who wish to get pregnant [24].

The unique posology of cladribine tablets, allows patients to take oral medication for only two weeks per year in Year 1 and 2 to achieve a sustained efficacy lasting over four years (with no further treatment required in Year 3 and 4), delivering robust and durable clinical benefit without continuous immunosuppression vs. other high-efficacy DMTs. Cladribine tablets are, therefore, well-positioned to fulfil an unmet medical need in a larger population of MS patients and potentially reduce health inequalities in addition to the anticipated benefits below:

- Improve short- and long-term clinical outcomes of patients in a minimally disruptive way due to the convenience of a short-course oral treatment

- Allow access to a preferred MS treatment option by both clinicians and patients [23, 24], and as stated earlier, expand access to patients impacted by socio-economic inequalities, who may have limited access to full services offered by NHS England [24]

- Reduce disproportionate impact on younger patients by allowing more patients to plan their families without the need for pauses in treatment or continuous immunosuppression during pregnancy [24], which is important as the majority of newly diagnosed MS patients are women of childbearing age [22].

B.2. Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all RCTs describing efficacy and safety of cladribine tablets and comparator treatments for RRMS, relevant to the NICE decision problem. The SLR assessed the efficacy, health-related quality of life (HRQoL), safety, and tolerability outcomes associated with key interventions in the treatment of adult patients with RRMS as defined by clinical or imaging features. The literature search was conducted on 5 February 2016, updated on 4 January 2017 and 16 April 2023, and finally updated on 6 February 2024 to ensure all evidence from database inception until 6 February 2024 was included. The full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised are summarised in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Pivotal Phase III trials (CLARITY and CLARITY-EXT)

CLARITY (phase III, n=1,326) and CLARITY-EXT (phase IIIb, n=806) form the key evidence base for the efficacy, safety and tolerability of 3.5 mg/kg cladribine tablets in the RRMS population relevant to the Decision Problem (Section B.1.1). Both of these studies evaluated cladribine tablets as a monotherapy for the treatment of patients with active RRMS and both were included in the marketing authorisation application to the MHRA for cladribine tablets and the prior NICE submission (TA493/TA616) [4] (Table 4).

The CLARITY trial has been included in the indirect treatment comparison and the economic model and forms the basis of the evidence supporting cladribine tablets. The CLARITY-EXT trial was not used to populate the economic model but is included in sections B.2.2 to B.2.6. This study was not included in the economic model due to the lack of a comparator arm. Additionally, due to the nature of extension studies and their inherent heterogeneity we were unable to include the CLARITY-EXT study in a comparative analysis such as the NMA. Results from the CLARITY-EXT trial demonstrates the long-term efficacy and safety of 3.5 mg/kg cladribine tablets over a 4-year period (2 years of the CLARITY trial and 2 years of the CLARITY-EXT trial). Therefore, results of this study support the posology of cladribine tablets i.e., support the claim that the majority of patients do not require further treatment following completion of the two indicated treatment courses of 3.5 mg/kg cladribine tablets and provide validation of the waning assumptions used in the cost-effectiveness model. The results from this study also form the basis of the switching analysis performed by Gorrod et al. (2019) to support the waning assumptions [76].

Table 4: Clinical effectiveness evidence for efficacy and safety of cladribine tablets

Study	Registration studies	
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**
Study design	Phase III double-blind, placebo-controlled, 96-week RCT	Phase IIIb double-blind, 96-week RCT; safety extension trial
Population	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study initiation • Clinically stable and no relapses within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	• Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks
Intervention(s)	• LL- cladribine tablets 3.5 mg/kg cumulative over 96 weeks • HL - cladribine tablets 5.25 mg/kg cumulative over 96 weeks	• Patients were randomised upon entry to receive either further doses of 3.5 mg/kg cladribine tablets or placebo: • LLPP - cumulative 3.5 mg/kg* • HLPP - cumulative 5.25 mg/kg (n=92) • LLLL- cumulative 7.0 mg/kg (n=186) • HLLL- cumulative 8.75 mg/kg (n=186) • PPLL - cumulative 3.5 mg/kg
Comparator(s)	Placebo (PP)	NA
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial is used in the economic model	Yes	No
Rationale for use/non-use in the model	• This was the pivotal trial for cladribine tablets and included the licensed dose and target patient population. Safety and efficacy results were incorporated into the economic model and NMA	• This was a pivotal trial supporting the duration of efficacy and safety for a further 2 years (treatment duration of 4 years in total). Safety results were incorporated in the economic model and the efficacy results were used to support sustained duration of efficacy (i.e., waning effect over 4 years)
Reported outcomes specified in the decision problem (bold	• **Relapse rate**	• Relapse rate • Disability (for example EDSS)

Study	Registration studies	
	CLARITY (NCT00213135)	**CLARITY-EXT (NCT00641537)**
text indicate outcomes incorporated into the economic model)	• **Disability (for example EDSS)** • Freedom from disease activity (e.g., MRI lesions) • **Adverse effects of treatment** • **HRQoL**	• Freedom from disease activity (e.g., MRI lesions) • Adverse effects of treatment
All other reported outcomes – pre-planned	*Secondary endpoints* • Proportion of patients qualifying relapse-free • Mean number of new T1 Gd+, active T2, T1 hypointense and CU lesions *Tertiary endpoints* • Time to first qualifying relapse • Proportion of patients with no new T1 Gd+, active T2, T1 hypointense or CU lesions • Proportion of patients rescued with Rebif (interferon beta-1a)	• Proportion of patients qualifying relapse-free • Time to first qualifying relapse • Time to second qualifying relapse • Time to treatment with rescue medication • Mean number and cumulative number of new T1 Gd+, active T2, T1 hypointense and CU lesions • Proportion of patients with no new T1 Gd+, active T2, T1 hypointense or CU lesions
Post-hoc analyses	• NEDA-3 • Time to 6-month confirmed disability progression	• NEDA-3 • Time to 6-month confirmed disability progression
References	[5, 7, 77-79]	[6, 8, 80, 81]

Source: See table

* Licensed dose of cladribine tablets

CDMS: Clinically defined multiple sclerosis; CU: Combined unique; EDSS: Expanded Disability Status Scale; HDA-RRMS: High disease activity relapse-remitting multiple sclerosis; Gd+: Gadolinium-enhancing; HL: cladribine 3.5 mg/kg in Year 1 followed by cladribine tablets 1.75 mg/kg in Year 2 (cumulative dose of 5.25 mg/kg); HLLL: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4; HLPP: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4; HRQoL: Health-related quality of life; LL: cladribine tablets 1.75 mg/kg in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); LLLL: cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4; LLPP: cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; MRI: Magnetic resonance imaging; NA: Not applicable; NEDA; No evidence of disease activity; NMA: Network meta-analysis; PP: Placebo in Year 1 followed by placebo in Year 2; PPLL: Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4; RCT: Randomised controlled trial; RRMS: Relapsing-remitting multiple sclerosis

Safety evidence

In addition to the safety data presented in the CLARITY and CLARITY EXT trials (Section B.2.10), an integrated safety analysis, including safety data from CLARITY, CLARITY EXT, ORACLE MS and PREMIERE, provides additional safety data for the use of cladribine tablets in patients with RRMS.

PREMIERE study is a prospective, 8-year observational registry study (n=1,148) that provides safety data of patients who participated in cladribine tablet clinical studies (CLARITY, CLARITY-EXT, ONWARD, ORACLE MS, and the pantoprazole drug-drug interaction study) [82].

ORACLE MS is a 96-week Phase III, double-blind, randomized, placebo-controlled, multicentre study that evaluated the safety and efficacy of cladribine tablets over 2 years in patients with a first clinical demyelinating event to clinically definite MS [83].

PREMIERE and ORACLE MS do not provide relevant efficacy data to support the 3.5 mg/kg dose of cladribine tablets in an active RRMS population; however, they do provide vital safety data for its use in patients with RRMS. As such, the safety outcome from PREMIERE and ORACLE MS are incorporated into an integrated safety analysis in addition to CLARITY and CLARITY-EXT (Section B.2.10.3).

Following the completion of the integrated analysis, a post-market real-world study provides safety data that assessed the oral monotherapy cohort from the safety analysis set combined with a post-approval cohort (the first 18,463 patients treated with cladribine tablets [August 2017 to Jul 2020]) [84].

Supporting evidence

In addition to the two pivotal trials, CLASSIC-MS is a multicentre, open-label, single-arm trial (n=435) that provides evidence of long-term clinical benefit in patients with active RRMS who previously participated in CLARITY and CLARITY-EXT studies (median treatment follow-up of 10.9 years) [85]. Summary of the results for CLASSIC-MS are described in Section B.2.6.3.

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

The RCTs identified as relevant to the decision problem in Section B.1.1.1 include CLARITY and CLARITY-EXT. These are the pivotal trials that supported the MHRA marketing authorisation for 3.5 mg/kg cladribine tablets in patients with active RRMS and relevant to the NICE decision problem [5, 6].

The methodologies of CLARITY and CLARITY-EXT are summarised in Table 5.

Table 5: Comparative summary of trial methodology

Trial	CLARITY	CLARITY-EXT
Trial design	Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week	Phase IIIb double-blind, parallel group, multicentre, 96-week

Trial	CLARITY	CLARITY-EXT
Eligibility criteria for participants	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study • Clinically stable and not had a relapse within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	• Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks
Settings and locations where the data were collected	155 investigative sites in 32 countries, including UK	133 investigative sites in 32 countries, including UK
Trial drugs - Interventions and comparators (dosing regimens are detailed in Section B.2.3.3)	Patients (N=1,326) were randomised to receive: • LL- Cladribine tablets 3.5 mg/kg cumulative over 96 weeks (n=433) • HL - Cladribine tablets 5.25 mg/kg cumulative over 96 weeks (n=456) • PP- Placebo (n=437)	Patients from CLARITY (N=806) were randomised (2:1) to receive either further doses of cladribine tablets (LL) or placebo (PP)**: • LLPP - cumulative 3.5 mg/kg* (n=98) • HLPP - cumulative 5.25 mg/kg (n=92) • LLLL - cumulative 7.0 mg/kg (n=186) • HLLL - cumulative 8.75 mg/kg (n=186) • PPLL - cumulative 3.5 mg/kg (n=244)
Trial drugs - permitted and disallowed concomitant medication	• Corticosteroids were permitted to treat acute relapses, however, long-term use (>14 days) necessitated patient withdrawal • Interferon beta-1a 44 µg (Rebif) was permitted as rescue medication following 24 weeks from the start of the trial – to qualify for Rebif rescue medication, patients had to meet the following criteria: ○ Patients who experience >1 qualifying relapse, and/or ○ Patients who have a sustained increase in their EDSS of ≥1 point (or ≥1.5 points if baseline EDSS was 0) over a period of 3 months or greater)	
Primary outcomes (including scoring methods and timings of assessments)	Qualifying ARR – defined as a two-grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement	Safety and tolerability
Other outcomes used in the economic model/specified in the scope	• Disability progression • Mortality • Adverse effects of treatment	• Outcomes from CLARITY-EXT were not included in the economic model

Trial	CLARITY	CLARITY-EXT
	• HRQoL • NEDA-3 (post-hoc) • 6-month CDP (post-hoc)	
Pre-planned subgroups	No subgroup analyses were conducted	

Source: [5, 6]

* Licensed dose for cladribine tablets

** Results from CLARITY demonstrated that there were no considerable differences in the efficacy and safety of 3.5 mg/kg cladribine tablets and 5.25 mg/kg cladribine tablets. As such, 5.25 mg/kg cladribine tablets was omitted from the CLARITY-EXT trial. Only LLPP is relevant and discussed in this submission.

ARR: Annualised relapse rate; CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; HDA-RRMS: High disease activity; HL: cladribine 3.5 mg/kg in Year 1 followed by cladribine tablets 1.75 mg/kg in Year 2 (cumulative dose of 5.25 mg/kg); HLLL: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4; HLPP: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4; HRQoL: Health-related quality of life; KFS: Kurtzke Functional Systems; ; LL: cladribine tablets 1.75 mg/kg in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); LLLL: cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4; LLPP: cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; PP: Placebo in Year 1 followed by placebo in Year 2; PPLL: Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4; RRMS: Relapsing-remitting multiple sclerosis

B.2.3.1. Trial design

The methodologies of each study are described in Table 4. Briefly, CLARITY is the pivotal Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week trial that supports the marketing authorisation for cladribine tablets [5]. CLARITY-EXT was a Phase IIIb double-blind, parallel group, multicentre, 96-week extension trial of CLARITY that provides supportive evidence for sustained efficacy (i.e., 2 years of treatment and no further treatment required in years 3 and 4) [6].

In CLARITY, from the total of 1,326 patients included, 433 patients received the licensed dose of cladribine tablets (3.5 mg/kg) (referred to as LL group; low dose cladribine tablets in Year 1 and low dose cladribine tablets in Year 2) and 437 patients received placebo (referred to as PP group; placebo in Year 1 and placebo in Year 2) [5]. The CLARITY trial formed the evidence base of the previous NICE submission; Evidence Review Group (ERG) considered the CLARITY trial as well designed and well conducted, with participant characteristics balanced across the two trial arms and deemed the pre-planned statistical methods used as generally appropriate [86].

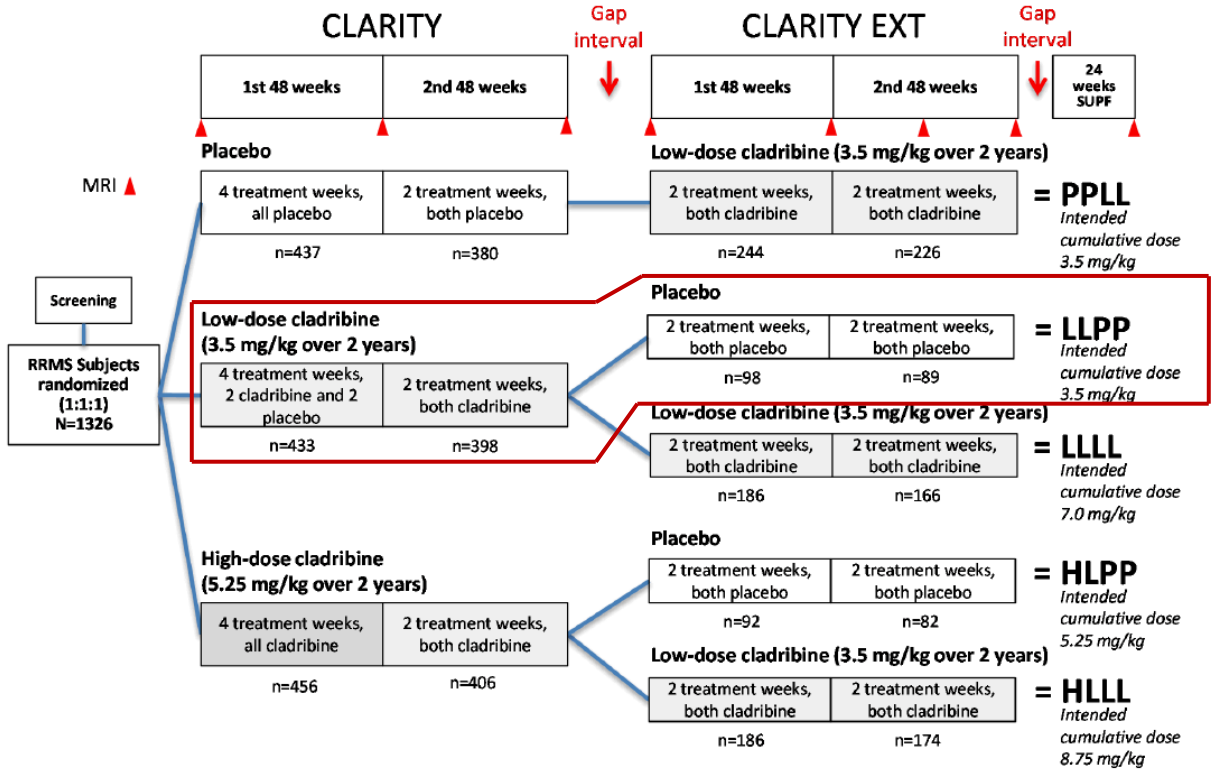
Upon completion of CLARITY, patients were then eligible for entry into CLARITY-EXT [6]. Overall, 806 patients eligible for inclusion in the CLARITY-EXT trial were re-randomised (2:1) to receive either 3.5 mg/kg cladribine tablets or placebo.

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

- LLPP (licensed dose; low dose cladribine tablets: 1.75 mg/kg in Year 1 and 1.75 mg/kg in Year 2, followed by placebo in Year 3 and placebo in Year 4) - cumulative 3.5 mg/kg cladribine tablets (n=98)
- PPLL (placebo in Year 1 and placebo in Year 2, followed by cladribine tablets, 1.75 mg/kg in Year 3 and 1.75 mg/kg in Year 4) - cumulative 3.5 mg/kg cladribine tablets (n=244)

Upon successful completion of the double-blind phase of CLARITY-EXT (up to 96 weeks), all patients were offered participation in the 24-week supplemental follow-up period. No treatment was given during the supplemental follow-up, and patients were followed for clinical, laboratory, and MRI assessments [6]. A schematic of the trial design incorporating both CLARITY and CLARITY-EXT trials is presented in Figure 7.

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



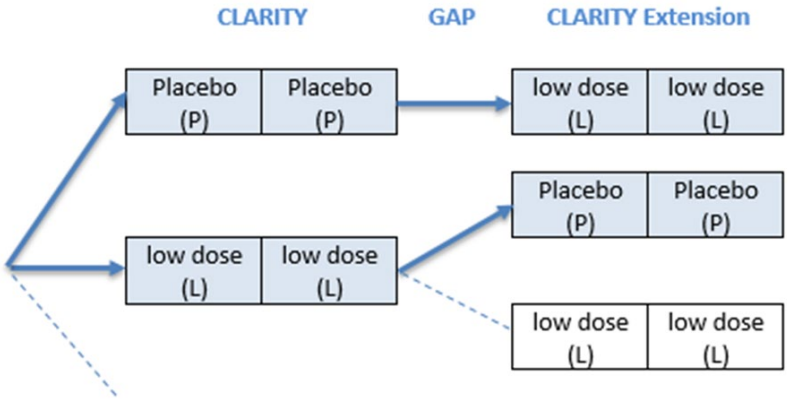
Source: [5, 6]

NOTE: Red box indicates the licensed dose of cladribine tablets (cumulative 3.5 mg/kg)

HLLL: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4; HLPP: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4; LLLL: cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4; LLPP: cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; PPLL: Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4; RRMS: Relapsing-remitting multiple sclerosis; SUPF: Supplemental follow-up

It should be noted that across the 4 years of study treatment, there was no continuous placebo arm. Patients randomised to the placebo arm during the 2-year CLARITY trial and continued into CLARITY-EXT were switched to cladribine tablets 3.5 mg/kg (Figure 8).

Figure 8: Treatment switching analysis



Source: [5, 6]

NOTE: Dotted line represents treatment arm not included in the assessment as the arm is not relevant to the decision problem; the high dose cladribine tablets arm from CLARITY has been excluded from the figure

L: Low-dose (1.75 mg/kg) cladribine tablets over 48 weeks; P: Placebo

B.2.3.2. Treatment gap period

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

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

- For patients with a gap period of less than 4 weeks, the CLARITY 96-week scan was used as a baseline measurement of MRI lesions for CLARITY-EXT

In the previous cladribine appraisal (TA493/TA616), it was concluded that results from the analysis of patients in the treatment gap period show that there was no consistent or meaningful relationship between the duration of the gap period and the majority of efficacy endpoints, suggesting that selection bias was not a concern. In fact, clinicians viewed the treatment gap as evidence of duration of efficacy beyond 4 years in some patients [6].

B.2.3.3. Trial drugs and concomitant medications

The licensed dose of cladribine tablets is a cumulative dose of 3.5 mg/kg body weight over 2 years, administered orally as one treatment course of 1.75 mg/kg per year, as described in the MHRA Summary of Product Characteristics [87]. For additional information on the posology of cladribine tablets, please refer to the summary of product characteristics found at https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf [3].

The CLARITY trial evaluated the licensed dose of cladribine tablets (low dose cladribine tablets 3.5 mg/kg cumulative) compared with placebo [5]. The CLARITY trial was divided into two 48-week treatment periods (Year 1 and Year 2) with four 28-day treatment cycles in Year 1 (Week 1, Week 5, Week 9, Week 12) and two 28-day treatment cycles in Year 2 (Week 48 and Week 52). Cladribine tablets or placebo was administered orally as one or two 10 mg tablets for the first 4 or 5 days of each 28-day treatment cycle. Cladribine tablets were given as 0.875 mg/kg/cycle. The number of tablets administered was standardised based on weight, using 10 kg weight ranges (i.e., 60 kg-69.9 kg, 70 kg-79.9 kg, etc.) [79] (Table 6).

Table 6: Dosing regimen for CLARITY

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

Source: [5]

C: Cladribine tablets (active dose) given as 0.875 mg/kg/cycle; LL: Low dose cladribine tablets in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); P: Placebo; PP: Placebo in Year 1 and Year 2

The dosing regimen in CLARITY-EXT was similar to that in CLARITY (Table 6), where patients were treated at Weeks 1, 5, 48 and 52 with cladribine tablets or placebo [6]. However, only

the LLPP arm (licensed dose), i.e., patients who received placebo in CLARITY-EXT, are of interest for this submission.

In addition to the trial drugs, the use of corticosteroids was permitted to treat acute relapses in both CLARITY and CLARITY-EXT. Patients requiring long-term use of corticosteroids (>14 days) were withdrawn from the trial [5, 6]. Patients experiencing a relapse during the trial were given the option to use 'rescue therapy' after 24 weeks from the start of the trial, if they met the following criteria [5, 6]:

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

The preferred rescue therapy specified in CLARITY and CLARITY-EXT was interferon beta-1a, supplied by Merck. Other DMTs were also permitted if the patient and investigator decided that it was considered necessary for the patient's welfare. Patients who received rescue therapy were permanently discontinued from the trial medication but remained in the trial to provide all assessments according to the visit schedule [5, 6].

B.2.3.4. Trial outcomes

The key primary outcome for CLARITY and CLARITY-EXT was ARR and the key secondary outcomes included time to disability progression at 3 months (i.e., 3-month CDP), time to use of rescue therapy, proportion of relapse-free patients and MRI measures. The pre-specified primary and secondary outcomes for CLARITY and CLARITY-EXT are summarised in Table 7.

Table 7: Pre-planned trial outcomes for CLARITY and CLARITY-EXT

Outcomes	CLARITY	CLARITY-EXT
Primary outcome	• Qualifying ARR – defined as a two-grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement	• Safety and tolerability
Secondary/ exploratory outcomes	*Clinical efficacy:* • Proportion of relapse-free patients • Time to 3-month CDP • Time to first qualifying relapse *MRI efficacy:* • Mean number and proportion of	*Clinical efficacy:* • Qualifying ARR • Proportion of relapse-free patients • Time to first and second relapse • Time to 3-month CDP • Time to use of rescue therapy

Outcomes	CLARITY	CLARITY-EXT
	patients with: ○ T1 Gd+ lesions ○ T2 lesions ○ CU lesions ○ T1 hypointense lesions • Volume of: ○ T2 lesions ○ T1 hypointense lesions *Safety and tolerability:* • Proportion of patients with AEs *Other outcomes:* • HRU • HRQoL • Effect of treatment on relapses • Effect of treatment on disability • Mortality • Time to use of rescue therapy	*MRI efficacy:* • Mean number, cumulative number and proportion of patients with: ○ T1 Gd+ lesions ○ T2 lesions ○ CU lesions ○ T1 hypointense lesions • Volume of: ○ T2 lesions ○ T1 hypointense lesions *Other outcomes:* • HRU • HRQoL • Characterisation of immune cell subsets • Gene expression profiles

Source: [7, 8, 79, 81, 88, 89]

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

A summary of the post-hoc analysis are presented in Table 8.

Table 8: Post-hoc analyses for CLARITY and CLARITY-EXT

Trial	Outcome	Definition
CLARITY	NEDA-3	• No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions
	Time to 6-month CDP	• CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0
	Proportion of patients with 6-month CDP	
CLARITY-EXT	NEDA-3	• No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions
	Time to 6-month CDP	• CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0
	Proportion of patients with 6-month CDP	
	Clinical and MRI efficacy outcomes as described for pre-planned CLARITY analyses	• See CLARITY in Table 7

Source: [7, 8, 90]

CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; Gd+: Gadolinium-enhancing; MRI: Magnetic resonance image; NEDA: No evidence of disease activity

B.2.3.5. Patient characteristics

The baseline characteristics of the patients were generally well-balanced in all treatment arms. In CLARITY, a numerically higher percentage of patients in the placebo arm were treatment experienced ([redacted] vs. [redacted], respectively) [7]. Approximately two thirds of each treatment arm was female (65.9% in placebo arm, 68.8% in the 3.5 mg/kg cladribine tablets arm) [5]. The clinical presentation of RRMS symptoms was also similar between treatments arms (mean EDSS score, number of T1 Gd+ lesions and T2 lesions) [5, 6]. In the CLARITY-EXT trial, the LLPP treatment group had similar patient characteristics as those from the CLARITY trial, however only [redacted] of patients were treatment experienced within three months of the study and the mean disease duration was also lower; mean EDSS remained comparable [8]. The characteristics of patients at baseline for CLARITY and CLARITY-EXT are summarised in Table 9.

Table 9: Baseline characteristics of patients in CLARITY and CLARITY-EXT (ITT analysis)

Characteristic	CLARITY		CLARITY-EXT
	Placebo (n=437)	Cladribine tablets 3.5 mg/kg (n=433)	LLPP 3.5 mg/kg (n=98)
Mean (SD) age, years	38.7 (9.9)	37.9 (10.3)	[redacted]
Female, %	65.9	68.8	[redacted]
Previous DMT use, %	[redacted]	[redacted]	[redacted]
Mean (SD) disease duration, years	[redacted]	[redacted]	[redacted]
Mean (SD) EDSS score	2.9 (1.3)	2.8 (1.2)	[redacted]
Mean number (SD) T1 Gd+ lesions	0.8 (2.1)	1.0 (2.7)	[redacted]
Mean volume (SD) T2 lesions cm3	14.3 (13.1)	14.8 (16.3)	[redacted]

Source: [7, 8]

DMT: Disease-modifying treatment; EDSS: Expanded Disability Status Scale; Gd+: Gadolinium-enhancing; LLPP: 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; SD: Standard deviation

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

The primary objective in CLARITY was to evaluate the efficacy of cladribine tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in patients with active RRMS. To achieve this objective, the primary analysis was conducted in the intention-to-treat (ITT) patient population using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable in the model. As per the initial

statistical analysis plan (SAP), the responses for patients with missing relapse, EDSS progression, or MRI lesion status were imputed based on data for patients with a known status (i.e., either free or not free) at the end of 96 weeks. Imputation for secondary endpoints was performed according to the SAP [5]. However, Merck conducted re-analyses to support the 2017 EMA submission and the previous NICE submission (TA493/TA616). The revised approach used in the 2017 re-analysis was considered by the ERG as more appropriate [86]

A summary of the revised methodology is presented in the Table 10, below.

CLARITY-EXT was designed to evaluate the safety of extended treatment with cladribine tablets when administered according to a fixed annual dosing schedule to patients who completed CLARITY. The primary safety analysis was conducted in all patients who received at least one dose of cladribine tablets and had at least one safety assessment during the trial, efficacy analyses were performed using the ITT patient population. Missing data in the form of partial dates of patient history (including MS history, history of DMT use, relapse history, and relapses), concomitant medication use, AEs and AE severity, and unscheduled assessments were handled according to the SAP [81] .

A summary of the statistical analyses for both CLARITY and CLARITY-EXT are presented in Table 10.

Table 10: Summary of statistical analyses

Trial	CLARITY	CLARITY-EXT
Hypothesis objective	To evaluate the efficacy of cladribine tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in patients with RRMS	To evaluate the safety of extended treatment with oral cladribine when administered according to a fixed annual dosing schedule to subjects who completed CLARITY
Statistical analysis	• The ARR endpoint was analysed using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable • An approximate Chi-square test based on Wald statistics was used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error • The assumption for proportional hazards held for the ITT population and therefore the Cox regression methodology was appropriate; this was acknowledged by the ERG in TA493/TA616	
Sample size, power calculation	A sample size of 1,290 patients (430 patients in each treatment arm) provided 90% power to detect a clinically meaningful 25% relative reduction in ARR at 96 weeks when comparing each cladribine tablets arm to the placebo arm*	A total of 1,326 patients were randomized into CLARITY, of whom 867 completed CLARITY and enrolled in CLARITY-EXT. The number of patients eligible to enter CLARITY-EXT was limited by the enrolment, retention, and rollover of patients from the preceding CLARITY study. Therefore, no statistical estimation of the sample size was performed
Data management, patient withdrawals	• The investigator was responsible for data management, ensuring eCRFs were completed appropriately to ICH GCP standards • Patients could withdraw from the trial at any time, but were asked to continue with all trial assessments and return for the week 96/early termination visit • Withdrawal was mandatory if the patient-initiated treatment with another investigational drug, was non-compliant or violated protocol	

Source: [91]

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

ARR: Annualised relapse rate; eCRFs: Electronic case report forms; GCP: Good clinical practice; ICH: International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use; RRMS: Relapsing-remitting multiple sclerosis

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Table 11: Quality assessment of the relevant clinical effectiveness evidence

Trial	CLARITY	CLARITY-EXT
Was randomisation carried out appropriately?	Yes	Yes

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

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

B.2.6 Clinical effectiveness results of the relevant trials

The primary, secondary and tertiary analyses performed for CLARITY and CLARITY-EXT were conducted in the ITT patient population. Note that only the cladribine tablets 3.5 mg/kg treatment groups from CLARITY and CLARITY-EXT will be discussed in this submission given that this is the licensed dose. In line with previous NICE submission (TA493/TA616), most values presented in this submission come from a 2017 re-analysis of the CLARITY [7] and CLARITY-EXT [8] trials, which was conducted by Merck, and where the company amended the statistical approach with regards to missing data; the ERG agreed that the statistical approach used within the re-analysis is more appropriate than the original approach [86], which was used in the CLARITY [5] and CLARITY-EXT publications [6].

B.2.6.1. CLARITY

Overall, the results demonstrate that treatment with 3.5 mg/kg cladribine tablets was more effective than placebo in patients with active RRMS across a broad spectrum of clinical and MRI efficacy outcomes [5]. Cladribine tablets were shown to statistically significantly reduce the qualifying ARR compared with placebo ($p<0.001$) [5] and the risk of developing 6-month CDP was shown to be statistically significantly reduced compared with placebo [redacted] [7], as determined during the post-hoc analyses. Cladribine tablets 3.5 mg/kg was also associated with an overall improvement in MRI outcomes such as the mean number of new T1 Gd+ and active T2 lesions [5]. In a post-hoc analysis, the proportion of patients with NEDA-3 following

treatment with 3.5 mg/kg cladribine tablets was shown to be significantly higher compared with placebo [redacted] [90]. A full description of the results from CLARITY is described below.

B.2.6.1.1. Endpoints associated with relapses

Qualifying ARR and time to first qualifying relapse in CLARITY

In the ITT population, treatment with 3.5 mg/kg cladribine tablets was associated with a statistically significant [redacted] relative reduction in qualifying ARR compared with placebo ([redacted] vs. [redacted], respectively; [redacted]) and a significant delay in the time to first qualifying relapse compared with placebo ([redacted]) (Table 12) [7]. Based on the Kaplan-Meier estimates, at the end of the CLARITY trial, [redacted] of patients treated with 3.5 mg/kg cladribine tablets were relapse-free compared with [redacted]([redacted]) of patients treated with placebo [7].

Table 12: Qualifying ARR at 96 weeks in CLARITY

Outcome	3.5 mg/kg cladribine tablets (N=433)	Placebo (N=437)
Qualifying ARR at 96 weeks in CLARITY		
Qualifying ARR (95% CI)	[redacted]	[redacted]
Relative reduction in ARR, %	[redacted]	
Rate ratio (95% CI)	0.42 (0.33, 0.52)	
p-value	[redacted]	
Time to first qualifying relapse in CLARITY		
K-M estimate of relapse-free patients, % (95% CI)	[redacted]	[redacted]
HR (95% CI) for cladribine tablets vs. placebo	[redacted]	
p-value	[redacted]	

Source: [7, 78]

ARR: Annualised relapse rate; CI: Confidence interval; HR: Hazard ratio; K-M: Kaplan-Meier

Proportion of qualifying relapse-free patients

The proportion of patients who were qualifying relapse-free at 48 weeks was numerically higher in the cladribine tablets treatment group compared with placebo ([redacted] vs. [redacted]). At the 96 weeks, the number of patients who were qualifying relapse-free remained higher in the 3.5 mg/kg cladribine tablets treatment group compared with the placebo group ([redacted]) (Table 13) [7].

Table 13: Proportion of relapse-free patients at 96 weeks in CLARITY

Outcome	3.5 mg/kg cladribine tablets (N=433)	Placebo (N=437)
Qualifying relapse-free at 48 weeks, n (%)		
Relapse	[redacted]	[redacted]
Relapse-free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]
Qualifying relapse-free at 96 weeks, n (%)		
Relapse	[redacted]	[redacted]
Relapse-free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

Source: [7]

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

B.2.6.1.2. Endpoints associated with disability

3-month CDP

Treatment with 3.5 mg/kg cladribine tablets significantly prolonged the time to 3-month CDP over 96 weeks compared with placebo (Kaplan-Meier estimates for progression-free at last event: [redacted] vs. [redacted]) (Table 14), demonstrating a [redacted] reduction in the risk of disability progression at 96 weeks compared with placebo ([redacted]) [7].

The absolute number of patients who were considered to be 3-month CDP-free at 96 weeks was considerably higher in patients who were treated with 3.5 mg/kg cladribine tablets compared with those treated with placebo ([redacted] vs. [redacted]) (Table 14). Similarly, fewer patients treated with 3.5 mg/kg cladribine tablets had a 3-month CDP compared with placebo ([redacted] vs. [redacted]) [7].

Table 14: 3-month CDP in CLARITY

Outcome	3.5 mg/kg cladribine tablets (N=433)	Placebo (N=437)
Time to 3-month CDP		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for cladribine tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
Proportion of patients with 3-month CDP at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression-free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

Source: [7]

*Patients who withdrew early before week 96 with no 3-month CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP: Confirmed disability progression; CI: Confidence interval; HR: Hazard ratio; K-M: Kaplan-Meier

6-month CDP (post-hoc analysis)

In addition to a 3-month CDP analysis, the 6-month CDP status of the patient population was determined in a post-hoc analysis to demonstrate prolonged efficacy in the reduction of disability progression following treatment with 3.5 mg/kg cladribine tablets.

Treatment with 3.5 mg/kg cladribine tablets significantly prolonged the time to 6-month CDP over 96 weeks compared with placebo (Kaplan-Meier estimates for progression-free at last event: [redacted] vs. [redacted]), demonstrating a [redacted] reduction in the risk of disease progression compared with placebo ([redacted]) compared with placebo (Table 15) [7].

The time to 6-month CDP analysis was supplemented with absolute proportions of patients with 6-month CDP. Over 96 weeks, treatment with 3.5 mg/kg cladribine tablets resulted in fewer patients with a 6-month CDP compared with placebo ([redacted] vs. [redacted]) (Table 15) [7].

In the previous submission (TA493/TA616), the ERG was satisfied with the rationale of why the 6-month CDP analyses were conducted post-hoc, and considered the statistical approach employed by Merck for these analyses as appropriate [86].

Table 15: 6-month CDP in CLARITY (post-hoc analysis)

Outcome	3.5 mg/kg cladribine tablets (N=433)	Placebo (N=437)
Time to 6-month CDP		
K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for cladribine tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	
Proportion of patients with 6-month CDP at 96 weeks, n (%)		
Progression	[redacted]	[redacted]
Progression -free	[redacted]	[redacted]
Unknown*	[redacted]	[redacted]

Source: [7]
* Patients who withdrew early before week 96 with no 6-month CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP: Confirmed disability progression; CI: Confidence interval; HR: Hazard ratio; K-M: Kaplan-Meier

B.2.6.1.3. Other endpoints

MRI lesions

Results for endpoints associated with MRI lesions in CLARITY are presented in Appendix D.1.4.1.

In summary, treatment with 3.5 mg/kg cladribine tablets was shown to significantly reduce the overall number of T1 Gd+, active T2, combined unique (CU) and T1 hypointense lesions compared with placebo ([redacted]) [7]. Furthermore, the proportion of patients shown to be free of MRI lesion activity was numerically higher following treatment with 3.5 mg/kg cladribine tablets compared with placebo [7].

These results demonstrate the efficacy of 3.5 mg/kg cladribine tablets and support the results associated with relapses and disability progression.

NEDA-3 (post-hoc analysis)

NEDA-3 is a composite clinical outcome defined as no relapses, no 3-month CDP, and no MRI lesion activity (no new T1 Gd+ lesions and no active T2 lesions) over weeks 0-96. The results show that a significantly greater proportion of patients treated with 3.5 mg/kg cladribine tablets had no evidence of disease activity over the entire duration of the CLARITY trial ([redacted]) (Table 16) [90]. The proportion of patients who reached NEDA-3 at Year 1 and Year 2 was [redacted] and [redacted], respectively, for 3.5 mg/kg cladribine tablets compared with [redacted] and [redacted], respectively, for placebo [90].

In the previous submission (TA493/TA616), the ERG was satisfied with the rationale of why the NEDA-3 analyses were conducted post-hoc, and considered the statistical approach employed by Merck for these analyses as appropriate [86].

Table 16: Post-hoc analysis of patients with NEDA status in CLARITY

Outcome	3.5 mg/kg cladribine tablets (N=402)	Placebo (N=379)
K-M estimate of NEDA-3 status, % of patients (95% CI)	[redacted]	[redacted]
HR for cladribine tablets vs. placebo (95% CI)	[redacted]	
p-value	[redacted]	

Source: [90]

CI: Confidence interval; HR: Hazard ratio; K-M: Kaplan-Meier; NEDA: No evidence of disease activity

Rescue medication use

Fewer patients treated with 3.5 mg/kg cladribine tablets required rescue therapy (interferon beta-1a) during the CLARITY trial compared with patients from the placebo treatment group ([redacted] vs. [redacted]) (Table 17) [7]. The majority of patients who received rescue medication were

treated with Rebif, the preferred DMT as stated in the protocol ([redacted] patients in the 3.5 mg/kg cladribine tablets arm and [redacted] patients in the placebo arm). Patients were also rescued with glatiramer acetate, interferon beta-1b, natalizumab and mitoxantrone [7].

Table 17: Proportion of patients rescued at 96 weeks in CLARITY

Outcome	3.5 mg/kg cladribine tablets (N=433)	Placebo (N=437)
Patients receiving rescue therapy, n (%)	[redacted]	[redacted]
Mean duration of rescue medication, days (SD)	[redacted]	[redacted]

Source: [7]
SD: Standard deviation

HRQoL

The change from baseline in HRQoL of patients in the CLARITY trial was captured by the disease-specific HRQoL measure, Multiple Sclerosis Quality of Life-54 (MSQoL-54). Secondary HRQoL measures included the use of the EQ-5D visual analogue scale (VAS) and index. In addition, the short-form health survey (SF-36) was also implemented in the trial, however, this assessment was not initiated at the start of the trial and therefore the majority of baseline measurements were not reported. Consequently, it was not possible to perform treatment effect analyses on SF-36 scores [89].

Specifically, the MSQoL-54 physical function domain was used as the primary outcome measure in the CLARITY trial, as this was considered to be the most appropriate measure of assessing physical limitations. However, the MSQoL-54 physical function score demonstrated no statistically significant differences between the 3.5 mg/kg cladribine tablets and placebo groups, irrespective of the analysis method used ([redacted] and [redacted] based on non-imputed and imputed results, respectively) [89]. In the previous submission (TA493/TA616), the ERG was mostly satisfied with the HRQoL analyses methodology; while some concerns were raised about data handling, the ERG acknowledged that given that the imputed and non-imputed results were provided in the submission, there are no changes in conclusions [86].

MSQoL-54 outcome scores outside of the physical domain were assessed as secondary outcome measures [89]. Patients in the 3.5 mg/kg cladribine tablets treatment group demonstrated better outcomes in the health distress domain compared with placebo, although this difference was not statistically significant ([redacted]) [89]. The adjusted mean change in score from baseline to 96 weeks for 3.5 mg/kg cladribine tablets and placebo groups for the other secondary MSQoL measures did not show any statistically significant differences. The lack of statistical significance may have been due to high ceiling effects suggesting that patients tended to have a good level of HRQoL when entering the CLARITY trial, leaving little

room for improvement. This may partly explain the difficulty in showing any clear differences in change in MSQoL-54 scores between patients treated with 3.5 mg/kg cladribine tablets and those treated with placebo. Along with the generally good level of patients' HRQoL over the course of the trial, the use of generic PRO instruments, as well as the limited sample size for the MSQoL-54 questionnaire, may have contributed to the inconclusive results of the treatment effect analysis [89].

Assessment of patient reported outcomes in the EQ-5D VAS and index scores showed that 3.5 mg/kg cladribine tablets resulted in a slight numerical improvement in non-disease specific HRQoL [89]. Further analyses demonstrated that this improvement was statistically significant for both the EQ-5D VAS and EQ-5D index scores ([redacted] and [redacted], respectively) [89].

B.2.6.2. CLARITY-EXT

The primary objective of the CLARITY-EXT trial was to evaluate the longer-term safety and tolerability of 3.5 mg/kg cladribine tablets in active RRMS [6]. As such, the efficacy outcomes from the CLARITY-EXT trial were exploratory.

Qualifying relapses were considered in the analyses for the CLARITY-EXT trial, similar to the CLARITY trial. An exception to the definition of qualifying relapse was made for the gap periods between the CLARITY and the CLARITY-EXT trials and between the end of the CLARITY-EXT trial and the start of supplemental follow-up phase. As there was no prospective data collection during these periods, relapse data were captured retrospectively and self-reported by patients at the first visit of the following study or phase. Accordingly, all relapses reported during the gap intervals were included, whether or not their qualifying status was confirmed. Analyses that consider the entire period from CLARITY to CLARITY-EXT including the treatment gap period between the two trials, are reported in this section unless otherwise specified. Note that only the LLPP treatment group (cladribine tablets 1.75 mg/kg in Year 1 and cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4) is discussed in this submission given that this is the licensed dose for cladribine tablets [6].

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

B.2.6.2.1. Endpoints associated with relapses

Qualifying ARR

The ARR for patients who received a cumulative dose of 3.5 mg/kg cladribine tablets over 4 years (including the CLARITY trial) in the LLPP group was [redacted] (Table 18). In addition, the ARR was numerically higher during the CLARITY-EXT trial in the LLPP treatment group than that observed in the respective CLARITY treatment group, however this difference was not considered statistically significant ([redacted]) [8].

The Kaplan-Meier estimates show that at the end of the CLARITY-EXT trial, [redacted] of patients from the LLPP group were relapse-free [8].

During the CLARITY-EXT trial, a high proportion of LLPP patients were considered to be qualifying relapse-free ([redacted]) at 48 weeks. Over the course of the trial, the proportion of patients qualifying as relapse-free decreased slightly at 96 weeks ([redacted]) and by the end of the trial, [redacted] of patients from the LLPP treatment group were qualifying relapse-free [8].

Table 18: Qualifying ARR in CLARITY-EXT

Outcome	LLPP (N=98)
Relapses during CLARITY (N=433)	
Number of qualifying relapses, mean (SD)	[redacted]
ARR (95% CI)	[redacted]
Relapses during CLARITY-EXT (N=98)	
Number of qualifying relapses, mean (SD)	[redacted]
ARR (95% CI)	[redacted]

Source: [8]

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

ARR: Annualised relapse rate; CI: Confidence interval; LLPP: 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; SUPF: Supplemental follow-up

B.2.6.2.2. Endpoints associated with disability

3-month CDP

Based on Kaplan-Meier estimates for 3-month CDP at the end of the CLARITY-EXT trial, [redacted] of patients were 3-month CDP-free ([redacted]) [8].

The absolute number of patients from the LLPP treatment group who were 3-month CDP-free at 48 weeks was [redacted]. This proportion of patients decreased slightly at 96 weeks ([redacted]) and by end of the trial, [redacted] of patients from the LLPP treatment group were 3-month CDP-free (Table 19) [8].

Table 19: Proportion of patients with 3-month CDP at 48 weeks, 96 weeks and end of study in CLARITY-EXT

Outcome	LLPP (n=98)
3-month CDP at 48 weeks, n (%)	
Progression	[redacted]
Progression-free	[redacted]
Unknown*	[redacted]
3-month CDP at 96 weeks, n (%)	
Progression	[redacted]
Progression-free	[redacted]
Unknown*	[redacted]
3-month CDP at end of study, n (%)	
Progression	[redacted]
Progression-free	[redacted]
Unknown*	[redacted]

Source: [8]

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

CDP: Confirmed disability progression; LLPP: 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4

6-month CDP (post-hoc analysis)

Over the 96 weeks of the CLARITY-EXT trial, similar to the results in CLARITY, the absolute number of patients from the LLPP treatment group shown to be free from 6-month CDP was [redacted] (vs. [redacted]) and by the end of the study, [redacted] of patients were 6-month CDP-free (Table 20) [8].

Table 20: Proportion of patients with 6-month CDP at 48 weeks, 96 weeks and at end of study in CLARITY-EXT

Outcome	LLPP (n=98)
6-month CDP at 48 weeks, n (%)	
Progression	[redacted]
Progression-free	[redacted]
Unknown*	[redacted]
6-month CDP at 96 weeks, n (%)	
Progression	[redacted]
Progression-free	[redacted]
Unknown*	[redacted]
6-month CDP at end of study, n (%)	
Progression	[redacted]

Outcome	LLPP (n=98)
Progression-free	[redacted]
Unknown*	[redacted]

Source: [8]

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

CDP: Confirmed disability progression; LLPP: 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4

B.2.6.2.3. Other endpoints

MRI lesions

The reported MRI lesion activity in CLARITY-EXT [8] support the results observed during CLARITY [7]. Additional results on MRI lesion activity from CLARITY-EXT are in Appendix D.1.4.2.

NEDA-3 (post-hoc analysis)

In the CLARITY-EXT trial, the proportion of patients in the LLPP group who reached NEDA-3 at Year 1 and Year 2 was [redacted] and [redacted], respectively [90].

Rescue medication use

Of the 98 patients in the LLPP group in CLARITY-EXT, only [redacted] required treatment with rescue medication [8].

HRQoL

Over the course of CLARITY and CLARITY-EXT, there was an overall improvement in HRQoL of patients in the LLPP treatment group based on EQ-5D VAS and index scores, and MSQoL-54 mental and physical health composite scores [88].

B.2.6.3. Additional supporting evidence

B.2.6.3.1. CLASSIC-MS

Study Design

CLASSIC-MS is a global, multicentre, open-label, follow-up study in patients with active RRMS who were previously enrolled in the CLARITY/CLARITY EXT trials [85]. The analysis included patients who participated in the CLARITY trial, with or without subsequent enrolment to the CLARITY-EXT trial, for which the median time to follow-up in CLASSIC-MS since the last

parent study dose was 10.9 years (range: 9.3-14.9). To be eligible for inclusion, patients must have received at least one course of cladribine tablets or placebo (n=435 [patients never exposed to cladribine tablets i.e., placebo n=41; all patients exposed to cladribine tablets n=394; subgroup exposed to cladribine tablets 3.5 mg/kg n=160])

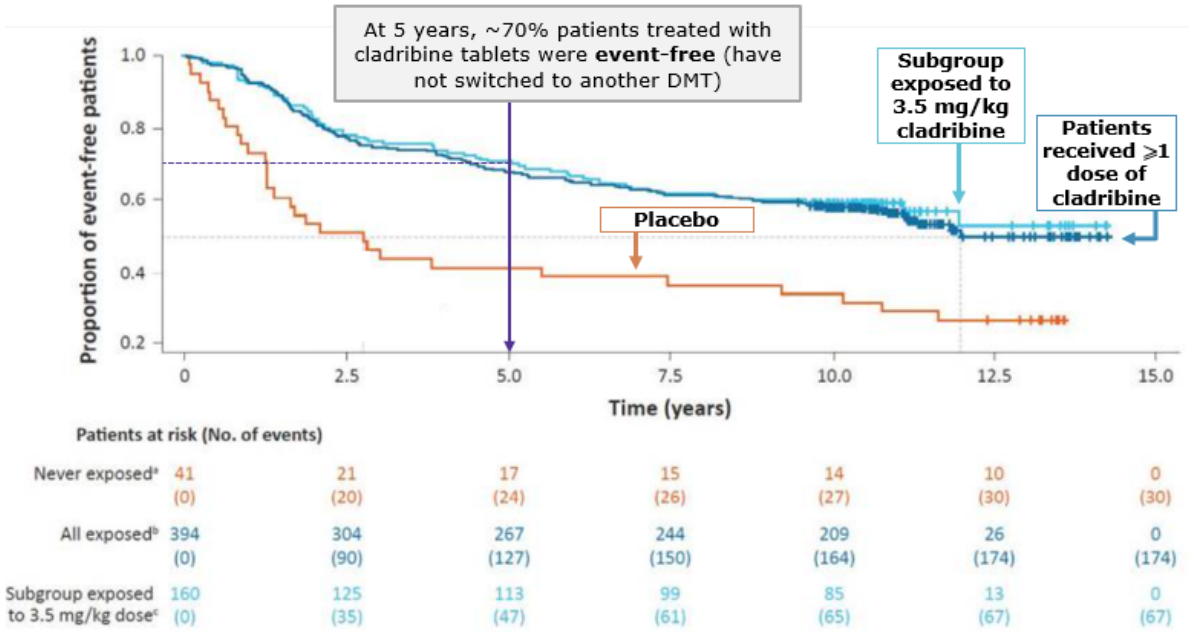
The primary objective was to evaluate long-term mobility beyond treatment courses received in the CLARITY/CLARITY-EXT trials (no wheelchair use in the 3 months prior to first visit in the CLASSIC-MS study and not bedridden at any time since last parent study dose, i.e., EDSS score <7). The secondary objective was to evaluate long-term disability status (no use of an ambulatory device [EDSS<6] at any time since last parent study dose). The tertiary objectives included determining real-world treatment patterns by assessing the number, type, and timing of subsequent DMT use [85].

Summary of results

The study demonstrated sustained long-term mobility and disability benefits in patients with active RRMS treated with cladribine tablets, with a lower risk of reaching EDSS 6 or 7 during the median 10.9 years of follow-up compared with patients who were never exposed to active treatment with cladribine tablets [85].

Over the period since last parent study dose, a greater proportion of patients exposed to treatment with cladribine tablets reported no subsequent treatment compared to patients never exposed (50.3% vs. 26.8%, respectively, not statistically significant). Additionally, the majority of patients who were exposed to cladribine tablets were also less likely to use further DMTs during the median 10.9-year period since last parent study dose (55.8% of the exposed cohort vs. 26.8% in the never exposed cohort; for patients receiving cladribine tablets 3.5 mg/kg over 2 years, 58.1% received no further DMTs). In addition, the time-to-event analyses indicated that patients exposed to cladribine tablets had a longer estimated median time until the first subsequent DMT (12 years vs. 2.8 years for the never-exposed cohort), with better outcomes over the 4 years since last parent study dose in the responder analyses (Figure 9) [85].

Figure 9: Kaplan–Meier curve for time to first subsequent DMT after last parent study dose in CLARITY/CLARITY-EXT (CLASSIC-MS)



Source: [85]

[a]Never-exposed cohort received only placebo during the parent studies.

[b]Exposed cohort includes all patients who received at least 1 dose of cladribine tablets during the parent studies.

[c]Subgroup of the exposed cohort in which patients received 3.5 mg/kg cumulative dose over 2 years during the parent studies (N = 160/394).

B.2.7 Subgroup analysis

There is no sub-group analysis relevant to the NICE decision problem to be presented.

B.2.8 Meta-analysis

A meta-analysis was not possible as only one study included cladribine tablets at the anticipated licensed dose (3.5 mg/kg as monotherapy) and target patient population (active RRMS).

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1. Summary

- A network meta-analysis (NMA) was conducted to assess the comparative effectiveness of cladribine tablets versus comparator DMTs in active RRMS. Of the 61 studies identified in the SLR (see section B.2.1), 38 trials were included in the NMA. Other studies were removed if the intervention or comparator were outside the scope

of this submission. The NMA was focused on all approved DMTs for active RRMS in UK, aligned with the final NICE scope in the company submission

- Overall, the methodology of the NMA when compared with NMAs accepted in recent NICE submissions in RRMS (e.g. TA533, TA699, TA767) [92-94] was similar in terms of the statistical model for the NMA analysis, included studies and population, and outcomes evaluated.
- The results of our NMA are comparable to recent NICE submissions in RRMS demonstrating that cladribine tablets are a comparatively effective and safe alternative to other DMTs in active RRMS.
- The present NMA also includes unpublished post-hoc analysis of 6-month CDP for interferon beta-1a versus placebo from the PRISMS trial [95]. This analysis was performed to improve the level of evidence available for 6-month CDP in active RRMS, and to improve the evidence connecting ocrelizumab which was studied versus interferon beta-1a, to the rest of the network.
- Limitations of the NMA include uncertainty arising from heterogeneity between trials included in the networks, due to differences in study designs and patient characteristics. The trials included in the NMA were conducted over a period of 35 years (1987 to 2022). These trials differed in study characteristics (diagnostic criteria, study phase, and blinding), patient population recruited (mean relapses in prior 1 year, disease duration, treatment history [previously treated versus treatment naïve]) and definitions of outcomes. Evidence networks involving small sample size and limited evidence do not allow Bayesian models to converge and hence, the NMA results are less reliable.
- There were variations in the definitions of 3-month and 6-month CDP across the included studies. A limited number of studies provided a consistent definition for these outcomes, and it was not feasible to conduct sensitivity analysis owing to limited evidence for each definition.

B.2.9.2. Methodology

RCTs identified in the SLR (detailed in Section B.2.1 and Appendix D) informed the NMA to establish the comparative effectiveness of cladribine tablets against DMTs listed in the NICE final scope in patients with active RRMS. Of the 61 studies identified in the SLR, 38 trials were included in the NMA. Studies were removed if the intervention or comparator were outside the scope of this submission. The NMA was focused on all NICE-approved DMTs for active RRMS in UK.

The CLARITY study was included in the NMA, however, the CLARITY-EXT study could not be considered in the NMA due to the lack of a common treatment arm with competitor trials and heterogeneity of the study designs associated with studies evaluating long-term (greater than 2 years) data for MS treatments.

The patient population in the included trials is restricted to that outlined in the scope of the decision problem. According to the review of the inclusion criteria, the selected trials were composed of adult patients (≥18 years) with a confirmed diagnosis of RRMS. However, some studies also included a small number of patients with progressive disease, despite RRMS being an inclusion criterion. Therefore, to ensure a majority focus on RRMS, trials with more than 20% of progressive patients were excluded from the NMA based on IQWiG guidance [96]. This approach is aligned with TA624 and TA767 [94, 97].

In line with recent NICE appraisals in MS (TA493/ TA616, TA533, TA624, TA699, TA767), the outcomes listed in the Decision Problem, and the outcomes considered in the cost-effectiveness model for cladribine tablets (described in Section B.3), NMAs were conducted for ARR, 3-month CDP, 6-month CDP and treatment discontinuations (all-cause treatment withdrawals). The 3-month and 6-month CDP were measured at 24-months of follow-up.

The NMA was conducted using a set of Bayesian Markov Chain Monte Carlo methods as described in the NICE Decision Support Unit Technical Support Document (NICE DSU TSD 2). The NMA was conducted using a statistical analysis plan. Vague or non-informative priors were used. Both fixed and random effects models were considered as part of this analysis. The choice of random versus fixed effects model was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC). The model with the lowest DIC and/or the closest total residual deviance to the number of data points in the model was considered the best-fitting model. In deciding the choice of fixed versus random effects models heterogeneity of trial designs, populations and evidence sources was also taken into account.

Overall, the methodology of the NMA when compared with NMAs accepted in previous NICE submissions in RRMS (e.g., TA533, TA699, TA767) was similar in terms of statistical model for the NMA analysis, included studies and population, and outcomes evaluated. The methodology was also closely aligned with the that used in the previous NICE submission for cladribine tablets (TA493/TA616), which was considered by the ERG as appropriate [86]. The inconsistency assessment was conducted by comparing the results with other NMAs; however as described later, cladribine tablets are often not included in published NMAs and the results of NMAs included in other NICE submissions in RRMS are redacted, making it not possible to compare the results of the present NMA with those in other submissions.

Additional information on the methodology used in the NMA, inclusion and exclusion criteria, the full list of included studies and exemplar code for the main analyses of each endpoint are provided in Appendix D.

A summary of the trials used in the main NMAs for the ITT population is provided in Table 21.

Table 21: Summary of trials used in the NMA of patients with RRMS

Study name (author, year)	Intervention (N)	ARR	3M-CDP	6M-CDP	Treatment discontinuation
ADVANCE (Calabresi 2014a) [98]	Peginterferon 125 µg Q2W (512)	✓		✓	
	Placebo (500)				
APEX 2019 (Saida et al. 2019) [99]	Dimethyl fumarate 240 mg (57)	✓			✓
	Placebo (58)				
APOLITOS 2022 (Kira et al. 2022) [100]	Ofatumumab 20 mg SC (43)	✓			✓
	Placebo (21)				
ASCLEPIOS I 2020 (Hauser et al. 2020) [101]	Ofatumumab 20 mg SC (465)	✓	✓	✓	✓
	Teriflunomide 14 mg PO (462)				
ASCLEPIOS 2 2020 (Hauser et al. 2020) [101]	Ofatumumab 20 mg SC (481)	✓	✓	✓	✓
	Teriflunomide 14 mg PO (474)				
BECOME trial (Cadavid 2009) [102]	Glatiramer acetate 20 mg QD (39)	✓		✓	✓
	Interferon beta-1b 250 µg QOD (36)				
BEYOND trial (O' Connor 2009) [103]	Glatiramer acetate 20 mg QD (448)	✓	✓		✓
	Interferon beta-1b 250 µg QOD (897)				
Bornstein 1987 [104]	Glatiramer acetate 20 mg QD (25)	✓	✓		
	Placebo (25)				
BRAVO trial (Vollmer 2014) [105]	Interferon beta-1a 30 µg IM QW (447)	✓	✓	✓	
	Placebo (450)				
Calabrese 2012 [106]	Glatiramer acetate 20 mg QD (55)	✓			
	Interferon beta-1a 44 µg SC TIW (55)				
	Interferon beta-1a 30 µg IM QW (55)				
CLARITY trial [5]	cladribine tablets 3.5 mg/kg (433)	✓	✓	✓	✓
	Placebo (437)				
CombiRx trial (Lublin 2013) [107]	Glatiramer acetate 20 mg QD (259)	✓		✓	
	Interferon beta-1a 30 µg IM QW (250)				
CONFIRM trial (Fox 2012) [108]	Dimethyl fumarate 240 mg BID (359)	✓	✓	✓	✓
	Glatiramer acetate 20 mg QD (350)				
	Placebo (363)				
Copolymer1 trial (Johnson 1995) [109]	Glatiramer acetate 20 mg QD (125)	✓	✓		
	Placebo (126)				
DEFINE Trial (Gold 2012) [110]	Dimethyl fumarate 240 mg BID (411)	✓	✓	✓	✓
	Placebo (410)				

Study name (author, year)	Intervention (N)	ARR	3M-CDP	6M-CDP	Treatment discontinuation
Etemadifar 2006 [111]	Interferon beta-1a 30 µg IM QW (30)	✓			
	Interferon beta-1a 44 µg SC TIW (30)				
	Interferon beta-1b 250 µg QOD (30)				
European and Canadian Glatiramer trial (Comi 2001) [112]	Glatiramer acetate 20 mg QD (119)	✓			
	Placebo (120)				
EVOLVE-MS 2 2020 (Naismith et al. 2020) [113]	Dimethyl fumarate 462 mg PO (251)				✓
	Diroximel fumarate 240 mg PO (253)				
EVIDENCE trial (Schwid 2007) [114]	Interferon beta-1a 44 µg SC TIW (339)	✓			
	Interferon beta-1a 30 µg IM QW (338)				
Gala trial (Khan et al. 2013) [115]	Glatiramer acetate 40 mg TIW (943)	✓			✓
	Placebo (461)				
Gate trial (Cohen et al. 2015) [116]	Glatiramer acetate 20 mg QD (Generic) (355)	✓			✓
	Glatiramer acetate 20 mg QD (Branded) (357)				
	Placebo (84)				
IFNB MS trial (Duquette et al. 1993) [117]	Interferon beta-1b 250 µg QOD (124)	✓	✓		✓
	Placebo (123)				
IMPROVE trial (Stefano et al. 2012) [118]	Interferon beta-1a 44 µg SC TIW (120)	✓			
	Placebo (60)				
INCOMIN trial (Durelli et al. 2002) [119]	Interferon beta-1a 44 µg SC TIW (92)	✓			✓
	Interferon beta-1b 250 µg QOD (96)				
Kappos 2011 [120]	Interferon beta-1b 250 µg Q1W(55)	✓			
	Placebo (54)				
Knobler 1993 [121]	Interferon beta-1b 250 µg TIW(6)	✓			
	Placebo (7)				
MS200527-0086 (Montalban et al. 2019) [122]	Dimethyl fumarate 120 mg BID for 7 days, then 240 mg BID daily PO (54)	✓			✓
	Placebo (53)				
MSCRG trial (Jacobs et al. 1996) [123]	Interferon beta-1a 30 µg IM QW (158)	✓		✓	
	Placebo (143)				
O`Connor 2006 (O'Connor et al. 2006) [124]	Teriflunomide 14 mg QD (57)	✓			✓
	Teriflunomide 7 mg QD (61)				
	Placebo (61)				
Opera I trial [125]	Ocrelizumab 600 mg Q24W (410)	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW (411)				
Opera II trial [125]	Ocrelizumab 600 mg Q24W (417)				

Study name (author, year)	Intervention (N)	ARR	3M-CDP	6M-CDP	Treatment discontinuation
	Interferon beta-1a 44 µg SC TIW (418)	✓	✓	✓	✓
OPTIMUM 2021 (Kappos et al. 2021) [126]	Ponesimod 20 mg PO (567)	✓	✓	✓	✓
	Teriflunomide 20 mg PO (566)				
PRISM trial (Ebers et al. 1998) [95]	Interferon beta-1a 44 µg SC TIW (184)	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW (189)				
	Placebo (187)				
REFORMS trial (Singer et al. 2012) [127]	Interferon beta-1a 44 µg SC TIW (65)	✓			✓
	Interferon beta-1b 250 µg QOD (64)				
REGARD trial (Mikol et al. 2008) [128]	Glatiramer acetate 20 mg QD (378)	✓		✓	✓
	Interferon beta-1a 44 µg SC TIW (386)				
TEMSO trial (O'Connor et al. 2011) [129]	Teriflunomide 14 mg QD (359)	✓	✓	✓	✓
	Teriflunomide 7 mg QD (366)				
	Placebo (363)				
TENERE Trial (Vermersch et al. (2014) [130]	Teriflunomide 14 mg QD (111)	✓			✓
	Teriflunomide 7 mg QD (109)				
	Interferon beta-1a 44 µg SC TIW (104)				
TOWER trial (Confavreux et al. 2014) [131]	Teriflunomide 14 mg QD (372)	✓	✓	✓	✓
	Teriflunomide 7 mg QD (408)				
	Placebo (389)				

3M: Three month; 6M: Six month; ARR: Annualised relapse rate; BID: Twice daily; CDP: Confirmed disability progression; IM: Intramuscular; PO: Oral; QD: Once every day; QOD: Every other day; QW: Once a week; Q2W: Every 2 weeks; Q4W: Every 4 weeks; Q24W: Every 24 weeks; RRMS: Relapsing-remitting multiple sclerosis; SC: Subcutaneous; TIW: three times a week.

B.2.9.3. Results of the base case NMAs

The main analysis of the NMA evaluated the relative efficacy and safety of cladribine tablets compared with NICE-recommended DMTs for the treatment of patients with RRMS. Based on the model fit statistics, heterogeneity in the patient population and trial design, a random effects model was determined to be the best fit to analyse ARR, 3-month CDP, 6-month CDP and treatment discontinuations.

Across trials included in the NMA, there was uncertainty surrounding the disease duration at baseline, the mean number of previous relapses, and the mean EDSS score.

The INCOMIN trial (interferon beta-1a vs. interferon beta-1b) was excluded from the base case CDP analyses, as inconsistent results were being observed for the comparison between cladribine tablets and interferon beta-1b due to this trial. Additionally, a sensitivity analysis

excluding the INCOMIN trial as well as the ADVANCE trial (peginterferon vs. placebo) was conducted; see Section B.2.9.4.2 for more detail on the conducted sensitivity analyses.

Overall, results from the NMA indicate that 3.5 mg/kg cladribine tablets are an effective alternative to DMTs recommended by NICE in patients with active RRMS. Further, the NMA shows that 3.5 mg/kg cladribine tablets are associated with a significantly improved efficacy profile compared to placebo for efficacy outcomes (ARR, 3- and 6-month CDP). Using the fixed effects model showed similar results to the base case analysis.

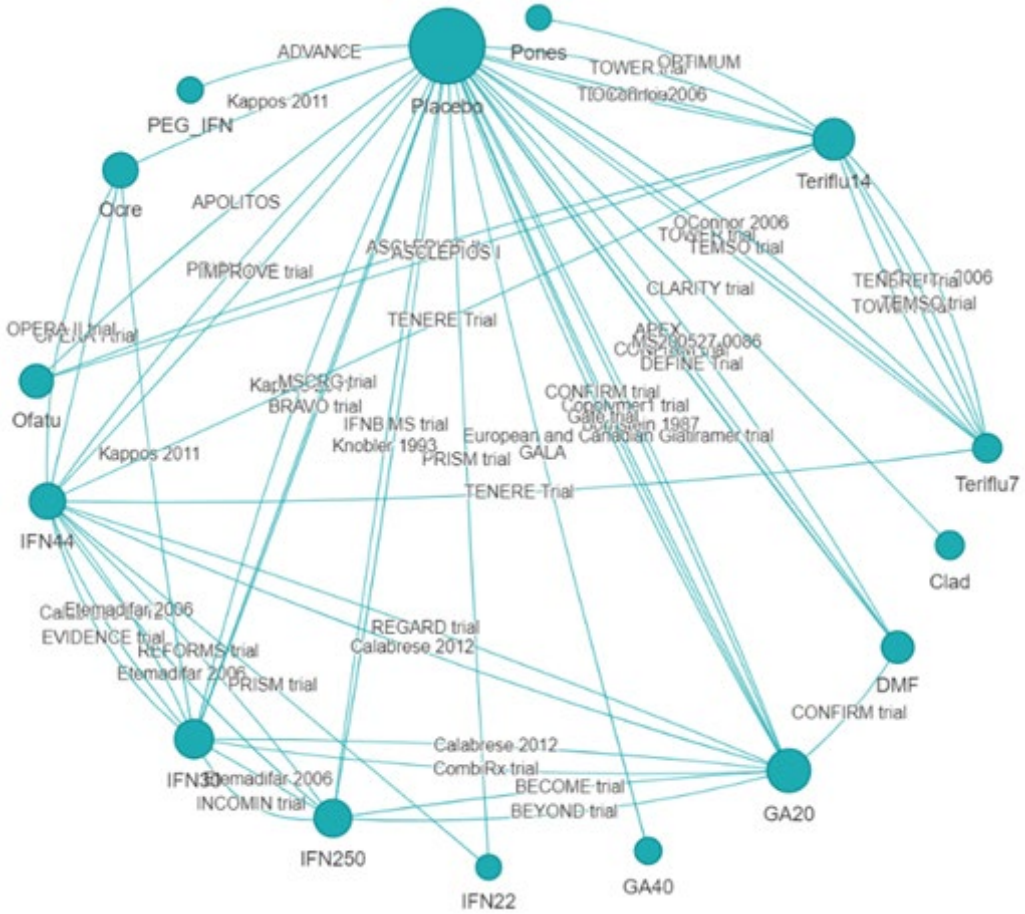
The NMA findings for the four outcomes of interest are summarised briefly in the sections below, with full results available in Appendix D.

The league tables and the SUCRA plots for the four outcomes of interest are provided in Appendix D.

B.2.9.3.1. ARR

There were 37 RCTs and 15 regimens (including placebo) included in the network for ARR (Figure 10). All DMTs specified in the population, interventions, comparators, outcomes, study design (PICOS) and at licenced dosages in the UK were represented in the network, with most connections supported by one or two trials.

Figure 10: Network diagram for the base case NMA of ARR

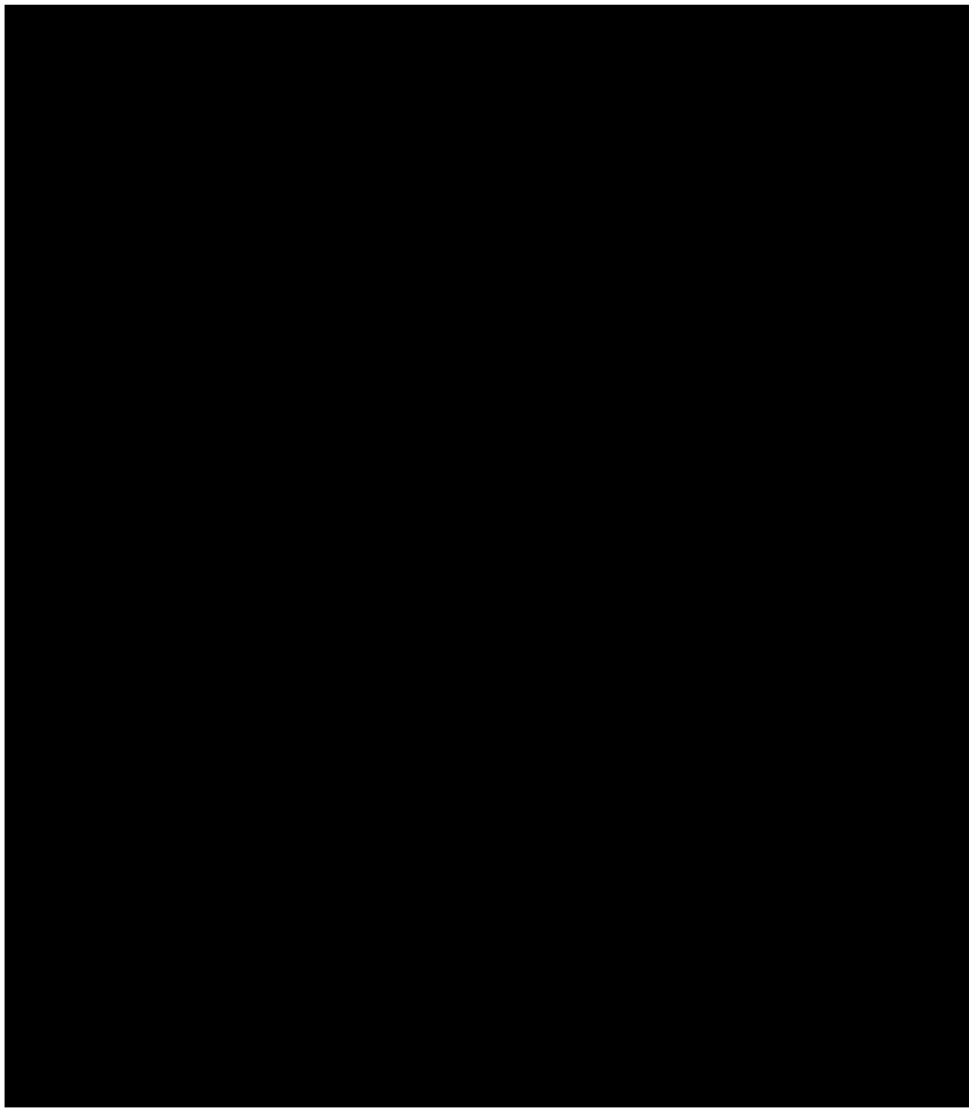


ARR: Annualised relapse rate; Clad: Cladribine tablets; DMF: Dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; NMA: Network meta-analysis; Ocre: Ocrelizumab; Ofatu: Ofatumumab; PEG_IFN: Peginterferon; Pones: Ponesimod; Teriflu: Teriflunomide

The results of the ARR analysis for cladribine tablets versus comparators in the ITT populations of the trials are presented in the forest plot in Figure 11 and a league table in Appendix D.

Treatment with cladribine tablets was associated with a significantly greater reduction in ARR compared with placebo, teriflunomide 14 mg, teriflunomide 7 mg, glatiramer acetate 20 mg, glatiramer acetate 40 mg, peginterferon, interferon beta-1a 22 µg, interferon beta-1a 44 µg, interferon beta-1a 30 µg and interferon beta-1b 250 µg. Additionally, the NMA results numerically favoured cladribine tablets over dimethyl fumarate and ponesimod. Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for ARR following [redacted]. The results are in line with previous appraisals TA533 and TA767.

Figure 11: Forest plot of treatments versus cladribine tablets in the base case NMA for ARR relative risk (95% CrI) (ITT population)

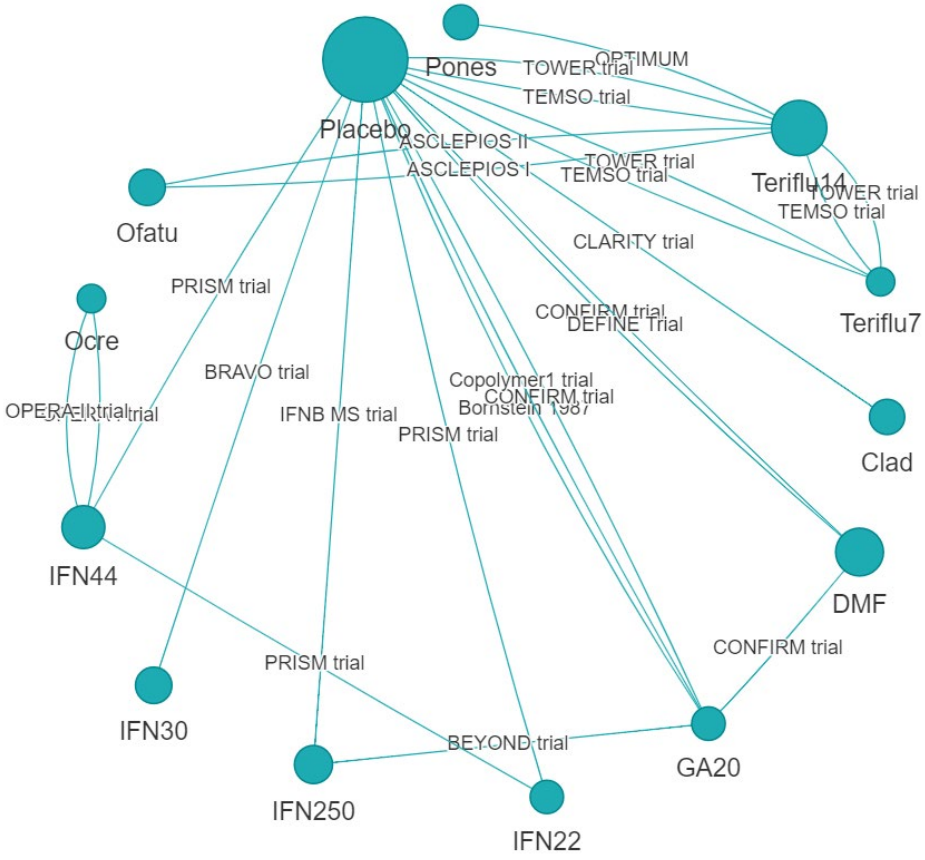


ARR: Annualised relapse rate; CrI: Credible interval; DMF: Dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; PEG_IFN: Peginterferon; Pones: Ponesimod; RR: Relative risk; Teriflu: Teriflunomide

B.2.9.3.2. 3-month CDP

There were 15 RCTs and 13 regimens (including placebo) included in the network for 3-month CDP (Figure 12). All DMTs specified in the PICOS, and all UK approved regimens except glatiramer acetate (40 mg) and peginterferon were represented in the network, as this outcome was not reported in the relevant studies for these DMTs.

Figure 12: Network diagram for the base case NMA of 3-month CDP (ITT population)



CDP: Confirmed disability progression; Clad: Cladribine tablets; DMF: Dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; ITT: Intention-to-treat; NMA: Network meta-analysis; Ocre: Ocrelizumab; Ofatu: Ofatumumab; Pones: Ponesimod; Teriflu: Teriflunomide

The results of the 3-month CDP analysis for cladribine tablets versus comparators in the ITT populations of the trials are presented in the forest plot in Figure 13 and a league table in Appendix D.

The NMA demonstrated no statistically significant differences in 3-month CDP between cladribine tablets and all DMTs included in the NICE decision problem. Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for 3-month CDP following [redacted]. These results are aligned with previous NMAs reported in TA533 and TA767.

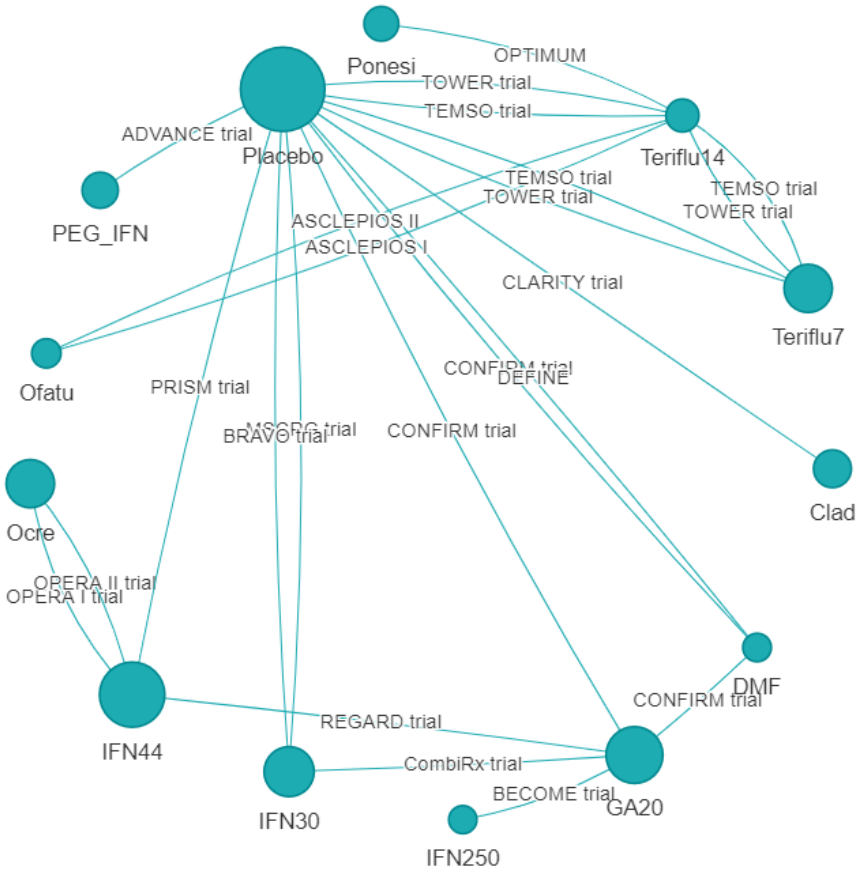
Figure 13: Forest plot of treatments versus cladribine tablets in the base case NMA for 3-month CDP hazard ratio (95% CrI) (ITT population)

CDP: Confirmed disability progression; CrI: Credible interval; DMF: Dimethyl fumarate; GA: Glatiramer acetate; HR: Hazard ratio; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; Pones: Ponesimod; Teriflu: Teriflunomide

B.2.9.3.3. 6-month CDP

There were 17 RCTs and 13 regimens (including placebo) included in the network for 6-month CDP (Figure 14). All DMTs specified in the PICOS, and all UK approved regimens except glatiramer acetate 40 mg and interferon beta-1a 22 µg were represented in the network, as this outcome was not reported in the relevant studies for these DMTs.

Figure 14: Network diagram for the base case NMA of 6-month CDP (ITT population)



CDP: Confirmed disability progression; Clad: Cladribine tablets; CrI: Credible interval; DMF: Dimethyl fumarate; GA: Glatiramer acetate; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; PEG_IFN: Peginterferon; Ponesi: Ponesimod; Teriflu: Teriflunomide

The results of the 6-month CDP analysis for cladribine tablets versus comparators in the ITT populations of the trials are presented in the forest plot in Figure 15 and a league table in Appendix D.

Treatment with cladribine tablets was observed to be significantly better than placebo for 6-month CDP with numerically better results compared to dimethyl fumarate, glatiramer acetate 20 mg, interferon beta-1a 30 µg, interferon beta-1a 44 µg, teriflunomide 14 mg, teriflunomide 7 mg, and ponesimod. The credible intervals were overlapping for the DMTs included in the network, and therefore there was no statistically significant difference between any of the DMTs. Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for 6-month CDP following [redacted]. These results are aligned with previous NMAs reported in TA533 and TA767.

Figure 15: Forest plot of treatments versus cladribine tablets in the base case NMA for 6-month CDP hazard ratio (95% CrI) (ITT population)

CDP: Confirmed disability progression; CrI: Credible interval; DMF: Dimethyl fumarate; GA: Glatiramer acetate; HR: Hazard ratio; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; PEG_IFN: Peginterferon; Ponesi: Ponesimod; Teriflu: Teriflunomide

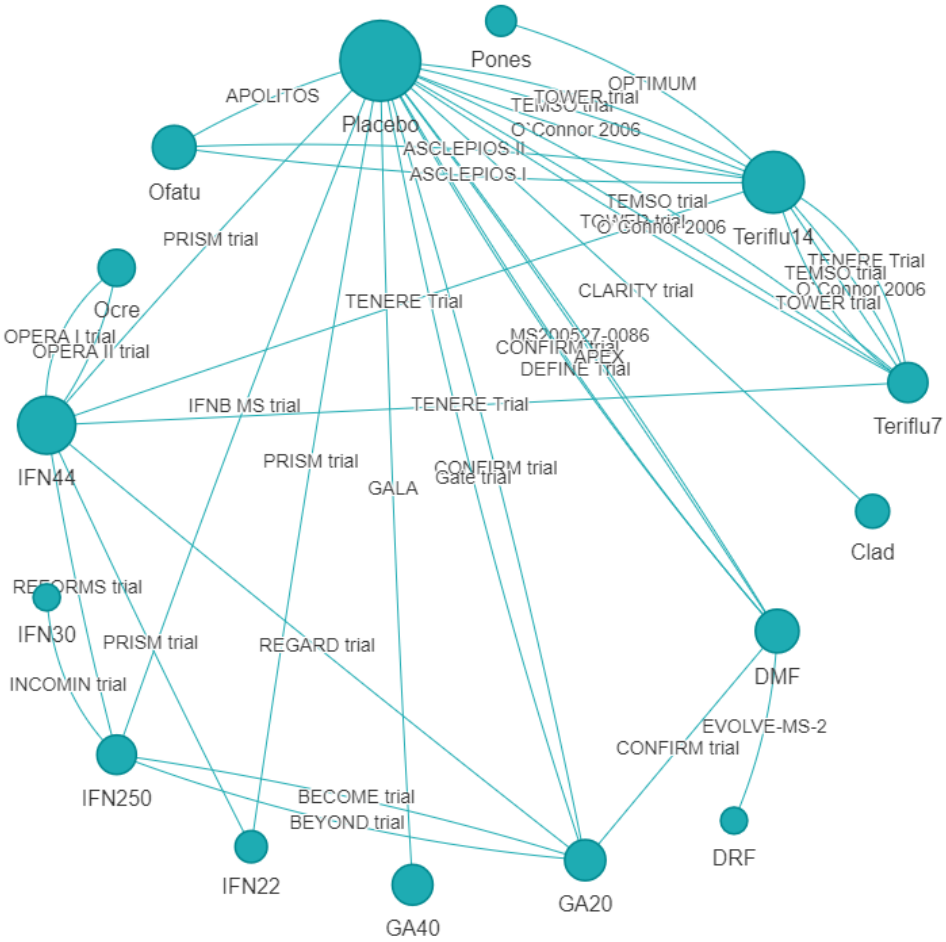
B.2.9.3.4. Discontinuation

There were 25 RCTs and 15 regimens (including placebo) included in the network for treatment discontinuations. All DMTs specified in the PICOS and at licenced dosages in the UK were represented in the network, with most connections supported by one or two trials (Figure 16).

The results of the treatment discontinuation analysis for cladribine tablets versus comparators in the ITT populations of the trials are presented in the forest plot in Figure 17 and a league table in Appendix D.

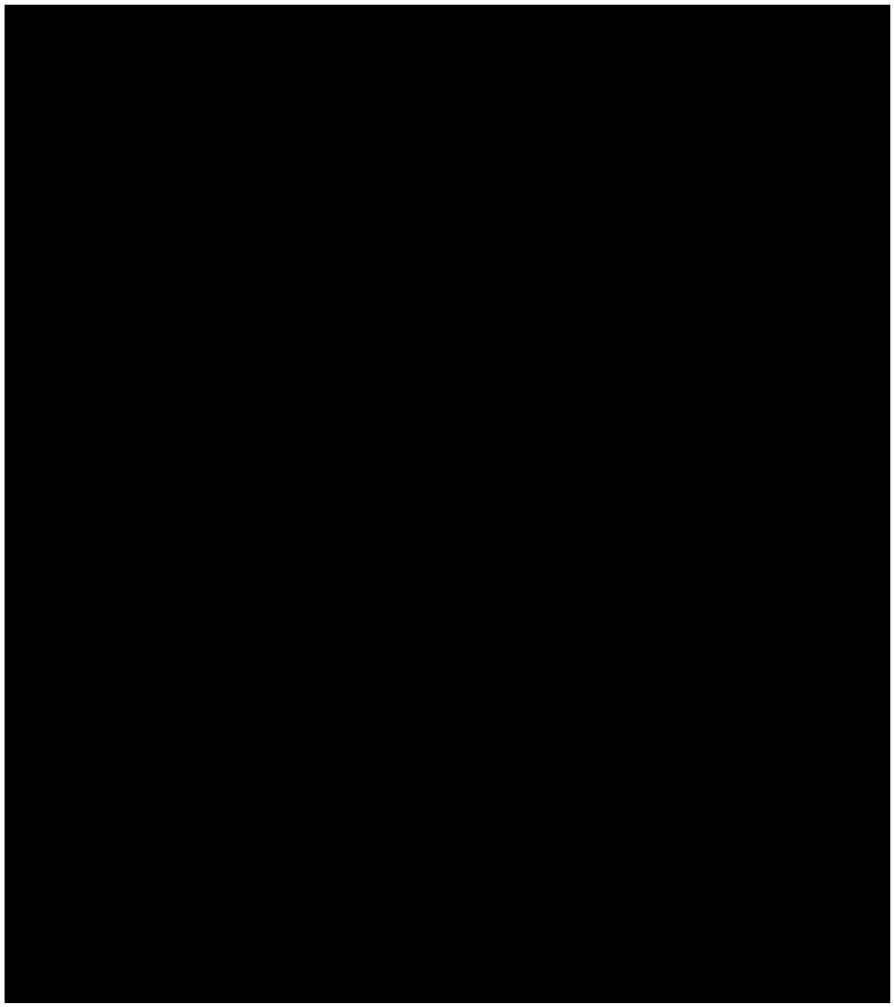
Treatment with cladribine tablets was observed to have the significantly lower risk of discontinuation than interferon beta-1a 44µg. Furthermore, the risk of all cause treatment discontinuation was numerically lower compared to all the other treatments included in this comparison. These results are aligned with previous NMAs reported in TA533, TA767.

Figure 16: Network diagram for the base case NMA of treatment discontinuation (ITT population)



Clad: Cladribine tablets; DMF: Dimethyl fumarate; DRF: Diroximel fumarate; GA: Glatiramer acetate; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; Pones: Ponesimod; Teriflu: Teriflunomide

Figure 17: Forest plot of treatments versus cladribine tablets in the base case NMA for discontinuations hazard ratio (95% CrI) (ITT population)



CrI: Credible interval; DMF: Dimethyl fumarate; DRF: Diroximel fumarate; GA: Glatiramer acetate; HR: Hazard ratio; IFN: Interferon; NMA: Network meta-analysis; ITT: Intention-to-treat; Ocre: Ocrelizumab; Ofatu: Ofatumumab; Pones: Ponesimod; Teriflu: Teriflunomide

B.2.9.4. Uncertainties in the indirect and mixed treatment comparisons

A limitation of the NMA is uncertainty arising from heterogeneity between trials included in the networks, due to differences in study designs and patient characteristics. As with traditional meta-analyses, NMAs are based on similarity of studies to generate exchangeable treatment effects. The trials included in the NMA were conducted over a period of 35 years (1987 to 2022). These trials differed in study characteristics (diagnostic criteria, study phase, and blinding), patient population recruited (mean relapses in prior 1 year, disease duration, treatment history [previously treated versus treatment naïve]) and definitions of outcomes. Evidence networks involving small sample size and limited evidence do not allow Bayesian models to converge and hence, the NMA results could be considered slightly less reliable as a result.

There were variations in the definitions of 3-month and 6-month CDP across the included studies. A limited number of studies provided a consistent definition for these outcomes, and it was not feasible to conduct sensitivity analysis owing to limited evidence for each definition.

For the CDP analyses, several MS trials for established DMTs do not report the data for 6-month CDP, as such these trials were not included in the NMAs to ensure that these analyses remained robust. The network for 3-month CDP did not include glatiramer acetate 40 mg and peginterferon, and the network for 6-month CDP did not include glatiramer acetate 40 mg and interferon beta-1a 22 µg. These missing data should not affect the outcomes substantially, given that both networks included alternate interferons and an alternate dose for glatiramer acetate 20 mg. This is aligned with previous appraisals whereby the evidence networks for 3-month CDP contain more data and may be considered slightly more reliable as compared to 6-month CDP, given that a greater proportion of trials in the 3-month CDP network defined the outcome as either a primary or secondary endpoint. The 6-month CDP networks have a higher degree of uncertainty.

A further source of heterogeneity in the evidence base arises from variations in treatment effects from the interferon trials, which has been acknowledged previously by NICE as lacking clinical validity [92, 93, 132]. The results of the INCOMIN trial (interferon beta-1a vs. interferon beta-1b) have suggested superiority of one interferon over the other, and the results of ADVANCE trial (peginterferon vs. placebo) demonstrate implausibly high results versus placebo. This is inconsistent with clinical experience, which has established that individual interferon beta treatments have similar clinical effectiveness. This “outlier” trial has been reviewed in the literature [133] as well as in previous NICE appraisals (TA767 and TA699), and clinical experts have recommended exercising caution when interpreting these results.

As a result, the INCOMIN trial reported results for 6-month CDP only, and was excluded from the base case, as inconsistent results were being observed for the comparison between cladribine tablets and interferon beta-1b 250 µg for 3-month and 6-month CDP. This is aligned with the approach taken in the NMA for ponesimod (TA767) and ofatumumab (TA699).

However, even without inclusion of the INCOMIN trial, interferon beta-1b 250 µg demonstrates better efficacy than cladribine tablets, ofatumumab, and ponesimod (all high-efficacy DMTs), though there were very wide credible intervals. This is due to the fact that results for interferon beta-1b 250 µg are governed by a single trial (BECAME), which consists of only 36 patients in the interferon beta-1b 250 µg arm, leading to wide credible intervals. A sensitivity analysis was also conducted with inclusion of the INCOMIN trial (see Section B.2.9.4.2).

Additionally, the network for 6-month CDP includes only one trial (ADVANCE) that included peginterferon as a treatment arm. Merck has included this trial based on its eligibility criteria

for the SLR and NMA; however, in previous appraisals for ocrelizumab (TA533) and ofatumumab (TA699), committee members and clinical experts have noted that the results from ADVANCE produced clinically implausible 6-month CDP results for peginterferon. As such, a sensitivity analysis was conducted with the exclusion of both INCOMIN and ADVANCE trials (see Section B.2.9.4.2).

B.2.9.4.1. Risk of bias

Baseline characteristics within the treatment groups were comparable across the included 38 studies. Overall, 87% (33) of the studies were associated with low risk of bias in terms of blinding; while blinding was judged to be high risk in one of the included studies (REFORM trial) and unclear in four studies.

Across the included studies, the method of generation of random sequence number was adequate in 71% (27) of the included trials, while in the remaining 29% (11) studies this information was unclear.

All the RCTs reported ITT or modified ITT analysis for evaluating efficacy outcomes. While some concerns were raised on the differences in definitions of outcomes, on balance, NICE concluded that the differences in outcomes were unlikely to have a large effect on the comparative effectiveness and concluded that the outcomes were broadly comparable across trials. The statistical analysis method was not reported in one study (Calabrese 2012). Across the included studies, reasons for withdrawals were adequately reported in 87% (33) of the studies. In 61% of the studies outcome reporting was associated with low risk of bias, while outcome selection and reporting were not clear in 39% of the studies.

A descriptive critical appraisal of included studies according to the NICE criteria is presented in Appendix D.

B.2.9.4.2. Sensitivity analysis

A sensitivity analysis was conducted with inclusion of the INCOMIN trial for 6-month CDP, where cladribine tablets were numerically better compared with glatiramer acetate 20 mg, dimethyl fumarate 240 mg, interferon beta-1a 30 µg, interferon beta-1a 44 µg, teriflunomide 7 mg, teriflunomide 14 mg and ponesimod. In this sensitivity analysis, the results of the 6-month CDP analysis showed interferon beta-1b 250 µg to be numerically better compared with cladribine tablets, while the results for 3-month CDP showed cladribine tablets to be better. The variation in results may be attributed to the INCOMIN trial, which reported a statistically significant improvement in CDP for interferon beta-1b 250 µg compared with interferon beta-1a 44 µg (HR: 0.44; 95% CI: 0.25, 0.80), i.e., suggesting superiority of one

interferon over the other. These results are inconsistent with other trial evidence in RRMS and clinical expectations of the interferon beta-1b 250 µg treatment effect in clinical practice.

Additionally, a sensitivity analysis was also conducted with the exclusion of INCOMIN and ADVANCE trials for 6-month CDP. As there was no trial informing peginterferon, no results for peginterferon are available. The results for cladribine tablets versus the other comparators are aligned with the base case analysis.

Full results are presented in Appendix D.

B.2.10 Adverse reactions

Adverse events (AEs) were reported in the pivotal CLARITY and CLARITY-EXT trials, where the study-specific safety analyses are presented in Section B.2.10.1 and Section B.2.10.2, respectively [5, 6]. In addition, an integrated safety analysis was performed on combined data from CLARITY, CLARITY-EXT, ORACLE MS and the PREMIERE registry [82]

B.2.10.1. Overview of AEs in CLARITY

The safety analysis was performed on all patients who received at least one dose of study medication (Safety Population) with follow-up safety data in CLARITY [5].

B.2.10.1.1. TEAEs

During the 96-week of the CLARITY trial, the proportion of patients reporting treatment-emergent AEs (TEAEs) was similar between the 3.5 mg/kg cladribine tablets and placebo groups (80.7% and 73.3%, respectively) [5].

The most common types of TEAEs by the system organ class were [5, 79]:

- Infections and infestations – 3.5 mg/kg cladribine tablets ([redacted]; 47.7%); placebo ([redacted] 42.5%)
- Gastrointestinal disorders – 3.5 mg/kg cladribine tablets [redacted] placebo [redacted]
- Nervous system disorders – 3.5 mg/kg cladribine tablets [redacted] placebo [redacted]
- Blood and lymphatic system disorders – 3.5 mg/kg cladribine tablets [redacted] placebo [redacted]

The most frequent TEAEs (reported by ≥5% of patients) in both treatment groups were headache, nasopharyngitis, upper respiratory tract infection and nausea [5]. The frequency of nasopharyngitis and nausea were comparable between 3.5 mg/kg cladribine tablets and placebo groups (nasopharyngitis: 14.4% vs. 12.9%; nausea: 10% vs. 9%). Headache, lymphopenia and upper respiratory tract infections occurred more frequently in the 3.5 mg/kg cladribine tablets group compared with the placebo group (Table 22).

Table 22: Summary of TEAEs reported in ≥5% of patients in CLARITY

TEAE, n (%)	Cladribine tablets 3.5 mg/kg (LL) (n=430)	Placebo (PP) (n=435)
Headache	104 (24.2)	75 (17.2)
Lymphopenia	93 (21.6)	8 (1.8)
Nasopharyngitis	62 (14.4)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	42 (9.7)
Nausea	43 (10.0)	39 (9.0)

Source: [5]

LL: Low dose cladribine tablets in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); PP: Placebo in Year 1 and Year 2; TEAE: Treatment-emergent adverse event

Other TEAEs occurred with relatively low frequency (>1%) across both treatment groups [79]:

- Depression: 3.5 mg/kg cladribine tablets [redacted] placebo [redacted]
- Vertigo: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]
- Hypertension: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]
- Pyrexia: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]
- Alopecia: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]
- Rash: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]

In the CLARITY trial, relatively few treatment discontinuations due to TEAEs were observed. While a greater proportion of patients withdrew prematurely from treatment due to TEAEs in the cladribine tablets group compared with the placebo group (3.5% [n=15] and 2.1% [n=9], respectively), the difference was not significant suggesting that orally administered 3.5 mg/kg cladribine tablets were well-tolerated by patients with active RRMS during this 96-week double-blind trial [5, 79]. A summary of all TEAEs that led to treatment discontinuation reported in CLARITY are summarised in Table 23.

Table 23: Summary of TEAEs leading to treatment discontinuation in CLARITY

TEAE, n (%)	Cladribine tablets 3.5 mg/kg (LL) (n=430)	Placebo (PP) (n=435)
Any TEAE leading to discontinuation	15 (3.5)	9 (2.1)
Lymphopenia	[redacted]	[redacted]
Abnormal lymphocyte count	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]

TEAE, n (%)	Cladribine tablets 3.5 mg/kg (LL) (n=430)	Placebo (PP) (n=435)
Psychiatric disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Reproductive system and breast disorders	[redacted]	[redacted]

Source: [5, 79]

AE: Adverse event; LL: Low dose cladribine tablets in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); PP: Placebo in Year 1 and Year 2

B.2.10.1.2. Serious TEAEs

The proportion of patients experiencing serious TEAEs was low and without apparent significant differences in the nature or frequency of serious TEAEs between the 3.5 mg/kg cladribine tablets and the placebo groups [5]. During the 96-week trial period, 36 patients (8.4%) in the 3.5 mg/kg cladribine tablets group, and 28 patients (6.4%) in the placebo group experienced serious TEAEs. The system organ classes with the largest proportion of serious TEAEs were as follows [5]:

- Infections and infestations: 3.5 mg/kg cladribine tablets (n=10; 2.3%); placebo (n=7; 1.6%)
- Hepatobiliary disorders: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]
- Gastrointestinal disorders: 3.5 mg/kg cladribine tablets [redacted]; placebo [redacted]

A total of six deaths were reported during the CLARITY trial: two patients in the placebo treatment group, two patients in the 3.5 mg/kg cladribine tablets treatment group and two patients in the 5.25 mg/kg cladribine tablets treatment group. All deaths during CLARITY were considered unrelated to the study drug [5].

B.2.10.1.3. TEAEs of special interest

Lymphopenia was an expected event based on the mechanism of action of cladribine, occurring more frequently in the 3.5 mg/kg cladribine tablets treatment group (21.6%) compared with the placebo group (1.8%) (Table 24) [5]. In the "investigations" system organ class, decreasing lymphocyte and white blood cell count was reported only in the 3.5 mg/kg

cladribine tablets group, however, the incidence was infrequent and classed as non-serious. Lymphopenia resulted in treatment discontinuation in four patients randomised to the 3.5 mg/kg cladribine tablets group. At the end of the 96-week CLARITY trial, a total of three (0.7%) patients in the 3.5 mg/kg cladribine tablets group had Grade ≥3 lymphopenia at their final evaluation. Further follow-up of these patients showed that all recovered to a lymphocyte count of Grade 0 or Grade 1 [79]. There were no serious or opportunistic infections reported in these patients [5]. The issue of lymphopenia was discussed by the ERG in the previous submission (TA493/TA616). Clinical advice received by the ERG stated that in NHS clinical practice, lymphopenia is associated with treatment with DMTs, and poses an issue if it leads to infection. However, as demonstrated by the safety results of the CLARITY trial, the risk of developing a serious or opportunistic infection related to lymphopenia while treated with cladribine tablets appears to be similar to the risks associated with other DMTs used in the NHS [86].

Table 24: TEAEs and discontinuations relating to lymphopenia in CLARITY

System organ class preferred term, n (%)	Cladribine tablets 3.5 mg/kg (LL) (n=430)	Placebo (PP) (n=435)
Discontinuations due to lymphopenia	[redacted]	[redacted]
Discontinuations due to decreased or abnormal lymphocyte count	[redacted]	[redacted]
Number of patients reporting lymphopenia as a TEAE, n	93 (21.6)	8 (1.8)
Number of patients reporting lymphopenia as a serious TEAE	[redacted]	[redacted]
Number of deaths due to lymphopenia	[redacted]	[redacted]

Source: [5, 79]

LL: Low dose cladribine tablets in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg); TEAE: Treatment-emergent adverse event; PP: Placebo in Year 1 and Year 2

The system organ class with the greatest frequency of adverse events was infection and infestations. The incidence of infections and infestations was 47.7% in the cladribine tablets 3.5 mg/kg group and 42.5% in the placebo group. [5] Most of these infections involved the upper respiratory tract [79]. Reports of herpes infection were common in the cladribine tablets group, with eight patients experiencing herpes zoster infections. The majority of these infections were mild to moderate in severity, and all cases resolved without sequela, except for a single case of herpes oticus (Ramsay-Hunt), which was associated with persistent, intermittent right-sided ear pain, but which was reported to have stabilized by the end of the trial [79].

Three subjects treated with cladribine tablets in the CLARITY trial experienced isolated malignancies involving different organ systems – malignant melanoma, and ovarian and metastatic pancreatic carcinomas (the latter resulted in death) [5]. In the previous submission (TA493/TA616), the ERG noted that based on the CHMP report [134] provided to ERG during clarification procedure, the EMA has concluded that there is no conclusive evidence of an increased risk of malignancies in people with MS who are treated with cladribine tablets [86]. The EMA opinion was based on the results of the integrated safety analysis conducted by Merck and presented in Section B.2.10.3, below.

B.2.10.2. Overview of AEs in CLARITY-EXT

In the CLARITY-EXT trial, of the 98 patients in the LLPP treatment group included in the safety analysis, 74 (75.5%) patients reported at least one TEAEs. During the 96 weeks of the trial, 3 (3.1%) patients in the LLPP treatment group discontinued the treatment due to a TEAE [6] and [redacted] discontinued the trial [81], suggesting that treatment with cladribine tablets in Year 1 and Year 2 (CLARITY) followed by no active treatment in Year 3 and Year 4 (CLARITY-EXT) was well-tolerated by patients with active RRMS [6]. The reasons for treatment discontinuation were pregnancy, [redacted], and hepatitis B infection (n=1 for each), the reasons for study discontinuation were due to death and judged to be unrelated to the treatment with cladribine tablets [6]. These results suggest that treatment for two years with 3.5 mg/kg cladribine tablets followed by two years of no active treatment is not associated with a considerable increase in TEAEs, serious TEAEs and TEAEs of special interest among patients with RRMS [6]. For more detail see Appendix F.

B.2.10.3. Overview of AEs in integrated safety analysis

Safety data for cladribine tablets from three previously reported Phase III studies (CLARITY, CLARITY-EXT and ORACLE-MS), as well as the prospective, observational PREMIERE registry (which ran from November 2009 to October 2018, consisting of patients who had participated in at least one of the Phase III trials) were combined to provide safety data for the Monotherapy Oral cohort [82]. The Monotherapy Oral cohort comprised 923 patients who received 3.5 mg/kg cladribine tablets and 641 patients who received placebo.

The final integrated safety analysis published by Leist et al. [82] is summarised below. The interim analyses published by Cook et al. [135] are not included in this submission.

The safety data in the integrated safety analysis is presented as observation-adjusted incidence rates per 100 patient years of exposure and follow-up time to account for different follow-up times in the treatment arms. During the overall clinical development of cladribine tablets, a greater number of patients were recruited for cladribine tablets 3.5 mg/kg treatment

groups compared with placebo. This resulted in larger exposure in terms of patient-years of treatment and follow-up for cladribine tablets-treated patients compared with placebo (Table 25). The observation time for the placebo group is only about one third that of the cladribine tablets group, and therefore the comparison would not be meaningful if presented as percentages [82].

Table 25: Summary of treatment exposure in the integrated safety analysis

Outcome	Cladribine tablets 3.5 mg/kg	Placebo
Number of patients exposed to cladribine tablets, n	923	641
Total patient-years	3936.7	2421.5
Mean time on study, years (SD)	4.28 (2.54)	3.79 (2.67)
Time on study, ≥96 weeks (~2 years), n (%)	784 (84.9)	493 (76.9)
Time on study, ≥192 weeks (~4 years), n (%)	431 (46.7)	204 (31.8)
Time on study, ≥432 weeks (~9 years), n (%)	26 (2.8)	18 (2.8)

Source: [82]

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

SD: Standard deviation

B.2.10.3.1. Serious TEAEs

Overall, the reported number of serious TEAEs was marginally higher in the 3.5 mg/kg cladribine tablets group (14.4% of patients with at least 1 serious TEAE) compared with the placebo group (10.6% of patients with at least 1 serious TEAE). The corresponding incidence of serious TEAEs was 3.80 and 3.05 per 100 PY, respectively (Table 26) [82].

Table 26: Summary of serious TEAEs reported in the integrated safety analysis occurring in >0.15 events per 100 PYs

Serious TEAE	Cladribine tablets 3.5 mg/kg		Placebo	
	n	Adjusted AE per 100 PYs	n	Adjusted AE per 100 PYs
≥1 serious TEAE	133	3.80	68	3.05
Injury, poisoning and procedural complications	17	0.44	5	0.21
Investigations	14	0.36	6	0.25
Nervous system disorders	12	0.31	6	0.25
Gastrointestinal disorders	11	0.28	3	0.12
Pregnancy, puerperium and perinatal conditions	9	0.23	7	0.29
Respiratory, thoracic and mediastinal disorders	8	0.20	4	0.17
Reproductive system and breast disorders	8	0.21	3	0.12
Blood creatine phosphokinase increased	7	0.18	4	0.17
Cardiac disorders	7	0.18	6	0.25
Psychiatric disorders	4	0.10	5	0.21
Endocrine disorders	3	0.08	4	0.17

Source: [82]

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

B.2.10.3.2. TEAEs of special interest

Lymphopenia

In the 3.5 mg/kg cladribine tablets group, 4/923 patients had lymphopenia classified as a serious TEAE, resulting in an adjusted-AE of 0.10 per 100 PY, whilst there were no serious lymphopenia events in the placebo group [82].

Infections

The integrated analysis on infections was conducted using pre-defined Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The rate of serious infections and infestations was 2.5% (23/923 patients) in the 3.5 mg/kg cladribine tablets group and 1.6% (10/641 patients) in the placebo group, resulting in an adjusted-AE of 0.60 and 0.42 per 100 PY, respectively [82].

Two patients in the 3.5 mg/kg cladribine tablets cohort reported a serious herpes zoster infection resulting in an adjusted-AE of 0.05 per 100 PY; both of which were reported as resolved. The incidence of herpes zoster in the cladribine tablets group was higher during periods of Grade 3 or Grade 4 lymphopenia compared with periods where patients who were not experiencing Grade 3 or Grade 4 lymphopenia. There was one case each of tuberculosis

and pulmonary tuberculosis in the 3.5 mg/kg cladribine tablets group classified as serious, resulting in an adjusted-AE of 0.03 per 100 PY, each. The incidence of pneumonia was similar in both groups, with an adjusted-AE of 0.15 per 100 PY for 3.5 mg/kg cladribine tablets versus 0.12 per 100 PY for placebo. There was no obvious pattern of increase in other serious respiratory infections [82].

The incidence of severe infections was low in both the 3.5 mg/kg cladribine tablets group (adjusted-AE of 0.76 per 100 PY) and the placebo group (adjusted-AE of 0.81 per 100 PY). The incidence of opportunistic infections was an adjusted-AE of 0.31 per 100 PY for 3.5 mg/kg cladribine tablets and 0.17 per 100 PY for placebo; the difference was driven primarily by fungal infections. Fungal infections were mainly mucocutaneous and there were no systemic infections such as candida sepsis [82].

Given that cladribine tablets may cause lymphopenia due to its mechanism of action, the possibility of serious infections such as progressive multifocal leukoencephalopathy (PML) may be of concern. In clinical trials of cladribine tablets in MS, no cases of PML have been reported [82].

Malignancies

Overall, ten cases of malignant tumours were reported in the 3.5 mg/kg cladribine tablets group with an exposure of 3918.9 PYs, versus three cases in the placebo group with an exposure of 2414.8 PYs, with an adjusted-AE of 0.26 and 0.12 per 100 PY, respectively, which was not statistically different [82]. The observation-adjusted incidence of malignancies is lower than the incidence presented in previous reports [135] of the integrated safety analysis, due to the number of cases not changing despite the longer follow up period [82].

There was no clustering of malignancies of any type i.e., different cancer types were only reported once in 3.5 mg/kg cladribine tablets patients (with the exception of malignant melanoma, which was reported in two patients). The duration from first intake of study drug until a malignancy diagnosis was highly variable, ranging from 169 to 1853 days [82].

There was no increase in the risk of malignancy over time with cladribine tablets 3.5 mg/kg; the malignancy rate (adjusted-AE) for 3.5 mg/kg cladribine tablets during Years 1 to 4 was 0.29 per 100 PY and from Year 5 onwards was 0.17 per 100 PY. In contrast, the malignancy rate (adjusted-AE) in the placebo group during Years 1 to 4 was 0.06 per 100 PY but increased from Year 5 onwards to 0.29 per 100 PY; however, the overall number of events was small. Therefore, the incidence of malignancies was higher for 3.5 mg/kg cladribine tablets compared to placebo during the first 4 years of the program, whilst lower for the subsequent 4 years [82].

Based on the integrated safety analysis, while there were numerical differences in the number of reported malignancies between the 3.5 mg/kg cladribine tablets and the placebo groups, the safety data provided no conclusive evidence that the malignancy risk is increased with cladribine tablets. Furthermore, there was no dose-dependent relationship and no evidence of time pattern of the onset of malignancies in relation to the start of treatment with cladribine tablets [82]. The conclusions of the Leist at al. were in alignment with the CHMP report, which, following the analysis of the integrated safety analysis data presented at the time of the 2017 EMA submission, stated that there is no conclusive evidence of an increased risk of malignancies in people with MS who are treated with cladribine tablets, and that the risk minimisation measures including the safety information in the product information as well as the prescriber and patient guide were considered adequate to address any risks with cladribine treatment [134].

B.2.10.3.3. Summary

In summary, the integrated safety analysis consolidated over 8 years of safety data from the clinical development program of cladribine tablets and identified no new major safety findings. The additional PYs of observation presented in [82] did not significantly alter the conclusions of earlier interim analyses by Cook et al. [135]. These integrated analyses demonstrate the favourable AE profile and safety for cladribine tablets in patients with RRMS, which are now well characterised over long-term use and supported by the regulatory bodies, namely, the 2017 EMA approval [3, 134], and the recent extended MHRA approval [26].

B.2.11 Ongoing studies

There are no ongoing studies with cladribine tablets in the active RRMS population.

B.2.12 Innovation

Cladribine tablets are the first short-course, oral, high-efficacy DMT that can provide multiple benefits for patients, clinicians, and healthcare providers.

The key innovations for patients relate to the drug's unique posology and novel mechanism of action:

- **Unique mechanism of action:** cladribine tablets are referred to as an 'immune reconstitution therapy' (see Section B.1.2.1) as they provide long-term reduction in absolute lymphocyte counts and an overall reduction in pro-inflammatory activities accompanied with enhanced anti-inflammatory activity [3, 35, 37, 38], following a short-course therapy. As such, cladribine tablets are the first-in-class high-efficacy DMT that offers sustained efficacy over 4-year period without continuous immunosuppression.
- **Short-course, oral treatment with reduced administration and monitoring burden:** treatment with cladribine tablets constitutes of two short courses of oral treatment in Year 1 and 2, which are self-administered at home, providing sustained efficacy over a total of 4 years with no re-treatment required in Year 3 and 4. This allows patients to be treated with minimal disturbance to their lives, with fewer medications to take and fewer hospital appointments compared with other high-efficacy DMTs that require continuous/frequent treatment administration (e.g., ponesimod treatment requires dose titration over 14 days, followed by daily oral administration of the maintenance dose [136]; ofatumumab treatment requires subcutaneous injections at weeks 0, 1 and 2, followed by monthly injections of the maintenance dose starting at week 4 [137]; ocrelizumab requires initial intravenous infusion at weeks 0 and 2, followed intravenous infusions every 6 months [138]) and monitoring [17]. In contrast, for cladribine tablets, six monitoring follow-ups over a 2-year period are recommended.
- **Improved treatment adherence:** infrequent dosing of cladribine tablets provides advantages over maintenance therapies by reducing the treatment burden and treatment fatigue for patients [18-21], translating into improved treatment adherence and treatment persistence, which have been demonstrated in two RWE studies supporting cladribine tablets, GLIMPSE and CLARENCE (described in Appendix E.1.1).
- **Early intensive treatment with high-efficacy DMT:** With growing evidence demonstrating that early treatment with high-efficacy DMTs is associated with better long-term outcomes compared with escalation strategies [2, 68-72], early intervention

with cladribine tablets offers patients a convenient treatment option that has a potential to avoid irreversible disability, early disease progression and conversion to a SPMS.

- **Potential to improve healthcare equality:** the convenience of the home-delivered, short-course oral treatment offered by cladribine tablets, could potentially translate into increased health equality by offering a treatment option to patient groups impacted by socio-economic inequalities, who may have limited access to full services offered by NHS England and for whom the requirements for frequent administration and monitoring (associated with other high-efficacy DMTs) are restrictive [24].

- **Alternative treatment option for women of childbearing potential:** MS typically affects young adults between the age of 20 and 40 years and twice as many women than men. Due to unique posology and mechanism of action of cladribine tablets, which offer durable efficacy without continuous immunosuppression and a 2-year treatment-free period, cladribine tablets are an alternative treatment option for female patients who do not wish to receive active treatment while pregnant or for whom the continuous immunosuppression associated with most of high-efficacy DMTs may be contraindicated during pregnancy.

- **Patient preference:** the convenience of home-delivered, short-course, oral treatment with cladribine tablets was considered by the Association of British Neurologists (ABN) as a potential motivator to some patients, preferred over the frequent monitoring burden and adverse effects associated with infusions, a comment that was reflected in the responses from the MS Society and MS Trust in the NICE scope consultations (TA463/TA616) [4]. This was further supported by results of a Discrete Choice Experiment conducted in the UK, where MS patients considered that the attributes of cladribine tablets would provide a preferred treatment option (overall) and the most preferred oral treatment option in a future treatment landscape [23].

The key benefits of cladribine tablets from the clinicians' and healthcare systems' perspective are in form of saved time, reduced healthcare utilisation and cost savings, which arise primarily due to considerably lower administration and monitoring burden compared with other DMTs:

- **Reduced treatment administration burden:** Over the 4 years of cladribine tablets treatment, a total of 20 days of at-home, oral administration is required, with no need for treatment titration. This contrasts with continuous/frequent treatment administration required for other high-efficacy DMTs (described above, e.g., daily oral treatment with ponesimod treatment [136]; monthly ofatumumab injections [137]; infusions every 6

months [138]), which is often associated with visits to healthcare facilities, adding to the pressure on MS specialist nurses managing the provision of DMTs.

- **Reduced monitoring burden:** During the 2 years of treatment with cladribine tablets, patients require a baseline MRI, which should be performed before initiating the treatment (usually within 3 months) [5], and a total of six blood tests (patients with severe lymphopenia may require more tests) and monitoring for PML, which is a common opportunistic infection that can be fatal in patients with weakened immune systems (although no case of PML has been reported to date with cladribine tablets). In comparison, patients receiving diroximel fumarate or teriflunomide require multiple blood tests and additional analyses such as urinalysis or cardiovascular monitoring, contributing to financial and resource utilisation burden for the healthcare system. Monitoring burden is also associated with substantial time commitment from the HCPs; as demonstrated by Rog at al., compared with other infusion DMTs (alemtuzumab, natalizumab and ocrelizumab), cladribine tablets require the least amount of HCP time per patient spent on monitoring [17]. Overall, the reduced monitoring burden associated with cladribine tablets (vs. other DMTs) could increase capacity of MS services and the NHS as a whole.

The innovative aspects of the cladribine tablets highlighted in this section would result in a considerable change in the current treatment pathway by providing a high-efficacy, convenient oral agent which could potentially improve the overall management of active RRMS and the lifestyle of affected patients, as well as reduce financial and healthcare resource burden in an increasingly cost-constrained NHS.

B.2.13 Interpretation of clinical effectiveness and safety evidence

There is a wide range of DMTs currently available in the UK providing patients and prescribing neurologists with alternative treatment options for active RRMS:

- beta-interferon
- dimethyl fumarate
- glatiramer acetate
- teriflunomide
- ocrelizumab
- peginterferon beta-1a
- ofatumumab
- teriflunomide
- ponesimod
- diroximel fumarate

However, the broader availability of an increasingly diverse range of treatment options provides opportunities for better management in patients with MS.

Merck has summarised the relevant evidence from the clinical development programme for cladribine tablets (section B.2.6). The pivotal trials, CLARITY and CLARITY-EXT, provide the evidence base for the efficacy of cladribine tablets and, alongside other studies in an integrated safety analysis, characterise the safety of cladribine tablets in RRMS. The studies provide the evidence for the efficacy of 3.5 mg/kg cladribine tablets, delivered in a short-course regimen (two treatment weeks in Year 1 and then again in Year 2, and no further re-treatment in Years 3 and 4), which has the capacity to address the unmet needs of patients and the healthcare system for treatments with reduced administration and monitoring burden [5, 6, 10, 32, 85, 139, 140].

The CLARITY trial demonstrates that treatment with 3.5 mg/kg cladribine tablets was more effective than placebo in patients with active RRMS across a broad spectrum of clinical and MRI efficacy outcomes [5]. Cladribine tablets were shown to statistically significantly reduce the qualifying ARR compared with placebo [redacted] and post-hoc analyses showed that the risk of developing 6-month CDP was statistically significantly reduced compared with placebo [redacted] [7] (Section B.2.6.1). Clinical trial data from CLASSIC-MS demonstrate that efficacy observed in the RCTs is robust and reproducible in the post-approval setting [85].

The safety profile is particularly well-characterised through an integrated safety analysis which provides more than 3,000 patient years (PYs) of exposure data [82, 135]. In the interim analysis, the number of AEs per 100 PYs was marginally higher in patients exposed to cladribine tablets compared with placebo (103.29 and 94.26, respectively) [135]. Similarly, in the final analysis, the number of serious TEAEs per 100 PYs was similar (cladribine tablets: 3.80 vs. placebo: 3.05, respectively) [82]. In the interim analysis, treatment discontinuations per 100 PYs were generally low in both cladribine tablets and placebo cohorts (2.07 and 1.05,

respectively). There were no relevant differences in deaths per 100 PYs between cohorts (≤0.26 for both cohorts) (Section B.2.10).

An NMA conducted for this appraisal confirm that cladribine tablets are associated with a statistically significant reduction in ARR against beta interferon, peginterferon beta-1a, teriflunomide, and glatiramer acetate and in terms of 6-month CDP, cladribine tablets were numerically better in comparison to teriflunomide, dimethyl fumarate, glatiramer acetate, beta interferon, and ponesimod. Further, the NMA shows that cladribine tablets have comparable efficacy to other high-efficacy DMTs, with widely overlapping credible intervals. The results of the NMA are utilised in the economic modelling to build pairwise and incremental analyses for the comparators of interest in this appraisal (Section B.2.9).

In summary, the considerable clinical data available for cladribine tablets describes a positive benefit: risk profile, confirming its place alongside other high-efficacy DMTs for patients with active RRMS.

B.2.13.1. Key clinical issues

- Across the 4 years of study treatment, there was no continuous placebo arm. Due to ethical reasons, patients who were randomised to the placebo arm in the CLARITY trial were allocated to a cumulative 3.5 mg/kg dose of cladribine tablets in the EXT trials; therefore, there were no patients who exclusively received placebo across both CLARITY and CLARITY-EXT. To address this, Merck conducted a treatment switching analysis in collaboration with School for Health and Related Research (ScHARR), University of Sheffield, which concluded that for 3- month CDP, 6-month CDP as well as time to first qualifying relapse, the rank preserving structural failure time model (RPSFTM) and the iterative parameter estimation (IPE) algorithm- derived HRs for the LLPP cohort vs. the hypothetical continuous placebo arm (PPPP) were nominally closer to 0 than the HR for the ITT comparison, indicating a greater effect than what was apparent via ITT analysis. In addition, LLPP versus PPPP HRs were similar to the CLARITY ITT (LL versus PP) HR, indicating a sustained cladribine tablets treatment effect over the course of 4 years after only a 96-week treatment period [76, 141].
- Since the two pivotal trials (CLARITY and CLARITY EXT) did not provide a comparison between cladribine tablets and DMTs that are included in the decision problem, Merck conducted an NMA to assess comparative effectiveness of cladribine tablets vs. other DMTs. A limitation of the NMA is uncertainty arising from heterogeneity between trials included in the networks, due to differences in study designs and patient characteristics.

    - The trials included in the NMA were conducted over a period of 35 years (1987 to 2022).
    - These trials differed in study characteristics (diagnostic criteria, study phase, and blinding), patient population recruited (mean relapses in prior 1 year, disease duration, treatment history [previously treated vs. treatment naïve]) and definitions of outcomes.

- Another source of heterogeneity in the evidence base for the NMA arises from variations in treatment effects from the interferon beta trials, which has been acknowledged previously by NICE as lacking clinical validity. The results of INCOMIN suggested superiority of one interferon over the other, which is inconsistent with clinical experience that individual interferon beta treatments have similar clinical effectiveness. As such, the INCOMIN trial was excluded from the base case for 6-month CDP, aligned with the approach taken in the NMA for ponesimod (TA767) and ofatumumab (TA699).

B.3. Cost-effectiveness

B.3.1 Published cost-effectiveness studies

Published cost-effectiveness studies in active RRMS were identified via a systematic literature review of biomedical literature databases in accordance with the NICE methods guide [142]. Searches were conducted in February 2024 for the period between 2017 (since the year of TA493/TA616 publication, the initial NICE appraisal for cladribine tablets) and 2024, and the review covered:

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

Details of the methods used to identify and select the relevant studies are provided in Appendix G.

A summary of the results of the published economic studies is provided in Table 27. In summary, the searches identified 11 cost-effectiveness studies reporting from a UK perspective and published since 2017.

Additionally, the searches identified six economic models that had been submitted to NICE since 2017. One study reported the cost-effectiveness of cladribine tablets. A summary of the economic analysis features from previous NICE appraisals is provided in Table 28 in Section B.3.2.2.

Table 27: Summary list of published cost-effectiveness studies in RRMS (published since TA493/TA616)

Study	Year	Summary of model	Patient population (avg. age in years)	Time Horizon	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained)
Montgomery 2017 [143]	2015	• Cost-effectiveness of natalizumab and fingolimod in the RES-RRMS population from the perspective of the NHS in the UK • A DES model developed to track individual RES-RRMS patients, based on EDSS scores. Individual patient characteristics taken from the RES-RRMS sub-groups of the pivotal trials for fingolimod • The model simulates the events experienced based on patient-specific attributes and calculates the associated costs and utilities for each individual patient in the cohort	RES-RRMS (NR)	Lifetime	Fingolimod: £334,897.93 Natalizumab: £337,501.15	Fingolimod: 6.18 Natalizumab: 6.35	At a £20,000 WTP, the probability of fingolimod being cost-effective vs. natalizumab was 50.8%
Montgomery 2017(a) [144]	2015	• A DES was adapted to model relapse-triggered re-treatment with alemtuzumab and the effect of including ongoing QALY decrements for AEs that extend beyond previous 1-year Markov cycles. As the price to the NHS of fingolimod in the UK is unknown, due to a confidential PAS, a variety of possible discounts were tested. The interaction of re-treatment assumptions for alemtuzumab with the possible discounts for fingolimod was tested to determine which DMT resulted in lower lifetime costs. The lifetime QALY results were derived from modelled treatment effect and short- and long-term AEs	HA-RRMS (38.23)	Lifetime	NR	Fingolimod: 4.44 Alemtuzumab: 4.64 (considering the treatment effect alone)	Fingolimod was reported to be cost-effective vs. alemtuzumab. The observed variation between ICERs calculated for fingolimod vs. alemtuzumab: 1.54%*
Rog 2017 [145]	NR	• Cost-effectiveness/cost-utility analysis for alemtuzumab vs. other licensed DMTs in the UK from the NHS perspective. • The cost-effectiveness of alemtuzumab was evaluated in comparison to 11 DMTs with available 6-month CDP data over a lifetime horizon (i.e., 50 years) • Drug costs were obtained from the BNF 2016 and MIMS drug database • Costs of treatment administration, monitoring, and adverse event management were acquired from NHS from 2014–2015 (annual fiscal costs)	The population considered at least 80% of patients with RRMS (NR)	Lifetime (i.e., 50 years)	Alemtuzumab: £276,188 Comparators: ranged from £274,401 (glatiramer acetate) to £343,790 (natalizumab)	Incremental QALYs for alemtuzumab: Ranged from 1.26 (natalizumab) to 2.12 (interferon beta-1a 44 µg)	Alemtuzumab dominates almost every other licensed DMT. Alemtuzumab vs. glatiramer acetate: £863
Hettle 2018 [146]	2015 / 2016	• Cost-effectiveness of cladribine tablets in HDA-RRMS vs. alemtuzumab and natalizumab from the perspective of the NHS in England • A cohort-based Markov model with 11 health states	HDA-RRMS (NR)	Lifetime (i.e., 50 years)	Cladribine tablets: £92,484	Cladribine tablets: 9.45	Cladribine tablets dominant vs. alemtuzumab

Study	Year	Summary of model	Patient population (avg. age in years)	Time Horizon	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained)
		• Transition matrices from the BCMS registry used to model natural history of EDSS • Treatment effect on EDSS modelled using 6M-CDP HRs from an ITC • Relapses and drug-related AEs modelled via ARR and event probabilities, with associated costs and QALY losses. Utilities derived from trials and literature, and costs from NHS and literature sources			Alemtuzumab: £104,136 Natalizumab: £212,969	Alemtuzumab: 8.48 Natalizumab: 7.74	and natalizumab
Harty 2018 [147]	2016 / 2017	• CMA of cladribine tablets vs. alternatives in an NHS UK setting (assuming comparable efficacy vs. alemtuzumab, fingolimod, and natalizumab) • An economic model, based on a UK perspective, published by Hettle et al (2018)[146] was adapted to assume HRs of 1 for CDP and ARR vs. the comparators. • Discontinuation rates for each treatment were set to 0%. Safety profiles of the DMTs, based on clinical studies were included. Health state utilities were also incorporated • Costs: NHS reference tariffs and from the BNF	HA-RMS (NR)	Lifetime (i.e., 50 years)	Incremental savings of cladribine tables vs. alemtuzumab: £-8,453, fingolimod: £-199,635, natalizumab: £-234,430	Incremental QALY of cladribine tablets vs: Alemtuzumab: 0.007 Fingolimod: -0.004 Natalizumab: -0.003	NR
Phelps 2018 [148]	NR	• Cost-effectiveness of modelling subsequent treatment in RRMS from a UK NHS perspective • Markov model developed; analyses were run varying the cost and treatment effect of a hypothetical subsequent treatment compared with a scenario excluding subsequent treatment • Treatment efficacy and discontinuation rates for primary treatments were sourced from a NMA conducted by the Institute for Clinical and Economic Review. Costs and utility data were sourced from published literature	RRMS (NR)	NR	NR	NR	Natalizumab vs. fingolimod: Not including subsequent treatment: £29,500. Including subsequent treatment: ICER ranged from £855 (most costly and least effective subsequent treatment) to £33,058 (least costly and

Study	Year	Summary of model	Patient population (avg. age in years)	Time Horizon	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained)
							most effective subsequent treatment)
Rock 2019 [149]	2018	• Evaluate the economic impact in Europe (Sweden, France, Germany, UK, Spain, and Italy) of beginning and continuing treatment with dimethyl fumarate vs. initiating treatment with glatiramer acetate and switching to dimethyl fumarate after treatment failure • A Markov model with 10 health states (EDSS 0-9) and death over a lifetime horizon in MS patients using annual cycles from a societal perspective. • Efficacy inputs were estimated from a mixed treatment comparison, including 6M-CDP HRs, and risk ratios for ARR	RRMS (NR)	Lifetime	Cost offsets among RRMS patients initially treated with dimethyl fumarate: kr385,356 (Sweden), €9,910 (France), €46,414 (Germany), €825 (Italy) Cost increase: €7,442 (Spain), £56,949 (UK)	QALY gain after initiating DMF: 0.48 to 0.68 (Sweden, Germany, France, Italy) 0.48 to 0.50 (Spain, UK)	NR
Giovannoni 2019 [150]	2015 / 2016	• Costs for glatiramer acetate from the final 10-year analysis of the RSS. Expected progression of disability: continuous Markov model with a time horizon of 10 years • Separate model for cost-effectiveness: Markov model 50-year time horizon, 50% treatment waning effect imposed at 10 years, BCMS transition probabilities, costs inflated to 2015/16 prices, used NHS list price of glatiramer acetate (£513.95 per 28 days/£6,701 per annum)	RRMS (NR)	Lifetime (i.e., 50 years)	Glatiramer acetate: £513.95 per 28 days £6,701 per annum	NR	Cost per QALY: £17,841
Di Maio 2020 [151]	2019	• Estimate costs of ocrelizumab from socioeconomic perspective vs. dimethyl fumarate, natalizumab and cladribine tablets • A Markov-state model based on 1-point spaced EDSS states (0–9) was used to estimate costs associated with disease progression • EDSS at baseline and transition probabilities derived from the OPERA trials and a natural history study. • Treatment effect on delaying disability progression modelled through 3M-CDP HRs derived from ITC	RMS (NR)	5 years	Socioeconomic value of ocrelizumab vs. dimethyl fumarate, natalizumab, and cladribine tablets in the UK estimated to be £72.2	NR	Ocrelizumab for RMS offers substantial socioeconomic benefits versus relevant first- and second-line DMTs in the UK.

Study	Year	Summary of model	Patient population (avg. age in years)	Time Horizon	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained)
		• Resource use and cost inputs at 2019 prices derived from a cross-sectional study of patients with MS that was published in 2017 or from national statistics databases • Data on RMS prevalence and proportion of patients treated with DMTs in the UK obtained from Roche epidemiologic forecasts and a RW study			million, £27.9 million and £18.7 million, respectively		
Spelman 2022 [152]	2019	• Cost-effectiveness of natalizumab vs. fingolimod in patients with RRMS using a UK third-party payer perspective • A Markov-based structure with an annual cycle length and integer EDSS-based health states, consistent with previous cost-effectiveness analyses • The model structure included separate EDSS health states for RRMS (EDSS 0–9.0) and for SPMS (EDSS 1.0–9.0). Disability worsening was possible in both RRMS and SPMS; disability improvement was assumed possible in RRMS only. Conversion from RRMS to SPMS was assumed to be associated with a 1-point EDSS increase, consistent with modelling precedent in MS, based on the expectation that conversion to SPMS increases disability. Transitions of ≥ 1.0 EDSS score in a single cycle were allowed	RRMS (natalizumab mean: 36.9; fingolimod mean: 37.6; MSBase registry)	Lifetime	Natalizumab: £459,047 Fingolimod: £479,890	Natalizumab: 7.87 Fingolimod: 7.42	Natalizumab dominant vs. fingolimod Net monetary benefit £30,000 per QALY gained: £34,430
Spelman 2024 [153]	2021	Cost-effectiveness of natalizumab vs. fingolimod in patients with RES-RRMS from a UK NHS perspective	RES-RRMS (mean age for natalizumab and fingolimod: 36; MSBase Registry)	Lifetime	Natalizumab: £492,341 Fingolimod: £509,482	Natalizumab: 7.86 Fingolimod: 7.56	Natalizumab dominant vs. fingolimod: −£56,725

* An ICER was not presented for this analysis, as the fingolimod price to the NHS was lower than that modelled in this scenario

AE: Adverse event; ARR: Annualised relapse rate; BCMS: British Columbia Multiple Sclerosis; BNF: British National Formulary; CDP: Confirmed disease progression; CMA: Cost-minimisation analysis; DES: Discrete-event simulation; DMT: Disease-modifying treatment; EDSS: Expanded disability status scale; HA: Highly active; HDA: High disease activity; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; ICER: Institute for Clinical and Economic Review; ITC: Indirect treatment comparison; MIMS: Monthly Index of Medical Specialities; MS: Multiple sclerosis; NHS: National Health Service; NMA: Network meta-analysis; NR: Not reported; PAS: Patient Access Scheme; QALY: Quality-adjusted life year; RES: Rapidly evolving severe; RMS: Relapsing multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; RSS: Risk Sharing Scheme; RW: Real-world; SPMS: Secondary progressive multiple sclerosis; SW: South-west; UK: United Kingdom; WTP: Willingness-to-pay

B.3.2 Economic analysis

A cost-effectiveness model submitted as part of initial, 2017 NICE submission for cladribine tablets (TA493/TA616) and published by Hettle 2018 [146] was updated to assess the incremental cost-effectiveness of cladribine tablets versus relevant alternative treatments within its recently expanded marketing authorisation for the treatment of adult patients with RMS with active disease as defined by clinical or imaging features. Further detail on each aspect of the model is provided in later sections of the submission.

B.3.2.1. Patient population

As outlined in the Decision Problem (Section B.1.1), the marketing authorisation for cladribine tablets is for the treatment of adult patients with RMS with active disease as defined by clinical or imaging features.

In line with the final scope for this appraisal, the economic analysis focuses on the use of cladribine tablets in people with active RRMS. Population characteristics and clinical parameters are described in detail in Section B.3.3.

B.3.2.2. Model structure

The model uses a Markov-based cohort approach to simulate the costs and effectiveness of cladribine tablets versus NICE-recommended DMTs in people with RRMS. An annual cycle length was adopted with outcomes evaluated over a time lifetime horizon of 50-years. The length of the cycle period is based on approaches accepted in the previous appraisal of cladribine tablets (TA493/TA616) [25].

The model was programmed in Microsoft® Excel® for Microsoft 365 MSO (Version 2401 Build 16.0.17231.20290) 64-bit and used visual basic for applications for probabilistic and deterministic sensitivity analyses. In line with the NICE reference case, cost-effectiveness was assessed in terms of the cost per quality adjusted-life years (QALY) gained. Both costs and health outcomes were discounted at a rate of 3.5% per annum.

As outlined in Table 28, the cost-effectiveness model for cladribine tablets is similar to the model submitted for the previous appraisal of cladribine tablets (TA493/TA616), which the NICE committee considered as appropriate for decision making [86], and is a simplified version of the model structures used in previous NICE MS submissions (justification is provided in Section B.3.2.2.1). In all other respects, the model has been developed to be consistent with precedents set in previous NICE appraisals in RRMS.

Table 28: Features of the economic analysis

Factor	Interferon-beta and glatiramer acetate (TA527) [132]	Ocrelizumab (TA533) [92]	Peginterferon (TA624) [97]	Ponesimod (TA767) [94]	Ofatumumab (TA699) [93]	Cladribine tablets (TA493/TA616) [25]	Chosen value for this appraisal	Justification
Health state structure	21 health states	21 health states	21 health states	20 health states	21 health states	11 health states based on 10 EDSS states representing RR and SP forms of MS, and 1 death state	11 health states based on 10 EDSS states representing RR and SP forms of MS, and 1 death state	Simplification of 21 state model that combines RR and SP forms of MS together. Further justification provided in the following section
Time horizon	50 years	50 years	50 years	50 years	Lifetime	50 years	50 years	In line with TA493/TA616 and approaches in previous RRMS appraisals
Source of natural history EDSS	BCMS	BCMS	BCMS for transitions across EDSS for patients with RRMS London Ontario for transitions from RRMS to SPMS and during SPMS	BCMS for transitions across EDSS for patients with RRMS London Ontario for transitions from RRMS to SPMS	BCMS for transitions across EDSS for patients with RRMS London Ontario and EXPAND for transitions from RRMS to SPMS and during SPMS	BCMS	BCMS	BCMS is the most reliable and robust source available of natural history data in MS
Source of natural history relapse	UK MS survey	Patzold et al. (1982) combined with UK MS survey data	Patzold et al. (1982) combined with UK MS survey data	Patzold et al. (1982) combined with UK MS survey data	Patzold et al. (1982) combined with UK MS survey data	Placebo arm of CLARITY combined with BCMS data from Tremlett et al. (2010)	Placebo arm of CLARITY combined with BCMS data from Tremlett et al. (2010)	Relapse rate was modelled as a function of time to avoid double-counting of DMT treatment effect on both EDSS progression and relapse rate, and BCMS is the same source used for the natural history EDSS. Further justification provided in Section B.3.3.2.1
Source of MS mortality	Not applied	Pokorski (1997) extrapolated for EDSS states	Pokorski (1997) extrapolated for EDSS states	Pokorski (1997) extrapolated for EDSS states	Pokorski (1997) extrapolated for EDSS states	Jick et al. (2014)	Jick et al. (2014)	Published mortality ratio in the largest sample of people with MS in UK. Further justification provided in Section B.3.3.2.3

Factor	Interferon-beta and glatiramer acetate (TA527) [132]	Ocrelizumab (TA533) [92]	Peginterferon (TA624) [97]	Ponesimod (TA767) [94]	Ofatumumab (TA699) [93]	Cladribine tablets (TA493/TA616) [25]	Chosen value for this appraisal	Justification
Application of treatment effect	• ARR • CDP-6M • SPMS transition	• ARR • CDP-6M • SPMS transition	• ARR • CDP-6M • SPMS transition	• ARR • CDP-3M	• ARR • CDP-6M	• ARR • CDP-6M	• ARR • CDP-6M	In line with majority of previous RRMS appraisals
Treatment effect waning	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	25% after 2 years and 50% after 5 years	Not applied; all-cause treatment discontinuation acts as a proxy for waning	Cladribine tablets: Treatment effect at 100% for Years 0-4. NICE Committee preferred assumption of 25% waning in Year 4-5, and 50% waning after Year 5 Comparators: treatment effects at 100% in Years 0-2, 25% waning in Years 2-5 and 50% waning after Year 5	Treatment effect at 100% for Years 0-4, NICE Committee preferred assumption of 25% waning in Year 4-5, and 50% waning after Year 5 for cladribine tablets and comparators	As cladribine tablets have a 4-year posology, treatment effect at 100% for Years 0-4 assumed based on evidence from treatment switching analysis of CLARITY/ CLARITY EXT. The same is modelled for comparators as a conservative assumption due to lack of evidence around waning of comparators.
Treatment discontinuation	UK MS survey, Tappenden et al. (2001)	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	Trial data sourced from NMA, constant annualised rates	In line with TA493/TA616 and approaches in previous RRMS appraisals
Stopping rule	By individual treatment	EDSS ≥7.0 SPMS transition (scenario)	EDSS ≥7.0 SPMS transition	EDSS ≥7.0 SPMS transition	EDSS ≥7.0 SPMS transition	EDSS ≥7.0	EDSS ≥7.0	In line with TA493/TA616 and previous RRMS appraisals
Source of patient utilities	Orme et al. (2007)	Trial data and Orme et al. (2007)	Trial data and Orme et al. (2007)	Orme et al. (2007)	Pooled trial data and Orme et al. (2007)	EQ-5D in CLARITY study for EDSS 0-5, Hawton et al. (2016) for EDSS 6-8 and Orme at al. (2007) for EDSS 9	EQ-5D in CLARITY study for EDSS 0-5, Hawton et al. (2016) for EDSS 6-8 and Orme at al. (2007) for EDSS 9	Following preference for trial data supplemented by literature estimates. Literature estimates from best source identified in de novo literature review
Source of relapse disutility	Not applied	Orme et al. (2007)	Orme et al. (2007)	Orme et al. (2007)	Pooled ASCLEPIOS trials	Orme et al. (2007)	Orme et al. (2007)	In line with TA493/TA616 and approaches in previous RRMS appraisals

Factor	Interferon-beta and glatiramer acetate (TA527) [132]	Ocrelizumab (TA533) [92]	Peginterferon (TA624) [97]	Ponesimod (TA767) [94]	Ofatumumab (TA699) [93]	Cladribine tablets (TA493/TA616) [25]	Chosen value for this appraisal	Justification
Source of caregiver disutility	Acaster et al. (2013)	Loveman et al. (2006) and UK MS survey data	Acaster et al. (2013)	Acaster et al. (2013)	Loveman et al. (2006) and UK MS survey data	Acaster et al. (2013)	Acaster et al. (2013)	In line with majority of previous RRMS appraisals
Source of EDSS cost	Tyas et al. (2007)	Tyas et al. (2007)	UK MS survey (2005) (direct medical only), inflated to 2019	Tyas et al. (2007), inflated to 2019 for direct medical costs	UK MS survey data with values inflated to cost year	Hawton et al. (2016)	Hawton et al. (2016); Tyas et al. (2007) in sensitivity analysis	Preferred data source identified in de novo literature review; consistent with source of data used for health state utilities. Tyas et al. (2007) costs are uncertain given they need to inflate the costs from 2005
Source of relapse cost	Tyas et al. (2007)	Tyas et al. (2007)	Tyas et al. (2007)	Tyas et al. (2007), inflated to 2019	Hawton et al. (2016)	Hawton et al. (2016)	Hawton et al. (2016)	In line with TA493/TA616

AE: Adverse event; ARR: Annualised relapse rate; BCMS: British Columbia Multiple Sclerosis; CDP-6M: Confirmed disease progression-6 months; EDSS: Expanded disability status scale; EQ-5D: EuroQoL five dimensions questionnaire; MS: Multiple sclerosis; NICE: National Institute for Health and Care Excellence; NMA: Network meta-analysis; RR: Relapsing-remitting; RRMS: Relapsing-remitting multiple sclerosis; SP: Secondary progressive; SPMS: Secondary progressive multiple sclerosis; UK: United Kingdom

B.3.2.2.1. Overview of model structure

The cost-effectiveness model is comprised of two mathematical models:

1. A natural history reference model, developed using data on the disability and relapse status of people receiving best supportive care (BSC), and
2. A treatment-adjusted model, which combines the natural history reference model with data on the comparative efficacy and safety of DMT versus placebo

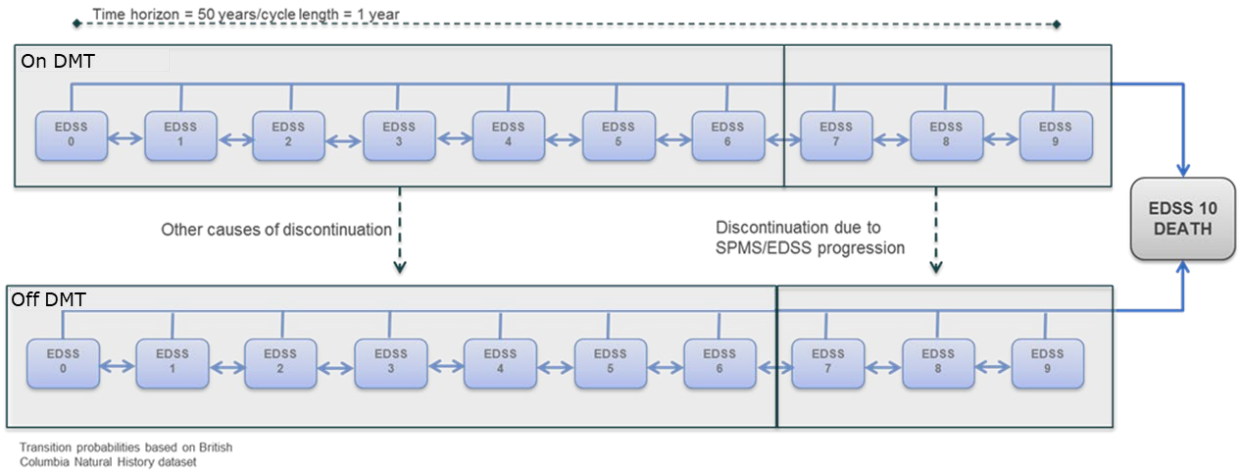
The reference and treatment-adjusted models use the same core 11-health state structure as illustrated in Figure 18. This structure comprises 10 health states representing disability status according to the EDSS and a single state for death from all causes. Health states were defined by the EDSS score as it is the primary measure used to define disease worsening in MS patients, and because EDSS scores are a critical factor in clinical care decision making.

The health state structure used in this appraisal is a simplified version of the 21-health state structure used in previous RRMS appraisals, and which included 10 EDSS states for RRMS, 10 EDSS states for SPMS, and a single state for death. The simplified 11-health state structure excludes the 10 EDSS states for SPMS and instead models disability progression in patients who develop SPMS together with those who remain relapsing remitting. As it is difficult to clearly identify the transition from the RRMS into the SPMS subtype, it is difficult to reliably model the conversion from one form to another.

Furthermore, the addition of SPMS-specific health states requires the use of SPMS-specific transition rates from the London Ontario registry as this is the only source of SPMS-specific natural history data. However, the London Ontario registry is subject to intrinsic flaws due to post-hoc data censoring; the natural history cohort from the London Ontario registry was found to contain retrospectively smoothed disability data (rather than actual, real-time collected disability scores), censoring any improvement in EDSS [154]. Comparing the uncensored cladribine tablets treated cohort to data retrospectively smoothed in this way would unpredictably underestimate any treatment effect. In addition, individual patient-level data were not available from the London Ontario cohort, which prevented precise baseline matching between the two cohorts, limiting our validation of the underlying (Markov) model for disease progression. There were also only 342 patients matching the ABN prescribing criteria from which to generate the models. Furthermore, the matrix does not allow for improvements in EDSS as observed in clinical studies and other natural history studies. Therefore, the London Ontario registry has been discredited as a reliable or robust source of natural history data in MS [154]. As such, the 21-health state approach is only explored in the sensitivity analysis; additional detail on the methodology is provided in Appendix M.

In TA493/TA616, the NICE committee accepted the company rationale that separating RRMS and SPMS forms of MS is not necessary for modelling as all health-related benefits of treatment would be captured by changes in EDSS state, and it is difficult to identify the transition to SPMS in clinical practice. The ERG was satisfied with the rationale for using the simplified 11 health-state model rather than a 21 health-state model, especially as the SPMS subtype does not significantly impact on costs or HRQoL. Whilst EDSS state transition probabilities for the SPMS subtype would differ from those for the RRMS subtype, the ERG considered that any incorporation of this detail into the model is limited by available data on transition to the SPMS subtype. The pooling of the RRMS and SPMS states in the 11-health state structure is consistent with the approach taken by Palace et al. when modelling the natural history of RRMS for the UK risk sharing scheme [154]. This included the use of all EDSS scores collected in people with RRMS, including those recorded after a person had developed SPMS. Differences in transition rates between the RRMS and SPMS stages are accounted for in the averaged transition rates reported by Palace et al. and then subsequently applied in the economic model for cladribine tablets. When developing the Markov model, Palace et al. did not consider MS course (i.e., RRMS versus SPMS) as a covariate in the analysis, as SPMS is "simply a later stage of the relapsing remitting form of the disease and the transition has considerable overlap" [154]. The model also has functionality for 21-health state for scenario analyses.

Figure 18: Health state structure of the 11-state model including periods on and off DMT



DMT: Disease-modifying treatment; EDSS: Expanded disability status scale; SPMS: Secondary progressive multiple sclerosis

B.3.2.2.2. Natural history reference model

At model entry, the patient cohort is proportionally assigned to the 10 EDSS states according to the baseline EDSS distribution in the CLARITY trial population (Table 29). Over yearly cycle periods, the cohort is at risk of:

- Experiencing disability progression (move to a higher EDSS state)

- Improving in disability status (move to a lower EDSS state),
- Remaining at their current level of disability (remain in their current EDSS state),
- Death

The modelled cohort is also at risk of experiencing one or more acute relapse events during each cycle. These events are modelled separately to EDSS-related disability progression and are calculated by applying an ARR to the number of patients alive in the model. This is in line with approaches adopted in previous appraisals [92-94, 97, 132].

The costs of managing MS are calculated by combining the time spent in each EDSS state combined with the costs assigned to each state, additionally, within each EDSS state, relapses and AEs are captured and costs assigned to these. This includes costs covered under the NHS and Personal Social Services (PSS) perspective, such as drug acquisition, administration, and monitoring, the costs of managing the disease and treatment given for relapse events, direct EDSS-related medical costs, and costs for managing drug-related adverse events.

In line with the approach in previous RRMS economic models (as mentioned in Table 28), the majority of costs are modelled based on the mid-cycle occupancy for each state, which is estimated from the average number of patients in each state at the start and end of each cycle (e.g., equivalent to half-cycle correction). The exceptions are the acquisition and administration costs for cladribine tablets, which are given at model entry and at the start of Year 1. These costs are applied to state occupancy at the start of each “treated” cycle. This is aligned with TA493/TA616 [25].

The health effects of treatment were modelled in terms of QALYs, a combined measure of the quality and duration of life. The QoL aspect was modelled using health state utilities (HSU) derived from various sources including literature [56, 155, 156] and EQ-5D questionnaires collected in the CLARITY trial [146]. The model includes the impact of disability progression, relapse rates, and drug-related adverse events on the HRQoL of the person with MS. In line with previous MS NICE appraisals and TA493/TA616, an additional QALY loss associated with the impact of disability status on the QoL of caregivers was also included [25, 92-94, 97, 132].

The QALYs accrued from the EDSS progression and infusion, and injection site reactions were modelled on the mid-cycle occupancy of each state (e.g., equivalent to half-cycle correction). The QALYs associated with relapse and all other AEs were modelled as QALY losses based on the number of events experienced.

The transition of patients between states is simulated over annual cycle periods, with outcomes evaluated over a time horizon of up to 50 years. The length of the cycle period is based on approaches used in previous models [157-162]. The cycle period and time horizon based on approaches used in previous models and best reflects the course of disease.

B.3.2.2.3. Treatment-adjusted model

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

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

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

There is no assumed effect of DMT on the probability of improving in EDSS and the probability of death, which are fixed to the values used in the natural history model. The probability of remaining in the same EDSS state was increased to reflect that fewer patients progress on DMT. This follows approaches accepted in TA493/TA616 and in all previous appraisals in RRMS [25, 92-94, 97, 132].

The effects of treatment are modelled based on the results of an NMA, which in turn is based on clinical trial data identified from a systematic literature review (see Section B.2.9 and Appendix D for methodology and results). Further detail is provided in Section B.3.6.1.

As in previous appraisals, patients are assumed to benefit from treatment while “on DMT”. These effects are assumed to gradually wane over time. In each model cycle, patients “on DMT” are at risk of discontinuing treatment for reasons such as loss of efficacy and tolerability. Further detail on the discontinuation rules is provided in Section B.3.2.3.2 (Table 28).

Patients who discontinue treatment are assumed to retain the cumulative benefits of DMT up to the point of discontinuation and switch to a BSC regimen. The future outcomes of BSC are modelled using the natural history model. No further treatment is given in line with models accepted in previous NICE appraisals in RRMS [25, 92-94, 97, 132].

The costs and outcomes of drug-related AEs are considered in the model and include macular oedema, hypersensitivity, autoimmune thyroid-related events, and “ongoing” events related to infusion and injection site reactions (Section B.3.5).

Relevant AEs were identified from a review of the summary of product characteristics for each drug in scope, from previous economic models [157-162], and following consultation with clinical experts.

B.3.2.2.4. Clinical justification for health state structure

The health state structure of the base case model (11-health state model) is based on the natural history transition matrix reported by Palace et al. (2014) and used in the UK risk sharing scheme [154], NICE multiple technology appraisal of interferon beta and glatiramer acetate (TA527) [132], and in TA493/TA616 [25].

The model uses the EDSS system for defining disability status and estimates the full impact of disease from pre-diagnosis at EDSS 0 (normal neurological examination) to EDSS 9.5 (confined to bed) and death. The EDSS is considered an appropriate tool for measuring disability in the model as increasing EDSS has been shown to correlate with increasing levels of health and socio-economic burden (e.g., productivity) and decreasing levels of HSU in people with MS [161, 163, 164].

The model also captures the independent effects of relapses on the costs and health related quality of life of people with MS. The inclusion of relapse events separately to EDSS progression is justified on the basis that relapses have been associated with an increase in visits to health care professionals, absenteeism from work, the need for additional support to undertake routine tasks, as well as impact on the health related quality of life of people with MS [165]. A number of studies have shown that these effects occur independently of EDSS state [56, 166]. Reduction in relapse events is also a key goal of DMT, and the primary endpoint of most clinical trials in RRMS highlighting its importance as measures of clinical effect in MS.

Patients who discontinue DMT or experience progression after cladribine tablets are assumed to receive BSC. In practice, some patients are likely to receive further DMT treatment upon discontinuation or evidence of progression. This has been noted in previous appraisals, where Committees have highlighted the inclusion of treatment sequencing to enhance generalisability of cost-effectiveness results to UK clinical practice. However, in TA303 [167], TA312 [168], and TA320[169], the NICE Committees concluded that the analysis of individual drugs (without a sequence) should be the basis for decision-making because of:

- Lack of an established common treatment pathway
- Differences in subpopulation treatment
- Availability of treatments with different modes of action
- Uncertainties related to the modelling of sequencing
- Difficulty with cross-model validation
- Treatment sequencing going beyond the scope of a single technology appraisal

The same approach (assuming all patients who discontinue DMT or experience progression receive BSC) was previously used and accepted by the NICE Committee in TA493/TA616, TA527, TA533, TA624, TA699 and TA767. Hence, following NICE precedent and acknowledging

the challenges with modelling treatment sequencing as stated above, the economic analysis for cladribine tablets does not consider the cost-effectiveness of treatment when given within a sequence of therapies.

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention and comparators

The cost-effectiveness model presented in this submission focuses on the use of cladribine tablets in people with active RRMS.

Comparators evaluated in this cost-effectiveness model are listed below (the differences between the final scope issued by NICE and the scope covered in this submission are explained in Section B.1.1):

- Optimised standard care with no DMT (BSC)
- Interferon beta-1a (Rebif® 22ug) (TA527)
- Interferon beta-1a (Rebif® 44ug) (TA527)
- Interferon beta-1a (Avonex®) (TA527)
- Interferon beta-1b (Extavia®) (TA527)
- Interferon beta-1a (Plegridy®) (TA624)
- Dimethyl fumarate (Tecfidera®) (TA320)
- Diroximel fumarate (Vumerity®) (TA794)
- Glatiramer acetate (Copaxone®) (TA527)
- Teriflunomide (Aubagio®) (TA303)
- Ocrelizumab (Ocrevus®) (TA533)
- Ofatumumab (Kesimpta®) (TA699)
- Ponesimod (Ponvory®) (TA767)

Note: Glatiramer acetate 20 mg and teriflunomide 14 mg are included in the model, whilst glatiramer acetate 40 mg and teriflunomide 7 mg are not included in the model. No data was available for glatiramer acetate 40 mg in the NMA and teriflunomide 7 mg is not the recommended dose for adults [170]. Additionally, diroximel fumarate treatment effect was assumed the same as dimethyl fumarate in the absence of NMA results for this drug. This is in line with the NICE appraisal for diroximel fumarate, in which the NICE committee concluded that diroximel fumarate and dimethyl fumarate are assumed to have clinical equivalence [171].

B.3.2.3.2. Discontinuation rules

The rules for discontinuing DMT in the economic analysis were based the NHS England Clinical Commissioning Policy for DMT in RRMS [172].

The 2015 revised ABN guidelines for prescribing DMT in RRMS state that clinicians should consider stopping treatment in the following scenarios:

- Significant side effects
- Development of non-relapsing SPMS
- Pregnancy

The ABN guidelines do not provide stopping rules that are specific to an individual DMT. Overall, the ABN guideline and NHS commission policy advocate similar criteria for stopping DMT.

The modelling of discontinuation due to the onset of SPMS causing an inability to walk was captured through the transition of patients between EDSS states, and the application of a "discontinuation rule" for patients who transition beyond a set EDSS level in the model. It was assumed that any patient transitioning to EDSS state 7.0 or greater would be considered SPMS and hence discontinued from therapy in line with previous appraisals [92-94, 97].

The modelling of discontinuations due to reasons unrelated to clinical diagnosis (e.g. tolerability) was captured through a separate annual discontinuation probability, based on the NMA, applied in each cycle; see Section B.3.3.3.5 for more detail.

B.3.3 Clinical parameters and variables

B.3.3.1. Population characteristics

The economic model is populated with baseline patient characteristic data obtained from the placebo arm of the CLARITY trial, whose characteristics are likely to best represent the targeted population for cladribine tablets in RRMS. The characteristics vary based on the population selected in the model to reflect the differences in the profiles across populations.

The ITT population in the CLARITY trial is considered generalisable to the population with MS in clinical practice in England, given that the profile of the active RRMS group in the CLARITY trial (e.g., intention to treat) is similar to that of patients enrolled to the UK multiple sclerosis risk sharing scheme (age 39.4 years, relapses in the past 2 years [median=3], disease duration 8.8 years) [154].

A summary of the characteristics of the ITT RRMS population of CLARITY is shown in Table 29.

Table 29: Patient characteristics in the economic analysis

Characteristic	ITT
Age at treatment (years): mean (SE)	38.7 (0.474)
Female to male ratio	1.933
Relapse in prior 12 months: mean (SE)	[redacted]
Average patient weight (kg)	[redacted]

Characteristic	ITT
Weight range (% of patient population)	
40-50kg	[redacted]
50-60kg	[redacted]
60-70kg	[redacted]
70-80kg	[redacted]
80-90kg	[redacted]
90-100kg	[redacted]
100-110kg	[redacted]
>110 kg	[redacted]
EDSS category (% of patient population)	
EDSS 0	[redacted]
EDSS 1.0	[redacted]
EDSS 2.0	[redacted]
EDSS 3.0	[redacted]
EDSS 4.0	[redacted]
EDSS 5.0	[redacted]
EDSS 6.0	[redacted]
EDSS 7.0	[redacted]
EDSS 8.0	[redacted]
EDSS 9.0	[redacted]
Sample (placebo), N	[redacted]

Source: [7, 146, 173]

EDSS: Expanded disability status scale; ITT: Intention-to-treat; SE: Standard error

B.3.3.2. Natural history reference model

The following section contains a summary of the data sources used to model acute relapse events, EDSS disability progression, and mortality in the natural history reference model.

B.3.3.2.1. Acute relapse events

The number of acute relapse events that occur in each cycle of the Markov model is calculated by multiplying the number of patients alive in each cycle by the ARR derived from the NMA.

The relapse rate is modelled as a function of time in the base case, as opposed to EDSS state, based on mean ARR obtained from the placebo arm of CLARITY. This differs to approaches used in previous appraisals, where relapse rates were modelled as a function of EDSS state using data from UK MS surveys conducted almost two decades ago.

By relating relapse rate to EDSS state, previous models incorporated an additional indirect effect of DMT on relapse rate through its effect on progression rate, which leads to double counting of the benefits of DMT when applying independent effects to both EDSS progression and relapse rate. This approach also relies upon historical data from previous UK MS surveys dating back at

least 10 years that may not accurately reflect relapse rates in contemporary practice given the trend towards lower annualised rates in the placebo arms of contemporary clinical trials [101, 126, 174]. For these reasons, the ARR in the model was assumed to be independent of EDSS. Relapse rate modelled on EDSS state is explored in the sensitivity analysis; additional detail on the methodology is provided in Appendix M.

Relapse rate as a function of time

The ARR is calculated as follows:

- Estimate the ARR during the first year of the simulation
- Estimate the change in ARR over time

The ARR in the first year is modelled on the rates from the placebo arm of the CLARITY trial to ensure consistency between relapse rate and the baseline characteristics of the modelled population (also from the CLARITY trial). The mean annual relapse rate for active RRMS is 0.34 (95% CI: 0.30 to 0.38).

The ARR in the second and subsequent years are modelled by combining the rate in the first year with the annual change in relapse rate per additional year of disease, via the following equation:

$$ARR(t) = \begin{cases} ARR(1) & if\ t = 1 \\ ARR(t-1) \times RR & otherwise \end{cases}$$

Where t is time period, ARR is annualised relapse rate, and RR is the change in relapse rate per additional year with MS.

The change in relapse rate was obtained from the published literature as clinical trials are not designed to provide assessments of the trend in relapse rate over time.

For consistency with the modelling of EDSS progression, data on the change in relapse rate over time were sought from the British Columbia Multiple Sclerosis (BCMS) registry. A single study by Tremlett et al. was identified [175], which reported the longitudinal relationship between ARR and the characteristics of sex, age at onset, current age and disease duration using patient-level data from BCMS registry [175].

The ARR in the BCMS decreased by an average of 17% every 5 years based on a median follow-up of 20.6 years, 51,120 person-years of exposure, and 11,722 post-onset relapses [175, 176]. The 17% reduction is the average decline for the whole cohort in the study (i.e., regardless of the onset age) and it is not used in the model.

The age of onset of MS was strongly associated with the rate of decline of ARR, with estimates of 30.5%, 22.9%, 16.9%, and 6.9% in people with onset ages of 40+ years, 30-40 years, 20-30 years and less than 20 years old respectively in the study [175, 176]. The mean age and disease

duration of the population in CLARITY was 38.7 years and 5.18 years respectively, with a mean age of onset of between 30 years and 40 years. Based on the data from Tremlett et al. [175, 176], it was therefore assumed that for the base case analysis the ARR would decline by 22.9% (95% CI: 19.4-26.2) for every 5 years of the simulated time horizon.

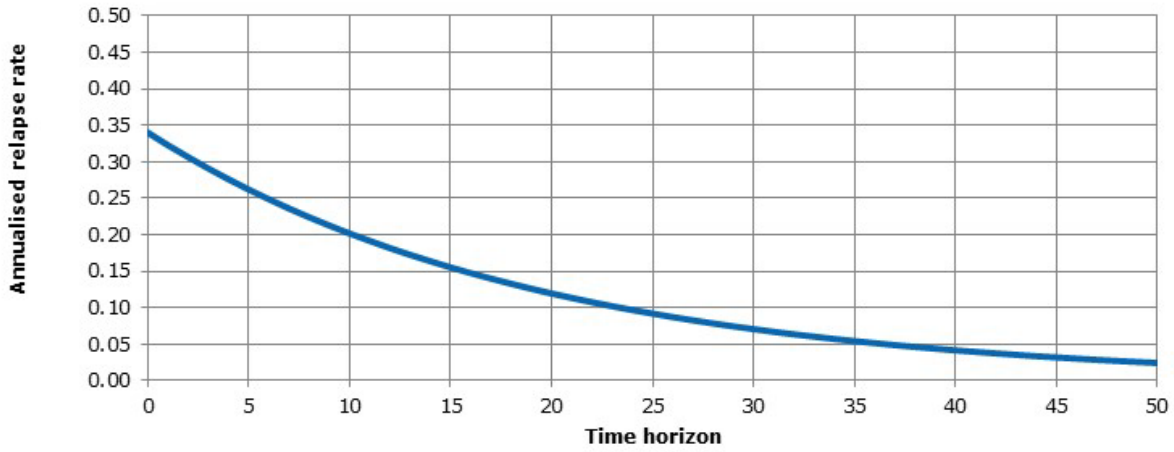
In the model, the 5-year decline in ARR is converted to a yearly decrement using the following formula:

$$RR = e^{(\frac{1}{t} \times \ln(RR_t))}$$

Where RR is the rate reduction and t is the time period over which the reduction occurs (e.g., 5 years). For the base case, the proportional reduction was estimated at 5.07% per year[1].

A plot showing the ARR over time for the BSC population in the active RRMS population is shown in Figure 19.

Figure 19: ARR over time for a BSC population using data from CLARITY in the first year combined with an estimated 5.07% decline in rate per year thereafter



ARR: Annualised relapse rate; BSC: Best supportive care

In the probabilistic analysis, the mean ARR is sampled using a log-normal distribution, and the proportional reduction in ARR is sampled using a beta distribution.

Duration of relapse event

The health effects of relapses are measured in terms of QALY losses and are calculated from the mean duration of each relapse event multiplied by the loss in utility associated with each relapse.

The mean duration of each relapse event was obtained from data collected in the CLARITY study (Table 30). Relapse data were summarised according to the requirement for hospitalisation and were pooled across treatment groups in CLARITY. The pooled data were applied to relapses

[1] Or 94.9% of ARR for each cycle in the model

experienced on all treatments in the analysis, including BSC. This is a conservative assumption as the mean duration of a relapse was shorter with cladribine tablets versus placebo.

Table 30: Duration of relapse event recorded in the ITT population of the CLARITY clinical study by treatment group and hospitalisation status

Event	Placebo, N=437	Cladribine tablets, N=433	Total
Duration of relapses requiring hospitalisation (days)	[redacted]	[redacted]	[redacted]
Duration of relapses not requiring hospitalisation (days)	[redacted]	[redacted]	[redacted]

Source: [177]

ITT: Intention-to-treat; SD: Standard deviation; SE: Standard error

B.3.3.2.2. Disability progression

In the natural history reference model, the transition of cohorts between each EDSS state is modelled using a Markov state transition matrix. The dimension of the transition matrix was 10x10 for the 11-health state structure. The 10x10 matrix contains transition probabilities for all possible EDSS-related transitions for a cohort who initially had RRMS and eventually comprised a mix of RRMS and SPMS. The 11th health state in the model corresponds to the death state, which was modelled separately to EDSS transitions.

Transition matrices for the natural history of RRMS were identified from previous NICE appraisals [167-169] and publications associated with the UK risk sharing scheme [154, 160].

A brief summary of the sources is provided in Table 31.

Table 31: Brief summary of data sources for modelling the natural history of RRMS

Source	Population	Notes
British Columbia	Population who meet the ABN criteria for disease modifying drugs • Naïve patients eligible for first-line therapy	Long-term study (~10 years); cohort characteristics matched to the UK risk sharing scheme population • Matrices allows for improvements in EDSS as observed in clinical studies and other natural history studies
London Ontario	• Data available in patients with active RRMS	Long-term study (up to 20 years); subject to intrinsic flaws due to post-hoc data censoring • Matrix does not allow for improvements in EDSS as observed in clinical studies and other natural history studies

Source: [154, 161, 178]

ABN: Association for British Neurologists; EDSS: Expanded disability status scale; RRMS: Relapsing-remitting multiple sclerosis; UK: United Kingdom

The transition matrices for the BCMS registry published in Palace et al. [154] were applied. Transition probability matrices were derived using continuous-time multi-state methods, and with and without baseline covariates.

Baseline covariates including sex, age at MS onset, and disease duration were considered in the statistical analysis. A model containing onset age as a binary covariate was deemed the most suitable model for the RSS analysis. The matrix based on a median age of onset of over 28 years was used in the base case given the mean baseline age (38.7 years) and disease duration (5.18 years) of the modelled population (Table 32).

Table 32: Annual transition probabilities (MS age of onset ≥28 years)

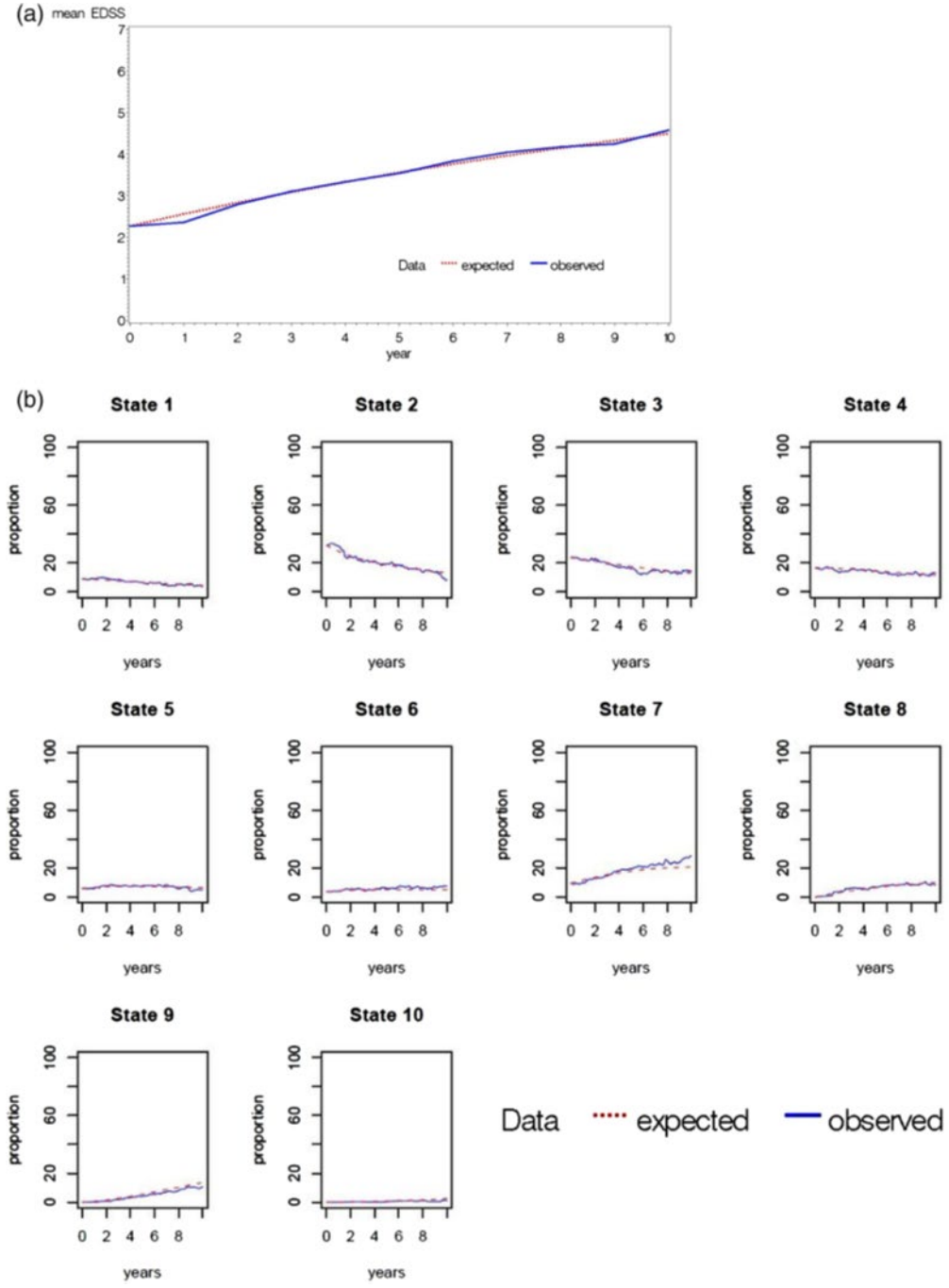
From \To	0	1–1.5	2–2.5	3–3.5	4–4.5	5–5.5	6–6.5	7–7.5	8–8.5	9–9.5	N
0	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000	326
1–1.5	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001	317
2–2.5	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004	317
3–3.5	0.00594	0.04960	0.12006	0.54422	0.09109	0.05845	0.11649	0.01030	0.00355	0.00030	317
4–4.5	0.00165	0.02214	0.06660	0.11519	0.48935	0.10388	0.16811	0.02580	0.00671	0.00056	317
5–5.5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.27310	0.03880	0.01883	0.00102	317
6–6.5	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74069	0.10897	0.04377	0.00423	317
7–7.5	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559	317
8–8.5	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01881	0.05574	0.90340	0.02066	317
9–9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832	317

Source: [154]

MS: Multiple sclerosis

Figure 20 shows a comparison of the predicted mean EDSS from the transition matrix versus the observed mean EDSS in the BCMS registry population reproduced from Palace et al. [154]. This figure shows the good fit of the matrices in predicting transitions to and from EDSS states, and in terms of mean EDSS.

Figure 20: Mean EDSS projected over ten years comparing the observed mean EDSS versus the expected mean EDSS using the continuous time model



EDSS: Expanded disability status scale

In the probabilistic analysis, the matrices were sampled using the Dirichlet distribution [179] based on the sample size for each EDSS transition. These data were not reported in Palace et al. [154], and therefore similar to the approach applied in TA493/TA616, had to be estimated by redistributing the total number of transitions reported in the study (6,357) across the 10 EDSS states in the two matrices (e.g. 50% of sample assigned to the matrix for below age of onset and 50% to above age of onset). The sample sizes were rounded down such that an integer number

were applied to each state. The sample was evenly distributed across EDSS states 1 to 9, with a higher sample size applied to EDSS 0 to maintain the correct total number of transitions in the analysis (0.5*6357).

This approach is likely to overestimate uncertainty at lower EDSS states and underestimate uncertainty at higher EDSS states given that more observations are likely at lower disability levels than higher levels. This was however considered a pragmatic approach given the lack of sampling information provided in Palace et al. [154].

A scenario analysis has been performed using the 21-health state model. Details on the approach are presented in Appendix M.

B.3.3.2.3. Mortality risk

The probability of death is modelled as a function of time to account for the increasing risk of death associated with the increasing age of the modelled cohort over time. This is estimated using all-cause mortality statistics (gender- and aged matched) from the general population that are inflated to account for the excess mortality associated with MS. Excess mortality is modelled using standardised mortality ratios comparing mortality in people with RRMS against the general population.

The risk of mortality is derived in three stages:

- A gender-averaged all-cause mortality rate is derived from Office for National Statistics for population all-cause mortality
- Mortality rate is inflated to account for the excess mortality risk for MS by multiplying age- and gender-specific rates by the standardized mortality ratios
- Inflated mortality rates are converted to annual probability and applied during each model cycle

The model includes the option of applying a single standardised mortality ratio to all people with MS irrespective of EDSS state (base case) or allowing the ratio to vary as function of EDSS state and form of MS.

For the base case the same standardised mortality ratio is applied to all people with MS on the basis that:

- The standardised mortality ratio can be estimated from a broad evidence base as it does not require data to be presented by EDSS state, and
- There is limited evidence to suggest an indirect effect of DMT on reduced mortality through delayed EDSS progression

The standardised mortality ratio for excess MS-related mortality was obtained from a systematic literature review of mortality studies in MS [180].

The mortality ratio for active RRMS in the base case analysis is modelled on data from Jick et al. [181] (1.68 [95% CI: 1.38-2.05]). This is the company preferred data source, which was accepted by NICE in TA493/TA616 [86], as this study reported mortality for the largest sample of people with MS (N=1,822), covered mortality across multiple regions of the UK, and had the second highest follow-up (14,295 person years) and total number of deaths (130) of the UK studies identified in the review. Sensitivity analyses are performed using data from Lalmohamed et al. (2012), which reported a mortality ratio of 3.51 [182].

In the probabilistic analysis, the standardised mortality ratio is sampled using a log-normal distribution [179].

Historically, a number of MS models have modelled mortality as a function of EDSS using data from a previous publication by Pokorski et al. reported in 1997 and re-analysed by Sadovnick et al. [183, 184]. The excess mortality risk associated with MS has been shown to decline over time implying that historical data may not adequately reflect the mortality risk in contemporary populations [185]. Although there is known uncertainty with estimates from Pokorski et al., this option of using EDSS-dependent mortality is provided as a sensitivity analysis; additional detail on the methodology is provided in Appendix M.

B.3.3.3. Treatment adjusted model

The following section contains a summary of the methods and data sources used to model the effect of DMT on relapse rates, EDSS progression, treatment waning, adverse events and treatment discontinuation.

B.3.3.3.1. Relapse rate

The link between DMT and reduction in the rate of relapse has been well established with data from CLARITY and other clinical studies showing a statistically significant effect of DMT on reducing the frequency of relapse versus placebo. These effects are modelled independently to DMT effects on disability progression.

The relapse rate for DMT ($\widehat{\mathrm{R}}_{\mathrm{DMT}}$) is calculated using the following formulae:

$$\widehat{\mathrm{R}}_{\mathrm{DMT}} = \widehat{\mathrm{R}}_{\mathrm{BSC}} \times \mathrm{RR}$$

Where RR is the rate ratio comparing DMT versus placebo and $\widehat{\mathrm{R}}_{\mathrm{BSC}}$ is the annualised relapse rate in the BSC population. The relapse rate ratios were obtained from the network meta-analyses outlined in the comparative efficacy section of the submission (Section B.2.9).

A summary of the relapse rate ratios used in the economic analysis is shown in Table 33.

Table 33: Relative risk ratio of annualised relapse rates comparing DMT versus placebo (random effects model)

Treatment vs. placebo	Mean risk ratio of annualised relapse rates	Upper 95% credible interval value	Lower 95% credible interval value
Cladribine tablets	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 µg	[redacted]	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]
Preferred model type in systematic review	Random effects; SD: [redacted]		
Goodness of fit statistics for preferred model	DIC: [redacted] (FEM) vs. [redacted] (REM) RD: [redacted] (FEM) vs. [redacted] (REM)		

Note: Glatiramer acetate 20 mg and teriflunomide 14 mg are included in the model, whilst glatiramer acetate 40 mg and teriflunomide 7 mg are not used in the model. 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 criteria; DMT: Disease-modifying treatment; FEM: Fixed-effect model; NMA: Network meta-analysis; RD: Residual deviance; REM: Random effects model; SD: Standard deviation

Based on goodness of fit (DIC and RD), the random effects model was preferred for the active RRMS population. See Section B.2.9 for details on the NMA.

In the probabilistic analysis, the annualised relapse ratio is sampled using a log-normal distribution [179].

B.3.3.3.2. Disability progression

The effect of DMT on disability progression is derived from the NMA using data on 6-month CDP, following Committee preferences for RRMS therapies [94]. See Section B.2.9 for details on the NMA.

A summary of the hazard ratios for 6-month CDP comparing DMT versus placebo is provided in Table 34.

Table 34: Hazard ratios of 6-month CDP comparing DMT versus placebo (random effects model)

Treatment vs. placebo	Median hazard ratio of 6-month CDP	Upper 95% credible interval value	Lower 95% credible interval value
Cladribine tablets	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 µg	[redacted]	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]
Preferred model type in systematic review	Random effects; SD: [redacted]		
Goodness of fit statistics for preferred model	DIC: [redacted] (FEM) vs. [redacted] (REM) RD: [redacted] (FEM) vs. [redacted] (REM)		

Note: Glatiramer acetate 20 mg and Teriflunomide 14 mg are included in the model, whilst glatiramer acetate 40 mg and teriflunomide 7 mg are not used in the model. Diroximel fumarate treatment effect was assumed the same as dimethyl fumarate in the absence of NMA results for this drug. Interferon beta-1a 22 µg treatment effect was assumed the same as interferon beta-1a 44 µg in the absence of NMA results for 6-month CDP for this drug.
CDP: Confirmed disease progression; DIC: Deviance information criteria; DMT: Disease-modifying treatment; FEM: Fixed-effect model; RD: Residual deviance; REM: Random effects model; SD: Standard deviation

With 6-month CDP, the preferred model for the active RRMS population was the random effects model based on goodness of fit (DIC and RD) and the level of heterogeneity between studies. The results of the NMA shows significant overlap in the credible intervals for the hazard ratios of 6-month CDP, with no therapy statistically dominating in terms of efficacy. Additionally, the INCOMIN trial was excluded from the base case NMA (see section B.2.9.4).

B.3.3.3.3. Waning of drug efficacy on disability progression and relapse rate

In line with previous economic evaluations [92, 94, 97, 132], the economic model for cladribine tablets allows for the waning of drug effect over time. Historically, waning effects were included to reflect uncertainty in the longer-term benefits of drug therapy, and to explore the impact of this uncertainty on the results of economic evaluations.

In the model, waning of drug effect is assumed to apply equally to disability progression and relapse rate. This is to maintain consistency when applying drug effects on these two aspects of disease over time. The waning effect is applied by adjusting the proportional reduction in drug effect via the following equation:

$$HR_w = (1 - (1 - HR_{NW}) \times W)$$

Where $\mathrm{HR_W}$ is the drug effect adjusted for waning, $\mathrm{HR_{NW}}$ is the drug effect without adjustment from the NMA described previously, and W is the proportional waning effect (e.g. 50%).

The assumptions about waning of treatment effects for cladribine tablets are informed by a post-hoc analysis of data collected throughout the CLARITY trial and into the CLARITY EXT trial, as presented in TA493/TA616 and published in Gorrod et al. (2019), which provides evidence supporting the sustained effect of cladribine tablets across 4 years (including the two years – Year 3 and Year 4 – when no active therapy was given) [76].

Across the 4 years of study treatment, there was no continuous placebo arm. Due to ethical reasons, patients who were randomised to the placebo arm in the CLARITY trial were allocated to a cumulative 3.5 mg/kg dose of cladribine tablets in the EXT trials; therefore, there were no patients who exclusively received placebo across both CLARITY and CLARITY-EXT. To address this, Merck conducted a treatment switching analysis in collaboration with ScHARR, which considered the efficacy of cladribine in CLARITY followed by placebo in EXT (LLPP) versus four years of placebo (PPPP), to provide an estimate of the potential comparative efficacy of cladribine tablets over a longer follow-up than CLARITY. The aim of the analysis was to demonstrate whether the treatment effect observed in CLARITY (LL versus PP) persists in the absence of additional treatment (LLPP versus PPPP), and hence understand whether the effect of cladribine tablets wanes over this extended period.

The analysis concluded that for 3- and 6-month CDP, as well as time to first qualifying relapse, the rank preserving structural failure time model (RPSFTM) and the iterative parameter estimation (IPE) algorithm-derived hazard ratios for the LLPP cohort vs. the hypothetical continuous placebo arm (PPPP) were nominally closer to 0 than the hazard ratio for the ITT comparison, indicating a greater effect than what was apparent via ITT analysis. In addition, LLPP versus PPPP hazard ratios were similar to the CLARITY ITT (LL versus PP) hazard ratio, indicating a sustained cladribine tablets treatment effect over the course of 4 years after only a 96-week treatment period. Details of the methodology are published by Gorrod et al. (2019) [76].

In summary, the CLARITY trial provides evidence on the comparative efficacy and safety of cladribine tablets when compared to placebo and is used to model the efficacy of cladribine tablets in the NMA, and for the first two years of the model time horizon. The CLARITY EXT trial provides evidence of the sustained effect of cladribine tablets in the years after active therapy and is therefore used to support the durability of its effect beyond initial treatment.

These analyses suggest that the effect of cladribine tablets was approximately constant throughout the duration of the CLARITY and the CLARITY EXT trials, and hence supports the

assumption of a durable drug effect during the 2 years of treatment (Year 1 and Year 2) and the 2 years of follow-up (Year 3 and Year 4).

In the base case analysis, 100% of treatment effect is assumed to apply to cladribine tablets in the first 4 years, and the NICE Committee preferred assumption of 25% waning in Year 4-5, and 50% waning from Year 5 onwards is applied. This aligned with the approach used in previous appraisal for cladribine tablets (TA493/TA616) [25] and other previous MS NICE appraisals [92, 94, 97, 132]. In the absence of treatment waning data for comparators, the assumptions applied to cladribine tablets have also been conservatively applied to comparators (i.e., non-differential waning assumptions). A sensitivity analysis, however, explores the differential waning assumptions previously included in TA493/TA616, and also explores no treatment waning for cladribine tablets and comparators.

A summary of the waning effects applied is provided in Table 35.

Table 35: Proportion of drug effect applied to cladribine tablets and comparators

Year	Proportion of treatment effect that is assumed to apply during each period of the model	Rationale
0-2	100%	Evidence of limited to no waning of drug efficacy over the first four years of treatment based on the treatment switching analysis of CLARITY and CLARITY EXT
2-4	100%	
4-5	75%	In line with NICE precedent and applying same assumptions across therapies
5+	50%	

NICE: National Institute for Health and Care Excellence

B.3.3.3.4. Safety and tolerability

The probability of experiencing drug-related AEs or tolerability issues was modelled based on clinical trial data identified in the systematic literature review, and from published literature sources (See Section B.2.10 and Appendix D). A summary of the absolute probabilities of AEs by DMT are presented in Table 36.

In summary, the following AEs are included: infusion and injection side reactions, macular oedema, hypersensitivity reactions, malignancy, gastrointestinal disorders, thyroid-related events, serious infections, and influenza-like illness. The list of AEs was developed following a review of the summary of product characteristics for each drug included in the model, and a review of previous economic models [157-162]. The list of included events was also confirmed by an external advisory panel comprising expert clinicians.

For most AEs, the rates from the RCTs were applied; for infusion and injection site reactions, the rates are applied whilst on treatment. For the other AEs, the rates are applied at the start of the treatment.

Where data was unavailable across all interferon beta-1a formulations, it was assumed that the probabilities are consistent across all formulations.

Malignancy events have been reported in clinical trials for cladribine tablets and comparators with the probability of malignancy for DMTs ranging from 0.2% to 1.1% across the studies identified in the systematic literature review. The risk of malignancy varied across both patients treated with a DMT and placebo (placebo risk ranged from 0.0% to 1.2%), with no clear trend towards either an increasing or decreasing malignancy risk with DMT therapy. The probability of an event is therefore estimated by pooling data from the clinical trials following the approach used in Pakpoor et al. [186]. This study reported a cancer risk of 0.34% in the pooled treatment group of CLARITY, and 0.60% in a pooled treatment group comprising outcome data for other DMTs. In the base case, it is conservatively assumed that the cancer risk is equal to 0.60% across all treatment groups.

Table 36: Absolute probabilities of AEs by DMT and event type

Treatment	Ongoing AEs that occur for each year of treatment		One-off AEs that occur at the start of the simulation						
	ISR	IJSR	ME	Malig-nancy	HR	GI	TRE	S.INF	ILS
Cladribine tablets	-	-	-	0.6%	-	31.6%	0.7%	2.3%	7.9%
Dimethyl fumarate	-	-	-	0.6%	-	26.1%	-	0.9%	-
Glatiramer acetate	-	24.5%	-	0.6%	11.7%*	7.2%	-	-	2.6%
Interferon beta-1a 22 µg	-	88.9%*	-	0.6%	1.2%	10.8%	4.2%	2.7%*	56.1%*
Interferon beta-1a 44 µg	-	37.9%	-	0.6%	1.2%	10.8%	4.9%	2.7%*	31.2%
Interferon beta-1a 30 µg	-	19.7%	-	0.6%	1.2%	20.8%	3.5%	1.5%	44.2%
Interferon beta-1b 250 µg	-	50.2%	-	0.6%	4.8%	10.6%	5.3%*	-	41.3%
Peginterferon	-	61.5%	-	0.6%	-	-	-	-	46.4%
Teriflunomide	-	-	-	0.6%	0.4%	20.9%	-	1.9%	1.2%
Ocrelizumab	34.3%*	-	-	0.6%	-	-	-	1.3%	4.3%
Ofatumumab	-	10.8%	-	0.6%	0.1%	23.7%	0.7%	2.5%	2.2%
Ponesimod	-	-	1.2%*	0.6%	-	0.7%	-	1.6%	-
Diroximel fumarate	-	-	-	0.6%	-	34.8%*	-	0.8%	-

* Indicates cells with the greatest value

AE: Adverse event; DMT: Disease-modifying treatment; GI: Gastrointestinal; HR: Hypersensitive reaction; ILS: Influenza like symptoms; ISR: Infusion site reaction; IJSR: Injection site reaction; ME: Macular oedema; TRE: Thyroid related event; S.INF: Serious infection

B.3.3.3.5. Discontinuation

The probability of treatment discontinuation (independent of EDSS progression; see Section B.3.2.3.2 for discontinuation rules) is modelled based on constant transition probabilities. The model includes the option of considering three periods of treatment discontinuation (Years 0-2, Years 2-10, and Years 10+) on the basis that withdrawal of therapy may vary over time with the influence of adverse events, compliance, and patient preference. In the base case, a constant discontinuation probability is applied across all three time periods for comparators. A sensitivity analysis was performed by halving the discontinuation rates after 2 years to test the sensitivity of results to variation in discontinuation probabilities over time for comparators. This is based on feedback from clinical experts stating that patients are more likely to stop treatment in the first two years of treatment than in the subsequent years.

Cladribine tablets is a fixed course treatment that has a posology that recommends two treatment courses administered over a 2-year period, with an interval of 12 months between first and second courses. For cladribine tablets, the summary of product characteristics states that “following completion of the two treatment courses, no further cladribine tablet treatment is required in Years 3 and 4. Re-initiation of therapy after Year 4 has not been studied”. For cladribine tablets, the usual concept of treatment “discontinuation” does not apply as patients are expected to receive two short courses of treatment and to then undergo observation for disease progression. The probability of discontinuation for cladribine tablets was therefore applied to the first cycle only to capture discontinuations between the first and second courses.

Patients who complete the two courses were assumed to remain “on DMT” without actively receiving drug, and hence were no longer considered at risk of discontinuation. For consistency with continuously administered drugs, it was also conservatively assumed that the effects of cladribine tablets would stop after a patient transitioned beyond EDSS state 7.0 (i.e., developed SPMS).

NMA of discontinuation

The model includes two options for estimating discontinuation probabilities, both of which have been adopted in previous models and appraisals in RRMS

- An NMA of all-cause discontinuation data in RRMS
- Pooled discontinuation data from across available trials

For the base case, the preferred option is the NMA of all-cause discontinuation data as it maintains randomisation and uses estimates of the comparative safety (e.g., odds ratios) anchored to a common placebo rate of discontinuation. This is important because the odds ratio of discontinuation is less likely to be biased by variability in protocol enforced discontinuations

across studies given that any such effects apply to both arms of each comparative assessment. This method is limited by the significant amount of heterogeneity present in the all-cause discontinuation network, with placebo rates varying between 3.57% and 36.09%. This has been noted in previous appraisals and submissions.

An alternative method is to pool arm-level estimates of discontinuation across studies. The main limitation of this method is that any variability in modelled discontinuation rates may be the result of protocol-led discontinuations as opposed to genuine tolerability issues. For example, the rate of discontinuation may appear higher for one drug versus another because one study applied more stringent or restrictive criteria for discontinuation than another study. This approach is included in the sensitivity analysis; detail on the methodology is provided in Appendix M.

The probabilities of discontinuation were derived from a NMA of all-cause discontinuation data reported in trials identified in the clinical systematic literature review (Section B.2.9.3 and Appendix D). There were 25 trials and 15 regimens (including placebo) included in the NMA for treatment discontinuations.

The analysis was performed using a binomial likelihood and cloglog link model of the following form:

$$cloglog(p_{i,k}) = \log(T_i) + \mu_i + \delta_{i,k}$$

Where T_i is follow-up time in weeks, μ_i is baseline risk in study i, and $\delta_{i,k}$ is the log-hazards ratio of drug k in study i. Absolute discontinuation probabilities were generated for each treatment directly from the NMA. This was estimated through combining the drug effects on discontinuation with the crude pooled baseline/placebo discontinuation rate from the clinical studies included in the network (20.97% at 2 years based on 643 events in 3,066 patients). The 2-year probability for placebo was converted to annualized probabilities in the analysis.

Both fixed and random effects models were considered, with preferred model chosen based on residual deviance and DIC, which was the random effects model.

A summary of the posterior samples from the random effects model is provided in Table 37.

Table 37: Summary of posterior mean, standard deviation, median and 95% credible interval of the absolute probabilities of discontinuation based on the random effects model

Treatment vs. placebo	Mean[a]	SD	Median	Lower 95% CrI	Upper 95% CrI
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine tablets[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment vs. placebo	Mean[a]	SD	Median	Lower 95% CrI	Upper 95% CrI
Interferon beta-1a 44 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 µg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preferred model type in systematic review	Random effects; SD: [redacted]				
Goodness of fit statistics for preferred model	DIC: [redacted] (FEM) vs. [redacted] (REM) RD: [redacted] (FEM) vs. [redacted] (REM)				

[a]Mean discontinuation probability estimates are applied in the model base-case

[b]Not considered in the economic model

Note: Glatiramer acetate 20 mg and Teriflunomide 14mg are included in the model, whilst glatiramer acetate 40 mg and teriflunomide 7 mg are not used in the model. Peginterferon treatment effect was assumed the same as interferon beta-1a 30 µg in the absence of NMA results for treatment discontinuation for this drug.

CrI: Credible interval; DIC: Deviance information criteria; FEM: Fixed-effect model; RD: Residual deviance; REM: Random effects model; SD: Standard deviation

The random effect model yielded a better fit to the data when assessed based on the DIC statistic. The absolute probabilities generated from the random effects model were incorporated in the economic model, given that this better captures heterogeneity across the studies.

The absolute probability of discontinuation for cladribine tablets used in the model (4.85%) was modelled based on the pooled probabilities from CLARITY study. This is to avoid overestimating discontinuation for this therapy as in the model tolerability events are only assumed to occur between the first and second courses of treatment, and hence applying discontinuation probabilities generated from a mean placebo probability over 2-3 years (e.g. placebo in clinical studies) would overstate discontinuation.

B.3.4 Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

EQ-5D-3L questionnaires were collected at regular intervals throughout CLARITY and CLARITY EXT, including at study day 1, weeks 24, 48, 72, at the week 96/early termination visit, and at each relapse evaluation. As required in the NICE methods guide, completed EQ-5D questionnaires were mapped to HSU index values using the UK social tariff.

[redacted] HSU values were generated from the EQ-5D data collected in the cladribine

tablets studies; CLARITY ([redacted]) and CLARITY EXT ([redacted]). Summary statistics from across both studies indicate no evidence of a meaningful difference in HSU across patient subgroups, and no difference in HSU by treatment group when stratified by EDSS. To reduce uncertainty in the analysis, the HSUs by EDSS were pooled across treatment and patient subgroups to provide inputs to the cost-effectiveness analysis.

Only baseline HSU were applied in the model as HSU captured during the study may be impacted by the effects of adverse events, which are accounted for separately in the analysis.

A summary of HSU by EDSS state at baseline is provided in Table 38.

Table 38: Summary statistics of HSU in CLARITY (baseline)

Health state	Mean	Standard error	Number of HSU
EDSS 0	0.906	0.026	20
EDSS 1.0	0.845	0.046	24
EDSS 2.0	0.804	0.012	221
EDSS 3.0	0.701	0.012	171
EDSS 4.0	0.655	0.013	167
EDSS 5.0	0.565	0.026	62
EDSS >5.0	0.573	0.225	32

Source: [146]

EDSS: Expanded disability status scale; HSU: Health state utility

B.3.4.2. Mapping

No mapping analyses were performed as EQ-5D level HSU were available from the CLARITY and the CLARITY-EXT trials.

B.3.4.3. Health-related quality-of-life studies

Published health related quality of life studies in RRMS were identified via a systematic literature review (search date February 6th, 2024) of biomedical literature databases. The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix H.

In summary, 143 unique published studies (from 160 publications) and six HTA submission documents were included. Of the 143 published studies, 61 reported HSU data considered applicable to the health state structure of the cost-effectiveness model for cladribine tablets, including HSU by EDSS (52 studies), HSU for relapse (28 studies) and HSU comparing RRMS (6 studies) versus SPMS (7 studies). The remaining studies reported HSU that were unrelated to EDSS or relapses, including studies of the direct effects of treatment or intervention on HSU, and studies reporting HSU for walking speed, walking distance and numerical rating scores for spasticity.

B.3.4.3.1. Health state utility by EDSS state for persons with MS

EDSS-related HSUs were reported in 52 studies and six HTA documents included in the review. Thirty-two of the 55 studies and all six of the HTA documents reported EQ-5D HSU derived using UK social preferences in line with the NICE reference case. From these studies, 41 unique sets of EQ-5D HSU data were reported, of which, 25 covered the range of EDSS levels in the economic model (e.g., EDSS 0-1 to EDSS 8.5-9.5). A summary of the literature sources is provided in Appendix H.

The company preferred data source for the base case was selected based on the quality of the included studies, by considering how patients were recruited, the rate of recruitment and response, and how HSU and disease severity were assessed across the literature. Preference was given to studies reporting large sample sizes, high response rates and used clinician assessed EDSS.

Based on this assessment, Hawton et al. (2016) [155] was selected as the preferred literature source for EDSS-related HSU given that it includes a large patient sample (1,406 participants and 6,066 completed EQ-5D questionnaires) that is representative of the UK MS population, a high recruitment rate (75% contacted had participated) and response rate (90% of those recruited had responded at 3.5 year follow-up), and used clinician-assessed EDSS.

Other literature sources that were considered relevant to this analysis include Orme et al. [56] (large sample, low response rate, self-assessed EDSS that was used in previous NICE appraisals), and Heather et al. [156] (large sample [UK MS Register, n=14,385 patients who provided responses to at least one preference-based measure, such as EQ-5D-3L, MSIS-8D, or MSIS-8D-P] and self-assessed EDSS).

A summary of the HSU data from the CLARITY trial and the preferred literature sources is provided in Table 39.

Table 39: Summary of mean EQ-5D HSU from UK social preferences in CLARITY, and key HSU publications

Health state	CLARITY [146]	Hawton et al. (2016) [155]	Orme et al. (2007) [56]	Heather et al (2023) [156]
Age	38.3	50.7	51.4	55.3
EDSS 0	0.906 (0.026)	0.846 (0.026)	0.870 (0.045)	0.906 (0.012)
EDSS 1.0	0.845 (0.046)	0.762 (0.025)	0.799 (0.093)	0.904 (0.017)
EDSS 2.0	0.804 (0.012)	0.711 (0.019)	0.705 (0.093)	0.849 (0.007)
EDSS 3.0	0.701 (0.012)	0.608 (0.029)	0.574 (0.097)	0.820 (0.006)
EDSS 4.0	0.655 (0.013)	0.609 (0.028)	0.61 (0.093)	0.688 (0.008)
EDSS 5.0	0.565 (0.026)	0.531 (0.031)	0.518 (0.092)	0.575 (0.013)
EDSS 6.0	Not available	0.496 (0.012)	0.460 (0.093)	0.503 (0.007)
EDSS 7.0	Not available	0.392 (0.032)	0.297 (0.094)	0.350 (0.012)
EDSS 8.0	Not available	0.025 (0.038)	-0.049 (0.109)	0.160 (0.022)
EDSS 9.0	Not available	Not available	-0.195 (0.119)	Not available

EDSS: Expanded disability status scale; HSU: Health state utility; UK: United Kingdom

The mean HSU by EDSS in CLARITY [146] and Heather et al. [156] were generally higher than values reported in Hawton et al. [155] and Orme et al. [56]. This may be due to the different age profile of patients in the studies, with patients in CLARITY being on average 12 years younger than individuals in Hawton et al. [155] and Orme et al. [56] (Table 39). Increasing age is a predictor of lower HSU in the general population and has been shown to be a predictor of HSU in MS patients independent of EDSS.

Additionally, the higher utility values in Heather et al. may be related to the difference in obtaining EDSS scores; Heather et al. reports patient-rated web EDSS scores whilst Hawton et al. and Orme et al. report clinician-rated EDSS scores. Although there is limited information on the comparability of the patient- and clinician-rated EDSS, multiple studies have found that the web-based patient-rated EDSS give higher scores than the clinician-rated EDSS, with greater agreement between the two observed for EDSS scores more than 5 [56, 155, 156].

In line with TA254, TA303, TA312, TA320, TA441, TA533, TA624 and TA699 that used HSU data from trial data and supplemented by literature, the HSU data from CLARITY were used for EDSS 0-5.0 and were supplemented by HSU data from Hawton et al. for EDSS 6.0-8.0, and Orme et al. for EDSS 9.0. All other relevant HSU sources were considered in the sensitivity analyses.

This approach is aligned with TA493/TA616. Additionally, in TA493/TA616, the ERG considered that the primary driver of utility would be the EDSS state and was satisfied that the values implemented in the company model were reasonable.

Table 40: Summary of literature sources for HSU related to EDSS chosen for economic analyses

Author: Study name	Country	Study design	N	Baseline age	Baseline disease severity	Baseline relapse history	Form of MS	Method	Respondent selection and recruitment, data collection method and response rate
Hawton 2016 [155]: Health utilities for multiple sclerosis	UK	Regional patient/research organisation longitudinal, prospective study	1,441 EQ-5D: 1,406 SF-36: 1,357	Mean (SD): 50.7 (11.7)	Mean EDSS (SD/range): 4.3 (2.3 /0-9) [n=289]	Relapse during last 12 months: Yes: 53.6% No: 33.3% Don't know: 13.2% No. of relapses in last 12 months mean (SD): 1.1 (1.2)	RRMS: 42% PPMS: 19.4% SPMS: 17.0% Benign: 3.3% Unknown: 18.4%	EQ-5D (UK tariff), SF-6D	Adult patients (>18-years old) with a clinically definite diagnosis of MS (McDonald or Poser criteria), or CIS, and resident in Devon or Cornwall, England, were identified from attendances to neurology outpatient clinics, hospital case notes, a survey of general practitioners, and self-referrals from public awareness campaigns. Data were collected on patient health status, including self-assessment of quality of life (EQ-5D). EDSS were assessed by clinicians, and identified from data collected at routine visits, where available. Study response rate: 75%
Orme 2007 [56]: The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK	UK	National patient/research organisation observational, cross-sectional study	2,048	Mean: 51.4	EDSS 0-3: 21.3% EDSS 4-6.5: 59.6% EDSS 7-9.5: 19.1%	Relapse during last 3 months: Yes 28.9% No 71.1%	RRMS: 35.3% SPMS: 37.2% PPMS: 27.3%	EQ-5D (UK tariff)	Questionnaires were mailed to 12,968 patients with MS registered with the UK MS trust. Data were collected on patient health status, including self-assessment of quality of life (EQ-5D), and patients determined disease steps, used as proxy for EDSS. Study response rate: 15.8%
Heather 2023 [156]: Multiple sclerosis health-related quality of life utility values from the UK MS register	UK	Prospective cohort study	14,385	Mean (SD): 55.3 (11.4)	Mean EDSS (SD): 5.1 (2.0)	NR	RRMS: 77.3% (7,211) SPMS: 8.0% (742) PPMS: 14.7% (1,372)	EQ-5D-5L	The study conducts biannual surveys of people with neurologist-confirmed MS aged 18 or over, resident in the UK via a web portal. Data were collected on patient health status, including self-assessment of quality of life (EQ-5D), and patients determined disease steps, used as proxy for EDSS. Study response rate: NR

CIS: Clinically isolated syndrome; EDSS: Expanded disability status scale; EQ-5D: EuroQoL 5 Dimension; MS: Multiple sclerosis; NR: Not reported; PPMS: Primary progressive multiple sclerosis; RRMS: Relapsing-remitting multiple sclerosis; SD: Standard deviation; SF-36: Short Form 36-item; SF-6D: Short Form 6 Dimension; SPMS: Secondary progressive multiple sclerosis; UK: United Kingdom

B.3.4.3.2. Health state utility by EDSS state for caregiver of person with MS

The review identified one study that reported the impact of MS on the HSU of caregivers of people with MS. Acaster et al. was a UK cross-sectional observational online survey study of the EQ-5D HSU of 200 caregivers and 200 matched controls (e.g. non-caregiver) [187]. The study reported an assessment of differences in HSU between caregiver and non-caregivers, including stratified by severity of MS.

Acaster et al. reported lower HSUs in caregivers when compared to matched controls (0.74 [Standard deviation (SD) = 0.28] versus 0.8 [SD = 0.25], p =0.003), with lower caregiver HSU being associated with lower levels of functioning in the person with MS (Table 41).

Table 41: Difference in mean HSU between caregivers and controls stratified by Patient Determined Disease Steps (PDDS) state

State	Mean	SE	95% CI
PDDS 0-1	-0.002	0.053	(-0.106607, 0.102512)
PDDS 2-3	-0.045	0.057	(-0.157389, 0.0675467)
PDDS 4	-0.142	0.062	(-0.26265, -0.0201414)
PDDS 5	-0.160	0.055	(-0.267741, -0.0515924)
PDDS 6	-0.173	0.054	(-0.278105, -0.0672276)
PDDS 7	-0.030	0.038	(-0.103954, 0.0454175)
PDDS 8	-0.095	0.075	(-0.240843, 0.0526273)

Source: [187]; 95% confidence interval estimated by digitisation of study graphs

CI: Confidence interval; HSU: Health state utility; PDDS: Patient Determined Disease Steps; SE: Standard error

Between PDDS 0 and 6, an increasing disability was associated with an increasing loss in HSU for the caregiver, when compared to the matched control. At PDDS 7 and 8 (wheelchair use and bedridden), the loss in HSU decreases when compared to PDDS 6 with values comparable to those estimated for PDDS 0-3. The authors state that the reason for this is unclear; although one explanation could be that at higher disability levels, caregivers receive greater governmental support, such as respite care, which can alleviate some of the burden placed on the caregiver.

Data from Acaster et al. [187] were used to model the impact of disability progression on caregiver HSU by mapping PDDS 0-1 to EDSS 0-2, PDDS 2-3 to EDSS 3, PDDS 4 to EDSS 4, PDDS 5 to EDSS 5, PDDS 6 to EDSS 6, PDDS 7 to EDSS 7 and PDDS 8 to EDSS 8-9.

This approach is aligned with the approach used in TA493/TA616 [25] and previous appraisals [92-94, 97, 132]. Additionally, in TA493/TA616, although the ERG considered that health outcomes for caregivers should not be included in the cost-effectiveness analysis, the NICE committee commented that it was important to recognise the impact that caring for people with MS has on caregivers and concluded that caregiver QoL decrements should be included in the cost-effectiveness analysis [86].

B.3.4.3.3. Health state utility by relapse state

The review identified 28 studies that reported the effect of relapses on HSU, of which 20 were derived using UK social preferences. The loss in HSU associated with each relapse event ranged from 0.014 to 0.8.

The preferred literature sources for modelling the impact of relapses on HSU were Orme et al. [56] and Ruutiainen et al. [166], as they reported HSU effects from regression analyses that adjusted for EDSS staging. Orme et al. was used in the base case, whilst Ruutiainen et al. was explored in the sensitivity analysis.

The same disutility values were applied to hospitalised and non-hospitalised events on the basis that neither preferred source reported data by hospital status. This has been applied to the previous cladribine submission (TA493/TA616) [25] as well as other previous MS NICE appraisals [92-94, 97].

Table 42: Summary of the HSU impact of relapse events in the model

Health state	Duration (days)	Orme et al. (2007) [56]	Ruutiainen et al. (2016) [166]
Relapse requiring hospitalisation	[redacted]	-0.071 (0.013)	-0.066 (0.013)
Relapse not requiring hospitalisation	[redacted]		

Source: [177]
HSU: Health state utility

B.3.4.4. Adverse reactions

The systematic review of HSU failed to identify studies reporting the HSU for treatment-related AEs in people with MS.

Additional ad-hoc searches were therefore performed to identify relevant data from previous RRMS appraisals and from other chronic conditions. These data were supplemented with estimates of the duration of AEs to provide estimates of the QALY loss from each event. A summary of the duration and disutility impact of treatment-related adverse events is reported in Table 43.

The QALY loss from treatment-related AEs ranged from -0.0002 (infusion site reaction) to -0.116 (malignancy). Events that had a large impact on total QALY were malignancy (-0.116) and thyroid related events (-0.110). Severe infections, influenza-like symptoms and gastrointestinal disease had a significant impact on the person's HSU but persisted for a shorter period of time (e.g., 14 days) than malignancy and thyroid events, and hence had a reduced impact on total QALYs.

Table 43: Duration and quality of life impact of adverse events

AE	Duration of event (days)	Source for duration	Dis-utility	Source for disutility	QALY impact
Infusion site reaction – Ocrelizumab	5	Alemtuzumab NICE submission [168]	-0.011	Same as injection site reaction [188]	-0.0002
Injection site reaction (daily)	365.25	Assumption: Every day lasting the full day	-0.011	Utilities and disutilities for attributes of injectable treatments for type 2 diabetes, Boye et al. [188]	-0.0110
Injection site reaction (every other day)	182.625	Assumption: Every other day lasting the full day	-0.011		-0.0055
Injection site reaction (every week)	52	Assumption: Every week lasting the full day	-0.011		-0.0016
Injection site reaction (every two-weeks)	28	Assumption: Every two-weeks lasting the full day	-0.011		-0.0008
Injection site reaction (monthly)	13	Assumption: Every month lasting the full day	-0.011		-0.0004
Severe infection	14	Assumption: Severe infection lasts for 2 weeks	-0.190	Utilities for treatment-related adverse events in type 2 diabetes, Shingler et al. [189]	-0.0073
Macular oedema	84	Alemtuzumab NICE submission	-0.040	Alemtuzumab NICE submission [168]	-0.0092
Gastrointestinal	8	Phillips et al. [190]	-0.240	Utilities for treatment-related adverse events in type 2 diabetes, Shingler et al. [189]	-0.0053
Hypersensitivity	7	Alemtuzumab NICE submission	-1.000	Alemtuzumab NICE submission [168]	-0.0192
Autoimmune thyroid-related event	365.25	Alemtuzumab NICE submission	-0.110	Alemtuzumab NICE submission [168]	-0.1100
Influenza-like symptoms	7	Assumption: Influenza like symptoms persist for one week	-0.210	Health state utilities associated with attributes of treatments for hepatitis C [191]	-0.0040
Malignancy	365.25	Assumption	-0.116	Breast Cancer in Young Women: Health State Utility Impacts by Race/Ethnicity, Trogdon et al. [192]	-0.1160

Source: See table

AE: Adverse event; NICE: National Institute for Health and Care Excellence; QALY: Quality-adjusted life year

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the health state utilities used in the base case model is shown in Table 44.

Table 44: Summary of health state utilities in base case and sensitivity analysis for EDSS and relapse events

Health state	Base case	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Relapse events	Orme et al. [56]	Ruutiainen et al. [166]	-	-
Relapse (hospital)	-0.071 (0.013)	-0.066 (0.013)	-	-
Relapse (non-hospital)			-	-
EDSS	CLARITY [146] and Hawton et al. (2016)[155] and Orme et al.(2007)[56]	Hawton et al.(2016)[155] and Orme et al. (2007)[56]	Orme et al. (2007)[56]	Heather et al. (2023)[156] and Orme et al. (2007)[56]
EDSS 0	0.906 (0.026)	0.846 (0.026)	0.870 (0.045)	0.906 (0.012)
EDSS 1.0	0.845 (0.046)	0.762 (0.025)	0.799 (0.093)	0.904 (0.017)
EDSS 2.0	0.804 (0.012)	0.711 (0.019)	0.705 (0.093)	0.849 (0.007)
EDSS 3.0	0.701 (0.012)	0.608 (0.029)	0.574 (0.097)	0.820 (0.006)
EDSS 4.0	0.655 (0.013)	0.609 (0.028)	0.610 (0.093)	0.688 (0.008)
EDSS 5.0	0.565 (0.026)	0.531 (0.031)	0.518 (0.092)	0.575 (0.013)
EDSS 6.0	0.496 (0.012)		0.46 (0.093)	0.503 (0.007)
EDSS 7.0	0.392 (0.032)		0.297 (0.094)	0.350 (0.012)
EDSS 8.0	0.025 (0.038)		-0.049 (0.109)	0.160 (0.022)
EDSS 9.0	-0.195 (0.119)			
AE	**QALY loss associated with each AE (source)**			
Infusion site reaction - alemtuzumab	-0.011 [188]			
Infusion site reaction – natalizumab	-0.011 [188]			
Injection site reaction (monthly)	-0.011 [188]			
Severe infection	-0.190 [189]			
Macular oedema	-0.040 [168]			
Gastrointestinal	-0.240 [189]			
Hypersensitivity	-1.000 [168]			
Autoimmune thyroid-related event	-0.110 [168]			
Influenza-like symptoms	-0.210 [191]			
Malignancy	-0.116 [192]			

Source: See table

EDSS: Expanded disability status scale; QALY: Quality-adjusted life year

B.3.4.6. Age-adjustment for utilities

Per the NICE reference case, utilities adjusted by age are applied in the base case analysis. The multiplicative method was selected as this is considered the most appropriate and preferred by NICE [193]. The general population utilities used are based on the most recent Health Survey for England (HSE) 2014 survey for adults aged 16 and over [194].

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The health care costs considered in the model include the costs of drug acquisition, administration, monitoring, the costs of managing the disease, and drug-related adverse events.

Relevant cost and health resource use data were identified from various sources including previous NICE appraisals, a systematic review of published costing studies, the British National Formulary, NHS reference costs, PSS research unit reports, and the summary of product characteristics for in-scope comparators. Further detail on the methods used to estimate costs is provided in the following sections.

B.3.5.1. Intervention and comparators' costs and resource use

The total cost of intervention and comparator treatment comprises three components:

- Drug acquisition
- Drug administration
- Drug monitoring

The costs of acquisition, administration and monitoring are assumed to apply for the duration that people remain on therapy. For continuously administered therapies, the number of people on therapy is estimated from the EDSS status of the population taking into account those that discontinue (e.g., patients reach EDSS ≥7.0 or discontinue for other reasons) in the previous cycle. All patients are assumed to adhere to therapy and take their full course in a given year.

For fixed course therapies, e.g., cladribine tablets, drug costs were estimated based on the proportion of patients eligible for therapy (EDSS <7.0) at the start of each cycle multiplied by the proportion treated. The model can accommodate re-initiation of treatment up to Year 10 of the simulated time horizon. Additionally, the total number of cladribine tablets administered to each individual patient is dependent on the patient's weight.

In the base case, the proportion of patients treated with cladribine tablets is set to 100% in Years 1 and 2. This was applied to all patients eligible for treatment after excluding those who progress beyond EDSS 7.0 or are intolerant to therapy. In the CLARITY trial, an estimated

91.2% of all randomised patients completed two courses of therapy. Reasons for not completing the course included disease progression and intolerance, which are accounted for separately in the model calculation.

For cladribine tablets, re-initiation of treatment after completion of their first 2 courses could be an option for a proportion of patients. However, Merck did not assume re-initiation after the first two courses in the economic model, as per previous NICE preference for the base case settings in TA493/TA616 [25] .

Table 45 provides a summary of the intervention and comparators costs applied in the economic analysis.

Table 45: Summary of cost inputs to the economic analysis for cladribine tablets in active RRMS

Treatment	Total annual drug costs (£)			Annual administration costs (£)		Annual monitoring costs (£)	
	Year 1	Year 2	Year 3+	Year 1	Year 2+	Year 1	Year 2+
Cladribine tablets	25,953	25,953	0	0	0	829	332
Dimethyl fumarate	17,910	17,910	17,910	0	0	1,014	262
Glatiramer acetate	6,704	6,704	6,704	216	0	483	483
Interferon beta-1a 22 µg	7,976	7,976	7,976	216	0	514	489
Interferon beta-1a 44 µg	10,572	10,572	10,572	216	0	514	489
Interferon beta-1a 30 µg	8,502	8,502	8,502	216	0	514	489
Interferon beta-1b 250 µg	7,264	7,264	7,264	216	0	514	489
Peginterferon	8,502	8,502	8,502	216	0	514	489
Teriflunomide	13,538	13,538	13,538	0	0	496	483
Ocrelizumab	19,160	19,160	19,160	2,036	1,373	269	246
Ofatumumab	20,895	17,910	17,910	216	0	266	240
Ponesimod	14,010	14,010	14,010	663	0	427	246
Diroximel fumarate	17,739	17,910	17,910	0	0	1,014	262

RRMS: Relapsing-remitting multiple sclerosis

B.3.5.1.1. Drug acquisition

The annual cost of drug acquisition is calculated from the list price of medication and the mean total dose of therapy administered in each year of the simulation. The list price of each medication was obtained from the British National Formulary. The total dose of therapy was modelled based on the posology stated in the summary of product characteristic for each individual drug in scope. For cladribine tablets, the cost of therapy is based on Year 1 and Year 2 of treatment only, with no acquisition and administration costs for Years 3 to 5.

For cladribine tablets, the cost of therapy is also dependent on the weight of the cohort, with dosing based on a target dose in milligrams per kilogram per dose. The dose of cladribine tablets is modelled based on the weight distribution of the cohort multiplied by the number of tablets needed to treat people within each weight class.

A summary of the weight distribution is provided in Appendix I, and the recommended number of tablets per category is outlined in the summary of product characteristics.

Given uncertainty over the discount rates applied to various DMTs, the list prices for each treatment were used in the base case analysis. In a scenario analysis, generic prices for dimethyl fumarate and teriflunomide were applied.

A summary of the total cost of drug acquisition by therapy is shown in Table 46.

Table 46: Total drug acquisition cost by therapy in the model (list price)

Therapy	Pack	Unit per pack	Unit cost	Dose	Units consumed per year			Total costs per year		
					Year 1	Year 2	Year 3+	Year 1	Year 2	Year 3+
Dimethyl fumarate	56 cap	56	£1,373.00*	120 mg BID for 7 days, then 240 mg BID	730.50	730.50	730.50	£17,910	£17,910	£17,910
Glatiramer acetate	1 syringe	1	£18.36	20 mg QD	365.25	365.25	365.25	£6,704	£6,704	£6,704
Interferon beta-1a 22 µg	1 syringe	1	£51.13	22 µg TIW	156.00	156.00	156.00	£7,976	£7,976	£7,976
Interferon beta-1a 44 µg	1 syringe	1	£67.77	44 µg TIW	156.00	156.00	156.00	£10,572	£10,572	£10,572
Interferon beta-1a 30 µg	30 mg	1	£163.50	30 µg QW	52.00	52.00	52.00	£8,502	£8,502	£8,502
Interferon beta-1b 250 µg	300 mg	1	£39.78	250 µg QOD	183.25	183.25	183.25	£7,264	£7,264	£7,264
Peginterferon	1 pen	1	£327.00	125 µg QOW	26.00	26.00	26.00	£8,502	£8,502	£8,502
Teriflunomide	28 tab	28	£1,037.84*	14mg QD	365.25	365.25	365.25	£13,538	£13,538	£13,538
Ocrelizumab	1x300mg	1	£4,790.00	Initially 300 mg, then 300 mg after 2 weeks; maintenance 600 mg Q24W	4	4	4	£19,160	£19,160	£19,160
Ofatumumab	1 pen	1	£1,492.50	20 mg at weeks 0, 1 and 2, followed by monthly dosing starting at week 4	14	12	12	£20,895	£17,910	£17,910
Ponesimod	28 cap	1	£1,073.97	20 mg QD (after dose titration)	356.25	356.25	356.25	£14,010	£14,010	£14,010
Diroximel fumarate	120 cap	1	£1,471.07	231 mg BID for 7 days/ 462 mg BID thereafter	1,447	1,461	1,461	£17,739	£17,910	£17,910

Note: For cladribine tablets, the number of tablets are reported in the MHRA SPC [87] and the weight distribution is provided in Appendix I.

*Base case uses the list prices from reference drugs only (e.g., Tecfidera and Aubagio). Generic prices were tested in a scenario analysis for teriflunomide at £882.16 unit cost (28 tablets), glatiramer acetate at £16.52 unit cost (pre-filled disposable injection), and dimethyl fumarate at £1,098.40 unit cost (56 capsules)

BID: Twice daily; QD: Once every day; QOD: Every other day; QOW: Every other week; QW: Once a week; Q24W: Every 24 weeks; TIW: three times a week.

B.3.5.1.2. Drug administration

The annual cost of drug administration was calculated from the unit cost of each administration resource multiplied by the number of resources consumed in a year of treatment.

Administration costs comprise admissions for infusions, additional medications provided alongside therapy, and any additional district nurse or neurologist visits required to support drug administration. The unit costs of drug administration are summarised in Table 47.

The number of resources consumed in the administration of DMT is presented in Table 48.

Table 47: Unit costs of drug administration resources

Administration unit	Unit cost	Source
Admissions for infusion	£662.92	AA30F: Medical Care of Patients with Multiple Sclerosis, with CC Score 0-1 [195]. Inflated to 2023 using Medical services CPI from ONS GOV [196]
Methylprednisolone 1g vial	£12.60	Electronic medicines information tool (eMit) [197]
Chlorphenamine 10mg (5 pack)	£7.84	Electronic medicines information tool (eMit) [197]
Paracetamol (16-tab pack)	£1.25	Electronic medicines information tool (eMit) [197]
Aciclovir 200mg (25 day pack)	£0.78	Electronic medicines information tool (eMit) [197]
Nurse visit	£72.00	£68 per hour of patient-related work (PSSRU 2022) including qualification [198] Inflated to 2023 using Medical services CPI from ONS GOV [196]
Neurology visit	£239.72	WF02A: Consultant-led Non-admitted face to face attendance, Follow-up Neurology [195] Inflated to 2023 using Medical services CPI from ONS GOV [196]

CPI: Consumer Price Index; ONS: Office for National Statistics

Table 48: Total costs of administration of DMT in people with multiple sclerosis

Therapy	Administration	Administration resources consumed per year of therapy	Total cost Year 1*	Total cost Year 2+*
Cladribine tablets	Oral	No administration requirements	£0	£0
Dimethyl fumarate	Oral	No administration requirements	£0	£0
Glatiramer acetate	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0
Interferon beta-1a 22 µg	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0
Interferon beta-1a 44 µg	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0
Interferon beta-1a 30 µg	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0

Therapy	Administration	Administration resources consumed per year of therapy	Total cost Year 1*	Total cost Year 2+*
Interferon beta-1b 250 µg	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0
Peginterferon	Injectable	Training for self-administration of device involving 3 hours of Nurse time	£216	£0
Teriflunomide	Oral	No administration requirements	£0	£0
Ocrelizumab	Infusion	Three admissions in first year (day 1, 15 and six months), and 2 admissions for each subsequent cycle (day 0 and six months of cycle)	£2,036	£1,373
Ofatumumab	Injectable	Training for self-administration of device involving 3 hours of nurse time	£216	£0
Ponesimod	Oral	Admission for ECG prior to treatment initiation	£663	£0
Diroximel fumarate	Oral	No administration requirements	£0	£0

*The total costs in Year 1 and Year 2+ are calculated by multiplying the cost of drug administration (Table 47) by the number of hours required

DMT: Disease-modifying treatment; ECG: Electrocardiogram; I/M: Intramuscular; S/C: Subcutaneous

B.3.5.1.3. Drug monitoring

The annual cost of drug monitoring is calculated from the unit cost of monitoring resources multiplied by the number of resources consumed in a year of treatment.

Monitoring costs comprise biochemistry tests, complete blood counts, human papilloma virus (HPV) tests, MRI scans, thyroid function tests, tuberculin skin tests, urinalysis, hepatitis B and C virus testing, John Cunningham's (JC) virus testing, and visits to health care practitioners to support the monitoring of DMT. The unit costs of monitoring resources are summarised in Table 49.

Table 49: Unit cost of drug monitoring resources

Monitoring resource	Unit cost*	Source
Biochemistry test	£1.64	Clinical biochemistry (DAPS04) [195]
Complete blood count	£3.13	Haematology (DAPS05) [195]
HPV test	£8.05	Immunology (DAPS06) [195]
MRI scan	£257.46	Magnetic Resonance Imaging Scan of two or three areas, with contrast (RD05Z) [195]
Neurology visit	£239.72	Consultant-led Non-admitted face to face attendance, Follow-up Neurology (WF01A) [195]
Ophthalmology visit	£176.44	Consultant led non-Admitted Face to Face Attendance, First (WF01B) [195]
Thyroid function test	£1.27	Northern Devon Healthcare NHS trust pathology department 2015-2016 unit costs– thyroid function test [199]

Monitoring resource	Unit cost*	Source
Tuberculin skin test	£33.70	NICE clinical guideline (Warwick evidence diagnosis of LTBI report) [200]
Urinalysis with urine cell counts	£5.09	Northern Devon Healthcare NHS trust pathology department 2015-2016 unit costs – Renal profile/Urea and electrolytes [199]
Anti-JCV test	£9.03	Microbiology (DAPS07) [195]
Hepatitis C test	£25.47	Shepherd et al. [201]
Hepatitis B test	£23.29	Shepherd et al. [201]

* Cost inflated to 2023 using Medical services CPI from ONS GOV [196]

CPI: Consumer Price Index; JCV: John Cunningham virus; LTBI: Latent Tuberculosis Infection; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; ONS: Office for National Statistics

The amount of resource consumed in the administration of DMT is presented in Table 50. For BSC, no administration and monitoring costs are included. Where available, the monitoring schedule for DMT was sourced from the summary of product characteristics for each drug and from assumptions made in previous NICE appraisals (e.g., additional neurologist visits as part of drug follow-up) [167-169]. The costs of drug monitoring were assumed to vary between the first and subsequent years to account for the increased testing typically required on initiation of therapy.

Patients treated with cladribine tablets are expected to require monitoring of lymphocyte count prior to and at 2 and 6 months after each course (e.g. Years 1 and 2), resulting in 3 complete blood counts in each year of therapy. A baseline MRI scan to detect for signs of PML, and Tuberculin, Hepatitis C, and Hepatitis B tests are also included based on recommendations from the summary of product characteristics. No additional monitoring is expected after completion of each course.

Table 50: Costs of DMT monitoring

Therapy	Administration	Source	Monitoring resources consumed in first year	Total cost Year 1	Monitoring resources consumed in subsequent years	Total cost Year 2	Total cost Year 3+
Cladribine tablets	Oral	Based on the CLARITY study and appropriate assumptions	1 x MRI scan 3 x complete blood counts 2 x neurology visits 1 x tuberculin skin test 1 x hepatitis C test 1 x hepatitis B test	£829	3 x complete blood counts 1 x neurology visits 1 x tuberculin skin test 1 x hepatitis C test 1 x hepatitis B test	£332	£0
Dimethyl fumarate	Oral	NICE TA320: Dimethyl fumarate for treating RRMS	1 x MRI scan 4 x biochemistry test 5 x complete blood counts 3 x urinalysis tests with microscopy 3 x neurology visits	£1,014	1.5 x biochemistry test 4 x complete blood counts 1.5 x urinalysis tests with microscopy 1 x neurology visits	£262	£262
Glatiramer acetate	S/C	NICE TA312: Alemtuzumab for treating RRMS	2 x neurology visits 2 x biochemistry tests	£483	2 x neurology visits 2 x biochemistry tests	£483	£483
Interferon beta-1a 22 µg	S/C	NICE TA312: Alemtuzumab for treating RRMS	4 x biochemistry tests 2 x complete blood count 2 x neurology visits 4 x urinalysis tests 1 x thyroid function test	£514	2 x biochemistry tests 2 x complete blood count 2 x neurology visits	£489	£489
Interferon beta-1a 44 µg	S/C						
Interferon beta-1a 30 µg	I/M						
Interferon beta-1b 250 µg	S/C						
Peginterferon	S/C						
Teriflunomide	Oral	NICE TA303: Teriflunomide for treating RRMS	8 x biochemistry tests 2 x neurologist visit 1 x complete blood count	£496	2 x biochemistry test 2 x neurology visits	£483	£483
Ocrelizumab	I/V	Summary of product characteristics	2 x complete blood count 1 x neurology visit 1 x hepatitis B test	£269	2 x complete blood count 1 x neurology visit	£246	£246

Therapy	Administration	Source	Monitoring resources consumed in first year	Total cost Year 1	Monitoring resources consumed in subsequent years	Total cost Year 2	Total cost Year 3+
Ofatumumab	S/C	Summary of product characteristics	1 x complete blood count 1 x neurology visit 1 x hepatitis B test	£266	1 x neurology visit	£240	£240
Ponesimod	Oral	Summary of product characteristics	2 x electrocardiograms 1 x biochemistry tests 3 x complete blood count 1 x neurology visit 1 x ophthalmology	£427	2 x complete blood count 1 x neurology visit	£246	£246
Diroximel fumarate	Oral	Summary of product characteristics	4 x biochemistry tests 5 x complete blood count 3 x urinalysis tests 3 x neurology visit 1 x MRI	£1,014	1.5 x biochemistry tests 4 x complete blood count 1.5 x urinalysis tests 1 x neurology visit	£262	£262

DMT: Disease-modifying treatment; I/M: Intramuscular; I/V: Intravenous; MRI: Magnetic resonance imaging; NICE: National Institute of Health and Care Excellence; RRMS: Relapsing-remitting multiple sclerosis; S/C: Subcutaneous

B.3.5.2. Health-state unit costs and resource use

Published costing studies in RRMS were identified via a systematic literature review (search date February 9th, 2024) of biomedical literature databases. The approaches used to identify studies in the review, and a full description and quality assessment of studies considered relevant to decision-making in England are provided in Appendix I.

In total, 135 unique published studies were included (130 from search, 1 following bibliographic searching, 4 by conference hand searching), of which six reported UK costs relevant to clinical practice in England [42, 165, 202-205].

A summary of the six UK studies identified in the review is provided in Appendix I.1.3.

Three of the six UK studies reported costs by EDSS state [42, 202, 203]. Karampampa et al. (2012) [42] and Tyas et al. (2007) [203] reported direct medical, direct non-medical and indirect costs from patient self-assessments of resource consumption, EDSS and relapse status. Hawton et al. (2016)[202] reported direct costs comprising visits to health care and social work professionals, plus the use of rehabilitation and respite services estimated through patient self-assessment, and combined with clinician assessed EDSS scores. Across all three studies, the sample size of the analysed populations ranged from 119 to 2048.

Four of the six UK studies reported relapse-related costs [42, 165, 202, 203], of which three reported direct medical costs in line with the NICE reference case. One study reported costs funded by out of pocket expenses[165]. One study reported costs for the management of injection site reactions [204].

B.3.5.2.1. Costs by EDSS state

Aligned with recent NICE appraisals, Hawton et al. (2016)[202] and Tyas et al. (2007) [203] were selected as the preferred source for direct medical costs by EDSS state. A summary of the annualised direct medical costs by EDSS state from the two UK studies is provided in Table 51.

Table 51: Annualised costs by EDSS state for medical direct costs/health care and social worker costs

	Hawton et al. (2016) [202] Adjusted to 2023		Tyas et al. (2007) [203] Adjusted to 2023	
Treatment	**Cost (£)**	**Standard error**	**Cost (£)**	**Standard error**
EDSS 0.0	1,510	415	513	4,053
EDSS 1.0	1,347	249	174	1,845
EDSS 2.0	1,060	136	437	1,781
EDSS 3.0	989	120	1,744	2,538

	Hawton et al. (2016) [202] Adjusted to 2023		Tyas et al. (2007) [203] Adjusted to 2023	
EDSS 4.0	1,483	163	1,654	1,814
EDSS 5.0	1,489	177	2,912	1,689
EDSS 6.0	1,930	139	4,437	1,746
EDSS 7.0	1,948	267	13,509	2,042
EDSS 8.0	4,914	585	22,083	2,194
EDSS 9.0	4,914	585	31,030	5,450

Source: See table

EDSS: Expanded disability status scale

The costs reported in Hawton et al. [155], and Tyas et al. [203] were inflated to the 2023 cost year using the medical services CPI inflation time series reported by the ONS GOV [196].

After inflation, the annual costs of direct medical care in Hawton et al. ranged from £989 for EDSS 3.0 to £4,914 for EDSS 8.0 (data not reported for EDSS 9.0). As noted in Hawton et al., the reduction in costs from EDSS 0 to EDSS 3 may be reflective of an initial peak in resource consumption around the time of diagnosis followed by a period of stabilisation. As MS deteriorates and walking impairment develops (EDSS > 4.0), the costs increase as greater medical support is needed [155].

In general, higher costs were reported Tyas et al. when compared to Hawton et al. In Tyas et al., annual costs ranged from £174 (EDSS 1.0) to £31,030 (EDSS 9.0) [203]. Tyas et al. included a broader range of medical costs including inpatient and outpatient services that may not be captured in Hawton et al.

It is noted that costs from Tyas et al. are uncertain given the need to inflate costs from 2005. On this basis, a conservative approach was taken by using the direct medical costs by EDSS from Hawton et al. [202] in the base case, in line with the approach used in TA493/TA616. Costs from Tyas et al. [203] are explored in the sensitivity analysis.

B.3.5.2.2. Costs by relapse status

For the base case, similar to the approach in TA493/TA616, the cost of relapse status was derived from Hawton et al. [202], who reported six monthly costs associated with no relapses, relapses not treated with steroids, relapses that limited everyday activities, relapses that required steroid therapy (oral, intravenous) and relapses that resulted in hospital admission. The costs associated with hospitalised and non-hospitalised relapse events were estimated by subtracting the costs in those with a relapse from the costs in those without relapse [202]. The relapse costs were inflated to the 2023 cost year using medical services CPI rates, published by ONS GOV [196] (Table 52).

Table 52: Cost of relapse events in the model

Relapse state	Inflated cost per event
Relapse without hospitalisation	£753
Relapse with hospitalisation	£4,959

B.3.5.3. Adverse reaction unit costs and resource use

A summary of the adverse reaction unit costs and resource use data is presented in Table 53.

Table 53: Adverse event unit costs and resource use

Adverse event	Total Cost	Unit costs*	Resource use
Infusion site reaction	£0	£0	Assumption that infusion site reactions are treated alongside administration of infusion
Injection site reaction	£7.20	Band 7 Nurse £68 per hour of patient-related work (PSSRU 2022) including qualification	Assumption of 6-minute nurse consultation or call
Severe infection	£3,426.37	(DZ22L – Total HRG cost for unspecified acute lower respiratory infection, with interventions, CC 0-8)	1 x NHS reference cost for respiratory infection
Macular oedema	£346.68	£178.29 (WF02B) Multiprofessional Non-Admitted Face to Face Attendance, First –Ophthalmology £149.15 (WF02A) Multiprofessional Non-Admitted Face to Face Attendance, Follow-up –Ophthalmology	2 x visits to ophthalmologist based on assumptions in manufacturer submission for TA312
Gastro-intestinal	£748.05	(FD05B) Total HRG for Abdominal Pain without Interventions	1 x NHS reference cost for abdominal pain without interventions
Hyper-sensitivity	£75.81	Consultant led multiprofessional non-admitted face-to-face meeting with allergy service (WF01B)	1 x NHS reference cost for use of allergy service
Autoimmune thyroid-related event	£549.10	Total HRG for Non-surgical thyroid disorders with CC Score 0-1 (KA07C)	1 x NHS reference cost
Influenza-like symptoms	£7.20	Band 7 Nurse £68 per hour of patient-related work (PSSRU 2022) including qualification	Assumption of 6 minute nurse consultation or call
Malignancy	£14,555.53	Total HRG for Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (CB01A)	Based on most expensive cancer NHS reference cost category of Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 9+ (CB0A1)

* Costs inflated to 2023 using Medical services CPI from ONS GOV [196]

CC: Complication and comorbidity; CPI: Consumer Price Index; HRG: Healthcare Resource Group; ONS: Office for National Statistics; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base case analysis inputs

A summary of the variables applied in the economic model is provided in Table 54.

Table 54: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table in submission)	Measurement of uncertainty and distribution: CI (distribution)	Section
Population characteristics	Table 29	Log-normal for age Dirichlet for weight distribution and baseline EDSS	B.3.3.1
Natural history model:			
ARR Year 1	0.34 (95% CI: 0.30-0.38)	Log-normal	B.3.3.2.1
Change in annualised relapse by time	22.9% per 5 years	Beta (converted to annualised effect after sampling)	B.3.3.2.1
Duration of relapse event	Table 30	Log-normal	B.3.3.2.1
EDSS transition matrix	Table 32	Dirichlet	B.3.3.2.2
All-cause mortality statistics	Appendix M	Not sampled	B.3.3.2.3
Standardised mortality ratio for MS related mortality	1.68 (95% CI: 1.38-2.05)	Log-normal	B.3.3.2.3
Treatment adjusted model:			
Annualised relapse rate ratio	Table 33	Log-normal	B.3.3.3.1
Hazard ratio for CDP	Table 34	Log-normal	B.3.3.3.2
Waning parameters	Table 35	Not sampled	B.3.3.3.3
AE rates	Table 36	Beta	B.3.3.3.4
Discontinuation rates	Table 37	Beta	B.3.3.3.5
Utilities: HSU by EDSS (patient and caregiver), relapse and AE	Table 39, Table 41	Log-normal on 1-HSU for HSU by EDSS (patient) Normal for HSU loss by EDSS (caregiver) Normal for HSU loss by relapse Normal for HSU loss by AE	B.3.4
Costs: drug costs (acquisition, administration, monitoring), EDSS, relapse and AEs	Table 45	Gamma for EDSS and relapse costs Drug and AE costs are not sampled	B.3.5

AE: Adverse event; CI: Confidence interval; CDP: Confirmed disease progression; EDSS: Expanded disability status scale; HSU: Health state utility; MS: Multiple sclerosis

B.3.6.2. Assumptions

A summary of the key assumptions in the base case model is outlined in Table 55.

Table 55: Summary of basic structural assumptions

Aspect	Assumption	Justification
Health states	EDSS captures the main health problems associated with MS	Numerous studies have shown a strong correlation between EDSS and resource consumption and health related quality of life. EDSS is the preferred tool for measuring disability in people with MS
Lifetable/half-cycle correction	EDSS and drug-related costs and QALYs are modelled based on midpoint estimates assuming patients, on average, transition mid-way through the model cycle The exception is the drug costs of cladribine tablets which is assumed to accrue at the start of the model cycle as therapy is given as a fixed course at the beginning of each treated year	Standard approach to mitigate the risk of under or over-estimating costs and effects
Natural history of MS – disability progression	Disability progression is modelled assuming a constant transition probability matrix over time	Consistent with approaches taken in previous economic models in RRMS Constant transition probability matrix shown to accurately predict EDSS status over 10-years, Figure 20
Natural history of MS – relapse	In the base case, relapses are modelled independently from EDSS state, and assumed to vary over time	This assumption has been applied to avoid double counting of DMT effect
Effectiveness of DMT - application	Sustained accumulation of disability and relapses are modelled independently, with independent treatment effects applied.	Consistent with approaches taken in previous economic models in RRMS Some treatments may be more effective in reducing relapses than slowing disease progression
Discontinuation of DMT or cessation of DMT benefits	People with MS are assumed to discontinue therapy upon progression to EDSS 7.0 People treated with cladribine tablets are also assumed to stop benefiting from therapy once progression to EDSS 7.0 or greater. The health benefits of DMT that are accrued up to the point of discontinuation or cessation of therapy benefits is maintained with future progression rates modelled based on a natural history data set	This is consistent with approaches taken in past economic models in RRMS Clinical trials in RRMS have typically focused on patients who have non-ambulatory RRMS including patients with EDSS <6.5 in study enrolment. No data are available on the effects of DMT in people with EDSS 7.0 or greater
Effectiveness of DMT – waning over time	The effectiveness of DMT is assumed to wane over time (assumption of 25% waning in Year 4-5, and 50% waning from Year 5 onwards is applied)	This is consistent with approaches taken in past economic models

Aspect	Assumption	Justification
No distinction made between RR and SP forms of MS	Any difference in the transition rate between RR and SP forms of MS is accounted for in the averaged transition rates used in the model	This is consistent with approach taken in the previous economic model for cladribine tablets (TA493/TA616) Transition rates used in the base case analysis were sourced from Palace et al. (2014) [154], which includes data from an RRMS cohort who are followed through to SPMS
Inclusion of adverse events	Relevant drug related adverse events include infusion and injection site reactions, macular oedema, malignancy, severe infections, autoimmune-thyroid events, hypersensitivity and allergic reaction	Infusion and injectable site reactions are commonly reported adverse events across the clinical trial literature and have been incorporated in previous models Cladribine tablets and other DMTs included in the NICE decision problem have been associated with an increased risk of the adverse events included in the analysis

DMT: Disease-modifying treatment; EDSS: Expanded disability status scale; MS: Multiple sclerosis; NICE: National Institute of Health and Care Excellence; QALY: Quality-adjusted life year; RR: Relapsing-remitting; RRMS: Relapsing-remitting multiple sclerosis; SP: Secondary progressive; SPMS: Secondary progressive multiple sclerosis

B.3.7 Base case results

In line with the final scope for cladribine tablets in the company submission, the base case results of the economic analyses are presented for active RRMS.

B.3.7.1. Base case incremental cost-effectiveness analysis results

The results of the deterministic base case analysis for the active RRMS population are provided below. Table 56 presents the pairwise comparison versus cladribine tablets and Table 57 presents the fully incremental analysis.

Table 56: Base case results for active RRMS at list price – Pairwise comparison (cladribine vs. comparator)

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine vs. comparator (£/QALY)
Cladribine Tablets	100,884	21.055	9.274	-	-	-	-
BSC	58,541	21.055	7.684	42,343	0.000	1.590	26,624
Interferon beta-1a 22 µg	89,216	21.055	8.028	11,669	0.000	1.246	9,363
Peginterferon	89,223	21.055	8.397	11,662	0.000	0.877	13,304
Glatiramer acetate	89,665	21.055	8.118	11,219	0.000	1.156	9,707
Interferon beta-1a 30 µg	89,765	21.055	8.137	11,120	0.000	1.137	9,777
Interferon beta-1a 44 µg	92,449	21.055	7.985	8,435	0.000	1.289	6,544
Interferon beta-1b 250 µg	99,398	21.055	8.667	1,486	0.000	0.607	2,449
Teriflunomide	115,470	21.055	7.946	-14,586	0.000	1.328	Cladribine tablets dominant
Ponesimod	115,494	21.055	8.169	-14,610	0.000	1.105	Cladribine tablets dominant
Diroximel fumarate	142,592	21.055	8.253	-41,708	0.000	1.021	Cladribine tablets dominant
Dimethyl fumarate	146,333	21.055	8.274	-45,449	0.000	1.000	Cladribine tablets dominant
Ofatumumab	151,488	21.055	8.509	-50,604	0.000	0.766	Cladribine tablets dominant
Ocrelizumab	153,574	21.055	8.626	-52,689	0.000	0.648	Cladribine tablets dominant

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Table 57: Base case results for active RRMS at list price – Fully incremental analysis (vs. BSC)

Technologies (from least to most expensive)	Total costs (£)	Total Lys	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs. baseline (BSC) (£/QALY)	ICER incremental (£/QALY)
BSC	58,541	21.055	7.684	-	-	-	-	-
Interferon beta-1a 22 µg	89,216	21.055	8.028	30,675	0	0.344	89,135	Extended dominance
Peginterferon	89,223	21.055	8.397	30,682	0	0.714	42,979	Extended dominance
Glatiramer acetate	89,665	21.055	8.118	31,125	0	0.435	71,609	Dominated
Interferon beta-1a 30 µg	89,765	21.055	8.137	31,224	0	0.453	68,917	Dominated
Interferon beta-1a 44 µg	92,449	21.055	7.985	33,908	0	0.301	112,549	Dominated
Interferon beta-1b 250 µg	99,398	21.055	8.667	40,857	0	0.984	41,541	Extended dominance
Cladribine Tablets	100,884	21.055	9.274	42,343	0	1.590	26,624	£26,624 vs. BSC
Teriflunomide	115,470	21.055	7.946	56,929	0	0.262	216,923	Dominated
Ponesimod	115,494	21.055	8.169	56,953	0	0.485	117,382	Dominated
Diroximel fumarate	142,592	21.055	8.253	84,051	0	0.569	147,608	Dominated
Dimethyl fumarate	146,333	21.055	8.274	87,792	0	0.590	148,738	Dominated
Ofatumumab	151,488	21.055	8.509	92,947	0	0.825	112,677	Dominated
Ocrelizumab	153,574	21.055	8.626	95,033	0	0.942	100,870	Dominated

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Cladribine tablets were dominant (less costly and more effective) versus ponesimod, ocrelizumab, ofatumumab, dimethyl fumarate, diroximel fumarate and teriflunomide in the pairwise comparisons. Cladribine tablets were also the dominant treatment strategy in the fully incremental analyses.

Cladribine tablets were the least costly high-efficacy DMT in the active RRMS population with a total discounted lifetime cost of £100,884. The most expensive high-efficacy treatment strategies were ponesimod (£115,494) followed by ofatumumab (£151,488) and ocrelizumab (£153,574). Cladribine tablets were cost-saving versus all three high-efficacy DMT comparators, with incremental costs of -£14,610 (ponesimod), -£50,604 (ofatumumab) and £52,689 (ocrelizumab). Cladribine tablets were the most effective strategy in the population versus high-efficacy DMTs, with a total discounted QALY of 9.274 compared with total QALYs of 8.169 for ponesimod, 8.509 for ofatumumab and 8.626 for ocrelizumab. The incremental QALYs comparing cladribine tablets versus ponesimod was +1.105, versus ofatumumab was +0.766, and versus ocrelizumab was +0.648 (Table 56).

Cladribine tablets were also highly cost-effective (ICERs under £13.5k per QALY) versus the remaining therapies (interferons and glatiramer acetate) (Table 57).

B.3.7.2. Severity modifier

Absolute and proportional QALY shortfalls were estimated using the online calculator from the University of Sheffield by providing the mean age and female proportion from the cladribine tablets cost-effectiveness model and total QALYs from BSC as the reference [206]. When applying these values to the QALY shortfall analysis calculator, the severity weighting of 1.0 was obtained and, therefore, a QALY shortfall was not applied in the model.

Table 58: Results of online QALY shortfall calculator

	QALY shortfall calculator (Sheffield online tool)
Remaining QALYs without the disease	18.91
Remaining QALYs with the disease	7.68
Absolute shortfall	11.23
Proportional shortfall	59.40%
QALY weight	**X 1.0**

Source: [206]

QALYs: Quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

A summary of the probabilistic distributions used in the sensitivity analysis is provided in Table 54. Further details on the derivation of sampling parameters (e.g. alpha and beta for individual distributions) are available in the Excel model.

A run of 1000 Monte-Carlo simulations was performed. This number of iterations was judged to be sufficient to achieve convergence in the expected cost and QALY for each intervention.

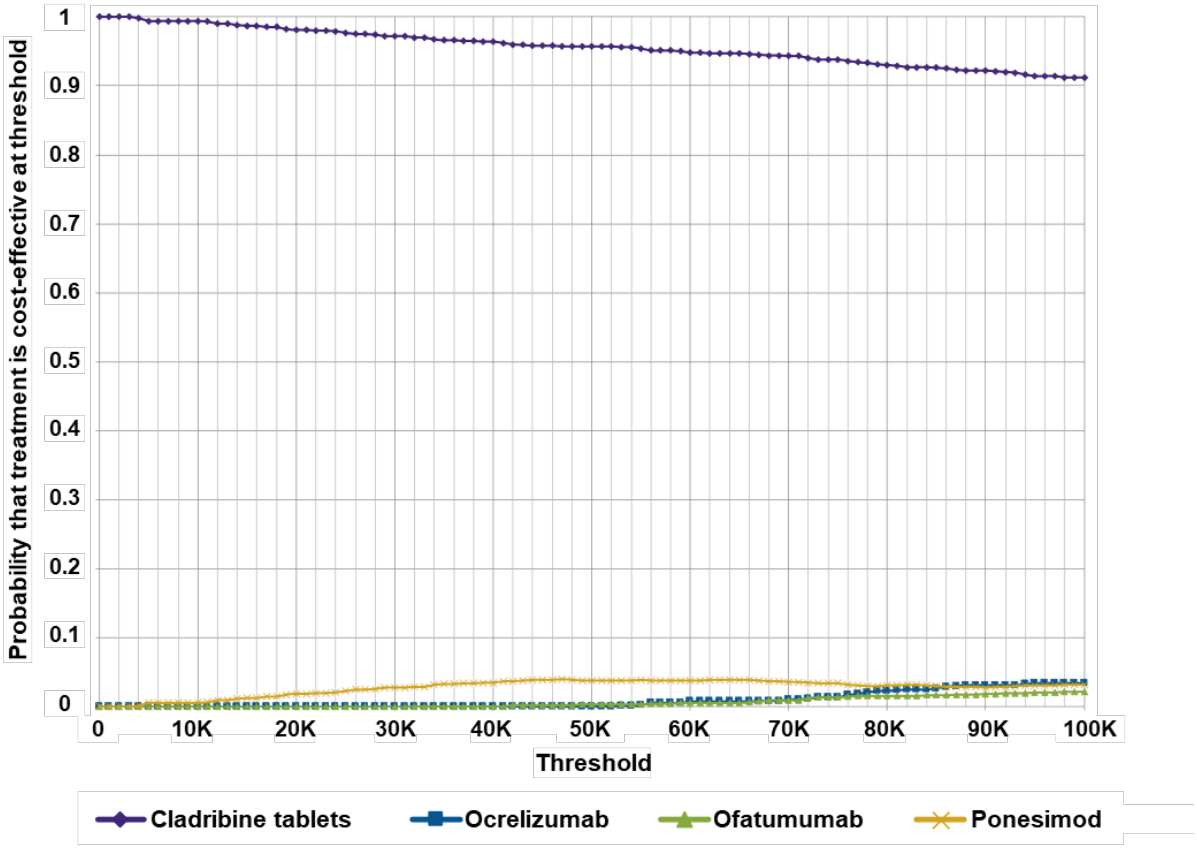
Results were summarised based on expected (e.g. mean) and 95% confidence intervals for total costs and QALY. The mean incremental total cost, QALY and associated incremental cost-effectiveness ratios were estimated from the difference in mean values from each set of sampled values. Multi-way cost-effectiveness acceptability curves were plotted for each population of interest. The expected probability of cost-effectiveness at thresholds of £20,000 and £30,000 were obtained and presented alongside the expected probabilistic results.

The results for the probabilistic sensitivity analysis are presented for the ponesimod, ofatumumab and ocrelizumab in this section, as they are the most relevant comparators given that they are also high-efficacy DMTs used to treat active RRMS. The results are summarised in Figure 21 and Table 59. The results versus all comparators in scope are presented in the Appendix J.

Cladribine tablets were the dominant strategy in the probabilistic sensitivity analysis as a result of being both less costly and more effective than the high-efficacy DMTs ponesimod, ofatumumab and ocrelizumab. The results of the probabilistic sensitivity analysis are consistent with the results of the deterministic analysis providing confidence in the base case results.

The probability that cladribine tablets are cost-effective versus ponesimod, ofatumumab and ocrelizumab in the active RRMS population was 98.3% at a threshold of £20,000 per QALY gained. The corresponding probability for cladribine tablets at £30,000 per QALY gained was 97.5%. At the same thresholds, the probability that ponesimod, ofatumumab or ocrelizumab are the optimal cost-effective strategy in the active RRMS population ranged from 0% to 2.8%.

Figure 21: Multi-way cost-effectiveness acceptability curve for active RRMS at list price



RRMS: Relapsing-remitting multiple sclerosis

Table 59: 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	100,669	94,123	108,873	9.322	7.490	10.902	-	-	-	98.3%	97.5%
Ponesimod	115,328	106,716	123,991	8.192	6.537	9.526	-14,659	1.130	Cladribine tablets dominant	1.7%	2.5%
Ocrelizumab	153,874	143,418	164,697	8.649	7.309	9.907	-53,205	0.673	Cladribine tablets dominant	0.0%	0.0%
Ofatumumab	151,487	141,801	162,027	8.540	7.071	9.848	-50,818	0.782	Cladribine tablets dominant	0.0%	0.0%

BSC: Best supportive care; DMT: Disease-modifying therapy; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

B.3.8.2. Deterministic sensitivity analysis

The results of the deterministic sensitivity analyses are summarised via a series of tornado diagrams. The aim of the analysis was to show the impact of variation in the values assigned to individual model parameters on the incremental net health effects of cladribine tablets versus high-efficacy 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 was dominant versus its high-efficacy 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) 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.

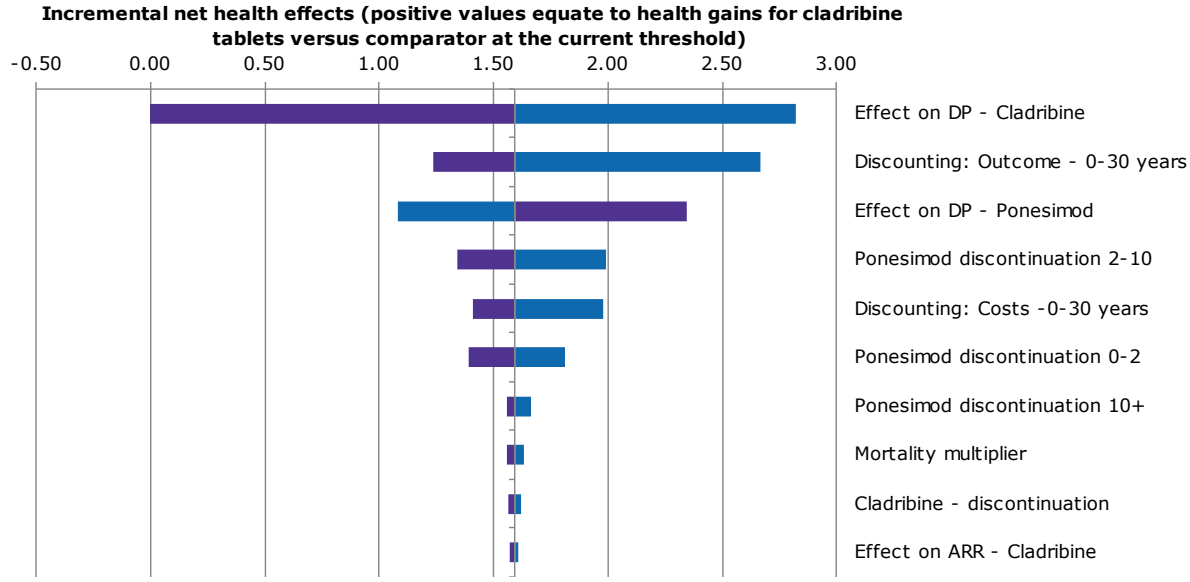
Each parameter in the analysis was varied between its lower and upper 95% confidence or credible interval, or by 50% of its mean value if statistical measures of variance were not available.

The results of the deterministic sensitivity analyses for active RRMS are summarised in the following tornado diagrams for comparisons versus ponesimod (Figure 22), ofatumumab (Figure 23) and ocrelizumab (Figure 24).

The tornado diagrams show that the analysis is 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 mortality multiplier, 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 ocrelizumab and ofatumumab was positive in all scenarios. Cladribine tablets were therefore judged to be cost-effective versus both ocrelizumab and ofatumumab 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 favour of cladribine tablets in most scenarios, except when varying the effect of DMT on disease progression where a negative net health effect was observed.

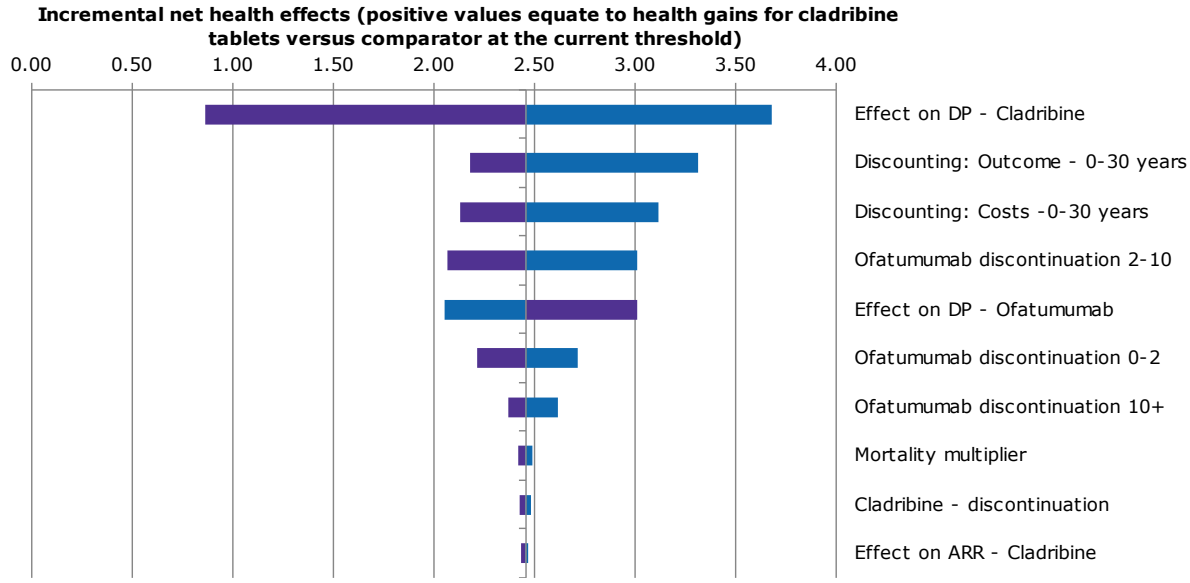
Figure 22: Tornado diagram for active RRMS, cladribine tablets versus ponesimod



Purple bars show high variation and blue bars show low variation

ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

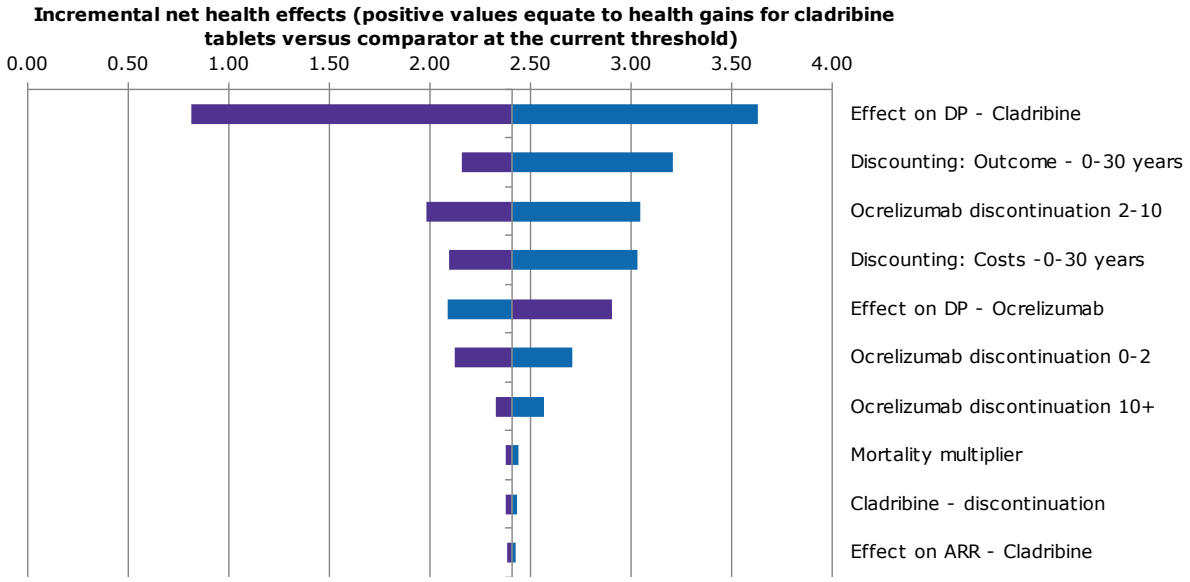
Figure 23: Tornado diagram for active RRMS, cladribine tablets versus ofatumumab



Purple bars show high variation and blue bars show low variation

ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

Figure 24: Tornado diagram for active RRMS, cladribine tablets versus ocrelizumab



Purple bars show high variation and blue bars show low variation

ARR: Annualised relapse rate; DP: Disease progression; RRMS: Relapsing-remitting multiple sclerosis

B.3.8.3. Scenario analysis

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

The full list of scenarios explored is presented in Table 60.

Table 60: Description of the scenario analysis

No.	Parameter	Base case	Scenario a	Scenario b	Scenario c
S1	**Model structure**	11-state with British Columbia data for RRMS	21-state with British Columbia data for RRMS	21-state with London Ontario data for RRMS	-
S2	**Treatment effect**	Relapse rate modelled as a function of time	Relapse rate modelled based on EDSS state	Relapse rate modelled as a function of time (doubled rate)	-
S3	**NMA data**	Random effects models for ARR, CDP and all-cause	Fixed effect models for ARR, CDP and all-cause	-	-
S4	**Mortality**	Mortality ratio applied irrespective of EDSS state from Jick et al. (2014)	Mortality ratio applied from Lalmohamed et al. (2012)	Mortality by EDSS; data from Pokorski et al.1997	-

No.	Parameter	Base case	Scenario a	Scenario b	Scenario c
S5	**Treatment discontinuation**	Trial data sourced from NMA	Pooled data from across trials	Discontinuation rates halved after 2 years for comparators	-
S6	**Treatment waning**	(Same assumptions) 100% treatment effect Years 0-4, 25% waning Year 4-5, and 50% waning Year 5+	(Same assumptions) No treatment waning	(Differential waning) For comparators only, 25% waning Year 2, 50% waning Year 5+	-
S7	**Patient utilities**	CLARITY, Hawton et al. (2016) and Orme et al. (2007)	Hawton et al. (2016) plus Orme 2007 et al. (2007)	Orme et al. (2007) only	Heather et al. (2023)
S8	**Relapse disutility**	Orme et al. (2007)	Ruutiainen et al. (2016)	-	-
S9	**Direct medical costs**	Hawton et al. (2016)	Tyas et al. (2007)	-	-
S10	**Drug acquisition costs**	Acquisition costs of reference drugs	Acquisition costs of generic drugs (dimethyl fumarate , glatiramer acetate, teriflunomide)	-	-
S11	**Stopping rule**	Stopping rule EDSS ≥7.0	No stopping rule	-	-

ARR: Annualised relapse rate; CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; NMA: Network meta-analysis; RRMS: Relapsing-remitting multiple sclerosis

Results of the scenario analyses demonstrated consistency with the base case results where cladribine tablets were the dominant treatment strategy yielding cost-savings for additional QALYs when compared to ponesimod, ofatumumab and ocrelizumab. Cladribine tablets were cost-saving and more efficacious than ponesimod, ocrelizumab and ofatumumab in all scenarios tested.

In comparison to ponesimod, incremental costs ranged from -£10,573 to -£46,372 (savings) with QALY gains ranging from 0.761 to 2.044. The corresponding incremental costs and incremental QALYs for cladribine tablets versus ocrelizumab ranged from -£45,148 to -£112,450 and incremental QALY ranging from 0.214 to 1.450. The corresponding incremental costs and incremental QALYs for cladribine tablets versus ofatumumab ranged from -£42,661 to -£80,873 and incremental QALY ranging from 0.489 to 1.578.

The results of the scenario analyses are summarised in Table 61.

Additional scenario analyses were run to test the impact of comparing cladribine tablets versus generic drugs only. Due to the decrease in the cost of generic treatments, the incremental cost increased versus generic dimethyl fumarate from -£45,449 to -£27,601 (an increase of £17,848), versus glatiramer acetate from -£13,682 to -£10,540 (an increase of £3,142), and versus generic teriflunomide from -£14,586 in the base case to -£6,079 in the scenario (an

increase of £8,507). As only the cost of treatment changed, the incremental QALYs did not change compared to the base case (Table 62).

Table 61: Results of scenario analyses for active RRMS population

Scenario		Cladribine tablets vs. ponesimod			Cladribine tablets vs. ocrelizumab			Cladribine tablets vs. ofatumumab		
		Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER
Base case		-14,610	1.105	Cladribine tablets dominant	-52,689	0.648	Cladribine tablets dominant	-50,604	0.766	Cladribine tablets dominant
S1a	**Model structure: 21-state with British Columbia data for RRMS**	-10,573	0.957	Cladribine tablets dominant	-45,148	0.503	Cladribine tablets dominant	-42,661	0.624	Cladribine tablets dominant
S1b	**Model structure: 21-state with London Ontario data for RRMS**	-11,279	0.761	Cladribine tablets dominant	-45,422	0.392	Cladribine tablets dominant	-43,130	0.489	Cladribine tablets dominant
S2a	**Relapse by EDSS**	-15,841	1.109	Cladribine tablets dominant	-53,996	0.653	Cladribine tablets dominant	-51,519	0.769	Cladribine tablets dominant
S2b	**Relapse rate modelled as a function of time (doubled rate)**	-15,974	1.110	Cladribine tablets dominant	-53,642	0.651	Cladribine tablets dominant	-51,320	0.768	Cladribine tablets dominant
S3	**NMA: Fixed effect models**	-14,612	1.115	Cladribine tablets dominant	-52,845	0.632	Cladribine tablets dominant	-50,638	0.769	Cladribine tablets dominant
S4a	**Mortality by EDSS**	-13,641	1.130	Cladribine tablets dominant	-52,036	0.666	Cladribine tablets dominant	-49,883	0.785	Cladribine tablets dominant
S4b	**Mortality by Lalmohamed (2012)**	-13,451	0.979	Cladribine tablets dominant	-51,004	0.549	Cladribine tablets dominant	48,802	0.661	Cladribine tablets dominant
S5a	**Discontinuation: pooled data from trials**	-46,372	0.895	Cladribine tablets dominant	-112,450	0.214	Cladribine tablets dominant	-70,791	0.624	Cladribine tablets dominant

Scenario		Cladribine tablets vs. ponesimod			Cladribine tablets vs. ocrelizumab			Cladribine tablets vs. ofatumumab		
		Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER
S5b	**Discontinuation: rates halved after 2 years for comparators**	-34,356	0.996	Cladribine tablets dominant	-87,394	0.432	Cladribine tablets dominant	-80,873	0.591	Cladribine tablets dominant
S6a	**Waning: No treatment waning**	-19,490	2.044	Cladribine tablets dominant	-58,698	1.450	Cladribine tablets dominant	-56,552	1.578	Cladribine tablets dominant
S6b	**Waning: Differential waning**	-14,578	1.143	Cladribine tablets dominant	-52,334	0.725	Cladribine tablets dominant	-50,316	0.831	Cladribine tablets dominant
S7a	**Utility (Hawton 2016 plus Orme 2007)**	-14,610	0.978	Cladribine tablets dominant	-52,689	0.576	Cladribine tablets dominant	-50,604	0.679	Cladribine tablets dominant
S7b	**Utility (Orme 2007 only)**	-14,610	1.099	Cladribine tablets dominant	-52,689	0.650	Cladribine tablets dominant	-50,604	0.764	Cladribine tablets dominant
S7c	**Utility (Heather 2023)**	-14,610	1.096	Cladribine tablets dominant	-52,689	0.639	Cladribine tablets dominant	-50,604	0.757	Cladribine tablets dominant
S8	**Utility – Relapse (Ruutiainen 2016)**	-14,610	1.105	Cladribine tablets dominant	-52,689	0.648	Cladribine tablets dominant	-50,604	0.765	Cladribine tablets dominant
S9	**Direct medical costs – (Tyas 2007)**	-38,841	1.105	Cladribine tablets dominant	-67,487	0.648	Cladribine tablets dominant	-67,665	0.766	Cladribine tablets dominant
S11a	**No stopping rule**	-23,793	1.323	Cladribine tablets dominant	-64,304	0.857	Cladribine tablets dominant	-65,392	0.968	Cladribine tablets dominant

ARR: Annualised relapse rate; CDP: Confirmed disease progression; EDSS: Expanded disability status scale; ICER: Incremental-cost effectiveness ratio; Network Meta-analysis; QALYs: Quality-adjusted life years; RRMS: Relapsing-remitting multiple sclerosis

Table 62: Results of scenario analyses for active RRMS population – generic drugs

Scenario		Cladribine tablets vs. dimethyl fumarate			Cladribine tablets vs. teriflunomide			Cladribine tablets vs. glatiramer acetate		
		Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER
S10	Base case	-45,449	1.000	Cladribine tablets dominant	-14,586	1.328	Cladribine tablets dominant	-13,682	1.156	Cladribine tablets dominant
S10a	Drug acquisition costs – generic drugs*	-27,601	1.000	Cladribine tablets dominant	-6,079	1.328	Cladribine tablets dominant	-10,540	1.156	Cladribine tablets dominant

Note: * List prices of the generic versions of these three DMTs were retrieved by the British National Formulary as their generic prices were not available from the Electronic medicines information tool.

ICER: Incremental-cost effectiveness ratio; QALYs: Quality-adjusted life years; RRMS: Relapsing-remitting multiple sclerosis

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

Validation of the cost-effectiveness analysis included consideration of its face validity, internal validity, cross validity, and external validity.

Face validity covers four aspects; model structure, data sources, problem formulation and results. The model structure and data sources used in the model were tested with clinical experts and external health economists from the UK, familiar with RRMS, who validated the base case assumptions applied in the cost-effectiveness model, including choice of structure (11 versus 21 states), and choice of inputs to the natural history model.

Internal validity, which is otherwise known as verification, considers the implementation of the mathematical calculations required in the model, and includes consideration of whether the equations used to inform the model are specified and implemented correctly. This was tested through the application of extreme value testing, and by examination of the model calculations by an independent modeller. Any discrepancies identified in this review were corrected prior to submission.

Cross validity can be assessed by comparing the results of the base case analysis to different models that address the same problem. It is not feasible to exactly replicate the results of other models given differences in, state structure (e.g., 21 versus 11 states), modelling methodology, model inputs, and as a large amount of information is marked as confidential in previous appraisals, cross validity can be a challenge. In addition, models published prior to January 2014 would not have access to the British Columbia Natural history model, which includes backward transitions to EDSS. Models published prior to this date typically used the London Ontario data for predicting lifetime EDSS status. This data set had censored for backward transitions resulting in models that predicted a faster overall rate of progression and an implausibly low accumulation of QALY relative to life years (discussed in TA312). The inclusion of backward transitions within the natural history models precludes any attempt to compare the results of this analysis to existing published studies. Hence, no formal cross validation of the model was performed.

Of note, none of the studies identified in the systematic literature review of economic evaluations in active RRMS included cladribine tablets as a comparator. The results of this analysis cannot be directly compared with other studies.

External validation compare's a model results with actual event data. To validate the model, the predicted change in mean EDSS shown in Appendix J, was visually compared to predictions from the British Columbia registry (Figure 20), to ensure the correct implementation of the natural history model. It can be seen by comparing these two sets of figures that the model correctly captures the trajectory of EDSS in patients with RRMS.

B.3.11 Interpretation and conclusions of economic evidence

The economic analysis used in TA493/TA616 was adapted to assess the incremental cost-effectiveness of cladribine tablets versus NICE-recommended DMTs in active RRMS (the ITT population of the CLARITY and the CLARITY-EXT trials). Closely following precedent set in previous NICE appraisals, a comprehensive set of economic analyses were performed using the best available evidence currently available on the costs, and clinical outcomes of treatments in RRMS.

The results of the base case analysis demonstrate that cladribine tablets are dominant (e.g. cost-saving and more effective) versus ponesimod, ocrelizumab, ofatumumab, dimethyl fumarate, diroximel fumarate and teriflunomide in pairwise comparisons. Cladribine tablets are also highly cost-effective (ICERs under £13.5k per QALY) versus remaining platform therapies (interferons and glatiramer acetate). Over a lifetime horizon of 50-years, the model predicts discounted cost-savings with cladribine tablets versus all three high-efficacy DMT comparators; -£14,610 versus ponesimod, -£50,604 versus ofatumumab and -£52,689 versus ocrelizumab. In most scenarios, the cost-savings result from a lower lifetime drug acquisition cost for cladribine tablets due to its unique fixed course posology (versus continuously administered treatments), in addition to cost-savings from delaying EDSS progression and the additional care required at more severe EDSS states. The associated QALY gains from cladribine tablets were +1.105 versus ponesimod, +0.766 versus ofatumumab, and +0.648 versus ocrelizumab over the lifetime time horizon of 50-years.

In the probabilistic sensitivity analyses (Figure 21), the probability that cladribine tablets is cost-effective versus ponesimod, ofatumumab and ocrelizumab at a threshold of £20,000 was 98.3% and 97.5% at a threshold of £30,000. Overall, the probabilistic analysis is characterised by wide confidence intervals surrounding the total costs and QALYs of each intervention. This uncertainty is borne out of the credible intervals surrounding the effect of DMT on 6-month CDP where none of the available DMTs demonstrated statistical superiority over other DMTs (see Section B.2.9.3.3 for the NMA results). The influence of DMT efficacy on 6-month CDP on the results of the analysis is further demonstrated in the deterministic sensitivity analysis (Figure 22-Figure 24). The effect of DMT on 6-month CDP and discontinuation rate for comparator DMTs are the main drivers of uncertainty in the cost-effectiveness analysis.

In summary, cladribine tablets offer a unique posology of two fixed oral courses of treatment given over 2 years leading to sustained benefits over a four-year period. The total cost of cladribine tablets over a four-year period is approximately £52,000, which is equivalent to an annualised cost of £13,000. These costs compare favourably to the annualised costs of alternative NICE-recommended high-efficacy DMTs ponesimod (£14,010), ocrelizumab (£19,160) and ofatumumab (£20,895), and hence support the prediction of cost-savings in the model. In terms of efficacy, cladribine tablets has demonstrated comparable efficacy on 6-month CDP to comparators in active RRMS, and has potential for health gains when allowing for a sustained effect over the first four years. The results of the economic analysis support the case that cladribine tablets are a cost-effective treatment in the active RRMS population.

In view of the various concerns raised over the assumptions and model inputs applied in previous NICE appraisals (referred to throughout section B.3), a comprehensive set of scenario analyses was performed to assess the robustness of the economic analysis. This included analyses using the 21-health state model, and the consideration of alternative input parameters (e.g., relapse rate modelled based on EDSS state, differential waning assumption for comparators). Cladribine tablets remained dominant (less costly and more effective) versus high-efficacy DMTs in all scenarios.

Relevance of the analysis to clinical practice in England

Where possible, the analyses have used input values from literature sources and/or previous NICE appraisals that have been considered generalisable to clinical practice in England. This includes the selection of cost inputs corresponding to the NHS and PSS perspective from patients with RRMS in England, where available, and the inclusion of HSU values derived from UK social preferences. In addition, the natural history model used to generate EDSS progression was based on the model used in the UK risk sharing scheme, which was developed with the intention of modelling the EDSS of the UK RRMS population.

Strengths and weaknesses

The key strengths of the analysis are shown below:

- The analysis allows for both improvements and progression in EDSS as modelled using the preferred British Columbia natural history data set, whilst the London Ontario set only allows progression in EDSS states.
- The model has the functionality to conduct detailed sensitivity analysis, including both 11-state and 21-state model configurations via the British Columbia and London Ontario data sets, to vary assumptions on waning effect over time
- Use of the NICE preferred endpoint of 6-month CDP

- Use of health state utility values from the CLARITY trial
- The post-hoc analysis of efficacy data in the CLARITY and the CLARITY-EXT trials provides the first “evidence-based” attempt to justify the waning of drug effect in RRMS. The complex analysis, using novel treatment switching techniques which makes best use of the available data from the CLARITY trial through the CLARITY-EXT trial, provides evidence in support of a sustained effect of cladribine tablets over 4 years.
    - Beyond Year 4, there remains uncertainty over its continued effect. However, this analysis provides bounds to that uncertainty suggesting that in conservative circumstances, the full effect may wane after Year 4 and in optimistic scenarios, the full effect may continue into the long-term.

The key limitations of the economic analysis are:

- The reliance on clinical efficacy and safety data from clinical trials that differ in many aspects including study design, population characteristics, and the long time frame over which data were collected (1990s to 2010s), and the uncertainty surrounding the long-term efficacy of all DMTs
- DMTs are assumed to only impact on EDSS progression and relapse rate. There is no effect of DMT on mortality.
- The health benefits of an oral drug are not fully captured in the QALY estimates given the need to assume the same utilities across different formulations. Similarly, in TA303 and TA320 it was recognized that oral drugs provide QoL benefits other than those captured in the QALY calculations. The analysis does not consider the cost-effectiveness of cladribine tablets when given in a sequence of therapies; the model assumes no further DMT treatment after cessation of therapy. This is in line with NICE precedent.

Overall, this cost-effectiveness analysis demonstrates that cladribine tablets are a highly cost-effective treatment option for active RRMS.

B.4. References

1. Zuvich, R.L., et al., *Genetics and pathogenesis of multiple sclerosis.* Semin Immunol, 2009. **21**(6): p. 328-33.
2. Freeman, L., et al., *High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing-Remitting Multiple Sclerosis.* CNS Drugs, 2022. **36**(12): p. 1285-1299.
3. European Medicines Agency, *Cladribine tablets SmPC*. 2024, EMA.
4. National Institute for Health and Care Excellence. *Cladribine for treating relapsing-remitting multiple sclerosis (TA616)*. 2019; Available from: https://www.nice.org.uk/guidance/ta616/resources/cladribine-for-treating-relapsingremitting-multiple-sclerosis-pdf-82608960149701.
5. Giovannoni, G., et al., *A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.* N Engl J Med, 2010. **362**(5): p. 416-26.
6. Giovannoni, G., et al., *Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study.* Mult Scler, 2018. **24**(12): p. 1594-1604.
7. Merck Group., *CLARITY GEVD Re-Analysis. Data on file.* 2017.
8. Merck Group., *CLARITY-EXT GEVD Re-Analysis. Data on file.* 2017.
9. Brownlee, W.A., Amerah; Ashton, Luke; Herbert, Alex,, *Real-World Evidence with Five-Year Data (2017-2022) on the use of Cladribine Tablets in Patients with Multiple Sclerosis in England: An Updated Analysis from the CLARENCE Study*, in *ECTRIMS*. 2023: Milan.
10. Brownlee, W., et al., *Real-world use of cladribine tablets (completion rates and treatment persistence) in patients with multiple sclerosis in England: The CLARENCE study.* Mult Scler Relat Disord, 2023. **79**: p. 104951.
11. Giovannoni, G., *Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm.* Curr Opin Neurol, 2018. **31**(3): p. 233-243.
12. Mayer, L., et al., *Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies.* Multiple Sclerosis and Related Disorders, 2019. **30**: p. 236-243.
13. Simpson, A., E.M. Mowry, and S.D. Newsome, *Early Aggressive Treatment Approaches for Multiple Sclerosis.* Current Treatment Options in Neurology, 2021. **23**(7): p. 19.
14. Croft, A., et al., *MS Forward View: a consensus for the future of MS services.* Mult Scler Trust, 2016. **9**: p. S5-S48.
15. Mynors, G., A. Bowen, and D. Doncaster, *MS Specialist Nursing in the UK 2016: Report on progress towards equitable provision.* Mult Scler Trust, 2016.
16. Costello, K. and J. Halper, *Multiple Sclerosis: Key Issues in Nursing Management.* 2004.
17. Rog, D., et al., *131 Understanding the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis.* Journal of Neurology, Neurosurgery & Psychiatry, 2022. **93**(9): p. e2.
18. Treadaway, K., et al., *Factors that influence adherence with disease-modifying therapy in MS.* J Neurol, 2009. **256**(4): p. 568-576.
19. Devonshire, V., et al., *The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis.* Eur. J Neurol, 2011. **18**(1): p. 69-77.
20. Menzin, J., et al., *Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis.* J Manag. Care Pharm, 2013. **19**(1 Suppl A): p. S24-S40.
21. Wicks, P., et al., *Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients.* Interact. J Med. Res, 2015. **4**(1): p. e6.

22. Walton, C., et al., *Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition.* Mult Scler, 2020. **26**(14): p. 1816-1821.
23. Jonker, M.F., et al., *Summarizing Patient Preferences for the Competitive Landscape of Multiple Sclerosis Treatment Options.* Med Decis Making, 2020. **40**(2): p. 198-211.
24. National Institute for Health and Care Excellence, *Response to stakeholder organisation comments on the draft remit and draft scope*. 2024.
25. National Institute for Health and Care Excellence, *Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA493)*. 2017.
26. Merck Group. *Great Britain is first across Europe to get regulatory approval of MAVENCLAD® (cladribine tablets) as the only short course oral treatment for active Relapsing Multiple Sclerosis patients*. 2024 23 April 2024]; Available from: https://www.merckgroup.com/uk-en/press-releases/GB-Mavenclad-27-Mar-2024-Local-Press-Materials-for-Announcements-press-release-for-the-label-expansion.pdf.
27. National Institute for Health and Care Excellence, *Cladribine for treating relapsing multiple sclerosis Final scope*. 2024.
28. BioSpace. *Merck announces innovative MS treatment MAVENCLAD® (Cladribine Tablets) selected for rapid uptake by the Accelerated Access Collaborative*. 2018 [cited 2024; Available from: https://www.biospace.com/article/merck-announces-innovative-ms-treatment-mavenclad-cladribine-tablets-selected-for-rapid-uptake-by-the-accelerated-access-collaborative-/.
29. Department of Health and Social Care. *Faster access to treatment and new technology for 500,000 patients*. 2018 [cited 2024; Available from: https://www.gov.uk/government/news/faster-access-to-treatment-and-new-technology-for-500000-patients.
30. National Institute for Health and Care Excellence. *Cladribine for treating relapsing–remitting multiple sclerosis – NICE guidance update*. 2019; Available from: https://www.nice.org.uk/guidance/ta616/resources/adoption-support-statement-nice-guidance-update-pdf-7019161885.
31. Advances in Clinical Neuroscience and Rehabilitation. *Multiple Sclerosis Patients in the UK to Receive Accelerated Access to MAVENCLAD® (Cladribine Tablets) Following Fast Tracked NICE Guidance Update*. 2019 [cited 2024; Available from: https://acnr.co.uk/multiple-sclerosis-patients-in-the-uk-to-receive-accelerated-access-to-mavenclad-cladribine-tablets-following-fast-tracked-nice-guidance-update/.
32. Spelman, T., et al., *Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry.* Mult Scler, 2023. **29**(2): p. 221-235.
33. Brownlee, W., et al., *Comparative Effectiveness of Cladribine versus Fingolimod in the Treatment of Highly Active Relapsing Multiple Sclerosis: The MERLYN (MavEnclad Real worLd comparative efficacY non-iNterventional) Study (P7-4.005).* Neurology, 2022. **98**(18 Supplement): p. 1370.
34. National Institute for Health and Care Excellence. *Cladribine for treating relapsing–remitting multiple sclerosis (TA616) - Update Information (21 May 2024)*. 2024 [cited 2024; Available from: https://www.nice.org.uk/guidance/ta616/chapter/Update-Information.
35. Leist, T.P. and R. Weissert, *Cladribine: mode of action and implications for treatment of multiple sclerosis.* Clin Neuropharmacol, 2011. **34**(1): p. 28-35.
36. National Institute for Health and Care Excellence. *British National Formulary (BNF).* June 2024]; Available from: https://www.nice.org.uk/bnf-uk-only.
37. Novakovic, A.T., A. Schindler, E. Jönsson, S. Munafo, A. Karlsson, MO., *Pharmacometric analysis of the relationship between absolute lymphocyte count, and expanded disability status scale and relapse rate, efficacy endpoints, in multiple sclerosis trials (manuscript accepted for publication)* 2018.
38. Albor, C., et al., *Ethnicity and prevalence of multiple sclerosis in east London.* Mult. Scler, 2017. **23**(1): p. 36-42.

39. Bar-Or, A., *The immunology of multiple sclerosis.* Semin. Neurol, 2008. **28**(1): p. 29-45.
40. AlSharoqi, I.A., et al., *Immune Reconstitution Therapy or Continuous Immunosuppression for the Management of Active Relapsing–Remitting Multiple Sclerosis Patients? A Narrative Review.* Neurology and Therapy, 2020. **9**(1): p. 55-66.
41. Giovannoni, G. and J. Mathews, *Cladribine Tablets for Relapsing–Remitting Multiple Sclerosis: A Clinician's Review.* Neurology and Therapy, 2022. **11**(2): p. 571-595.
42. Karampampa, K., et al., *Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries.* Mult. Scler, 2012. **18**(2 Suppl): p. 7-15.
43. World Health Organization *Atlas of multiple sclerosis 2013.* https://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf, 2013.
44. Montalban, X., et al., *ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis.* Mult Scler, 2018. **24**(2): p. 96-120.
45. Scolding, N., et al., *Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis.* Pract. Neurol, 2015. **15**(4): p. 273-279.
46. Ragonese, P., et al., *Mortality in multiple sclerosis: a review.* Eur J Neurol, 2008. **15**(2): p. 123-7.
47. Confavreux, C. and S. Vukusic, *The clinical course of multiple sclerosis.* Handb Clin Neurol, 2014. **122**: p. 343-69.
48. Marrie, R.A., et al., *Effect of comorbidity on mortality in multiple sclerosis.* Neurology, 2015. **85**(3): p. 240-7.
49. Hauer, L., J. Perneczky, and J. Sellner, *A global view of comorbidity in multiple sclerosis: a systematic review with a focus on regional differences, methodology, and clinical implications.* Journal of Neurology, 2021. **268**(11): p. 4066-4077.
50. Jick, S.S., et al., *Epidemiology of multiple sclerosis: results from a large observational study in the UK.* J Neurol, 2015. **262**(9): p. 2033-41.
51. Marck, C.H., et al., *Prevalence of Comorbidities, Overweight and Obesity in an International Sample of People with Multiple Sclerosis and Associations with Modifiable Lifestyle Factors.* PLoS One, 2016. **11**(2): p. e0148573.
52. Kowalec, K., et al., *Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study.* Neurology, 2017. **89**(24): p. 2455-2461.
53. Salter, A., et al., *Employment and absenteeism in working-age persons with multiple sclerosis.* J Med Econ, 2017. **20**(5): p. 493-502.
54. Oliva Ramirez, A., et al., *Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review.* BMC Neurology, 2021. **21**(1): p. 468.
55. Moore, H., et al., *Fatigue in multiple sclerosis: A UK MS-register based study.* Multiple Sclerosis and Related Disorders, 2022. **64**.
56. Orme, M., et al., *The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK.* Value Health, 2007. **10**(1): p. 54-60.
57. Parkin, D., et al., *Treatment of multiple sclerosis with interferon beta: an appraisal of cost-effectiveness and quality of life.* J Neurol Neurosurg Psychiatry, 2000. **68**(2): p. 144-9.
58. Baumstarck, K., et al., *Predictors of quality of life in patients with relapsing-remitting multiple sclerosis: A 2-year longitudinal study.* Revue Neurologique, 2015. **171**(2): p. 173-180.
59. Kobelt, G., et al., *New insights into the burden and costs of multiple sclerosis in Europe.* 2017. **23**(8): p. 1123-1136.
60. World Health Organization. *Atlas multiple sclerosis resources in the world*. 2008 4/2015]; Available from: https://iris.who.int/bitstream/handle/10665/43968/9789241563758_eng.pdf?sequence=1.

61. Fattore, G., M. Lang, and M. Pugliatti, *The Treatment experience, burden, and unmet needs (TRIBUNE) study - measuring the socioeconomic consequences of Multiple Sclerosis.* Mult Scler, 2012. **18**(2 Suppl): p. 5-6.
62. Rath, L., et al., *Patient Preferences for Time and Location of Infusible Therapies in Multiple Sclerosis and Neuroimmunologic Disorders.* Int J MS Care, 2021. **23**(3): p. 114-118.
63. Evans, C., et al., *Long-term persistence with the immunomodulatory drugs for multiple sclerosis: a retrospective database study.* Clin Ther, 2012. **34**(2): p. 341-50.
64. Bawand, R., et al., *Effects of disease-modifying treatments discontinuation in patients with relapsing-remitting multiple sclerosis: A 5 year prospective cohort study.* Multiple Sclerosis and Related Disorders, 2022. **63**: p. 103857.
65. Rae-Grant, A., et al., *Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.* Neurology, 2018. **90**(17): p. 777-788.
66. Dobson, R., et al., *UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines.* Pract Neurol, 2019. **19**(2): p. 106-114.
67. NHS England, *Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies. NHS England Reference: 170079ALG. Gateway reference: 07603. 20 June 2023.* 2023.
68. Filippi, M., et al., *Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis.* J Neurol, 2022. **269**(3): p. 1670-1677.
69. Casanova, B., C. Quintanilla-Bordás, and F. Gascón, *Escalation vs. Early Intense Therapy in Multiple Sclerosis.* J Pers Med, 2022. **12**(1).
70. Pipek, L.Z., et al., *Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis.* Mult Scler Relat Disord, 2023. **71**: p. 104581.
71. Harding, K., et al., *Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis.* JAMA Neurol, 2019. **76**(5): p. 536-541.
72. Prosperini, L., et al., *Induction Versus Escalation in Multiple Sclerosis: A 10-Year Real World Study.* Neurotherapeutics, 2020. **17**(3): p. 994-1004.
73. He, A., et al., *Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study.* Lancet Neurol, 2020. **19**(4): p. 307-316.
74. Ontaneda, D., et al., *Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis.* Lancet Neurol, 2019. **18**(10): p. 973-980.
75. Dobson, R., et al., *Social determinants of health in multiple sclerosis.* Nat Rev Neurol, 2022. **18**(12): p. 723-734.
76. Gorrod, H.B., et al., *Impact of Nonrandomized Dropout on Treatment Switching Adjustment in the Relapsing-Remitting Multiple Sclerosis CLARITY Trial and the CLARITY Extension Study.* Value Health, 2019. **22**(7): p. 772-776.
77. Giovannoni, G., et al., *Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis.* Lancet Neurol, 2011. **10**(4): p. 329-37.
78. Giovannoni, G., et al., *Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study.* Mult Scler, 2019. **25**(6): p. 819-827.
79. Merck Group., *CLARITY Clinical Trial Report. Data on file.* 2010.
80. Giovannoni, G., et al., *Durability of no evidence of disease activity-3 (NEDA-3) in patients receiving cladribine tablets: The CLARITY extension study.* Mult Scler, 2022. **28**(8): p. 1219-1228.
81. Merck Group., *CLARITY-EXT Clinical Trial Report. Data on file.* 2016.
82. Leist, T., et al., *Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis.* Mult Scler Relat Disord, 2020. **46**: p. 102572.

83. Leist, T.P., et al., *Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial.* Lancet Neurol, 2014. **13**(3): p. 257-67.
84. Giovannoni, G., et al., *Updated Post-Approval Safety of Cladribine Tablets in the Treatment of Multiple Sclerosis, with Particular Reference to Respiratory Viral Infections*, in *ACTRIMS-ECTRIMS*. 2020: Virtual 11–13 September (P0415).
85. Giovannoni, G., et al., *Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study.* Mult Scler, 2023. **29**(6): p. 719-730.
86. National Institute for Health and Care Excellence, *Cladribine tablets for treating relapsing-remitting multiple sclerosis - Committee Papers*. 2017.
87. Medicines and Healthcare products Regulatory Agency. *MAVENCLAD SPC*. 2024; Available from: https://mhraproducts4853.blob.core.windows.net/docs/c38ba13f05ae70ae828bf9facf6ea3326a64be0b.
88. Merck Group, *CLARITY-EXT Addendum to the Clinical Trial Report - PRO and HRU Data. Data on file.* 2017.
89. Merck Group., *CLARITY Addendum to the Clinical Trial Report – PRO data. Data on file.* . 2009.
90. Merck Group, *CLARITY and CLARITY-EXT GEVD Re-Analysis NEDA. Data on file.* 2017.
91. Merck Group., *Statistical Analysis Plan for Clinical Summary of Efficacy (CLARITY, CLARITY-EXT, ONWARD). Data on file.* 2015.
92. National Institute for Health and Care Excellence, *Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533).* 2018.
93. National Institute for Health and Care Excellence, *Ofatumumab for treating relapsing multiple sclerosis (TA699).* 2021.
94. National Institute for Health and Care Excellence, *Ponesimod for treating relapsing–remitting multiple sclerosis (TA767).* 2022.
95. Ebers, G.C., *Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.* The Lancet, 1998. **352**(9139): p. 1498-1504.
96. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), *Allgemeine Methoden. Version 4.2 vom 22.04.2015*. 2015.
97. National Institute for Health and Care Excellence, *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624).* 2020.
98. Calabresi, P.A., et al., *Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study.* 2014. **13**(7): p. 657-665.
99. Saida, T., et al., *A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries.* BMC Neurol, 2019. **19**(1): p. 5.
100. Kira, J.I., et al., *Effect of ofatumumab versus placebo in relapsing multiple sclerosis patients from Japan and Russia: Phase 2 APOLITOS study.* Mult Scler, 2022. **28**(8): p. 1229-1238.
101. Hauser, S.L., et al., *Ofatumumab versus Teriflunomide in Multiple Sclerosis.* N Engl J Med, 2020. **383**(6): p. 546-557.
102. Cadavid, D., et al., *Efficacy of treatment of MS with IFNβ-1b or glatiramer acetate by monthly brain MRI in the BECOME study.* 2009. **72**(23): p. 1976-1983.
103. O`Connor, *250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study.* The Lancet Neurology, 2009. **8**(10): p. 889-897.
104. Bornstein, M.B., Miller, A., Slagle, S., *A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis.* New England Journal of Medicine, 1987. **317**(7): p. 408-414.
105. Vollmer, T., et al., *A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis.* 2014. **261**: p. 773-783.

106. Calabrese, M., et al., *Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis.* Mult Scler, 2012. **18**(4): p. 418-24.
107. Lublin, F.D., et al., *Randomized study combining interferon and glatiramer acetate in multiple sclerosis.* 2013. **73**(3): p. 327-340.
108. Fox, R.J., et al., *Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.* 2012. **367**(12): p. 1087-1097.
109. Johnson, K., et al., *Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial.* 1995. **45**(7): p. 1268-1276.
110. Gold, R., et al., *Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis.* 2012. **367**(12): p. 1098-1107.
111. Etemadifar, M., Janghorbani, M., Shaygannejad, V., *Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis.* Acta Neurologica Scandinavica, 2006. **113**: p. 283-287.
112. Comi, G., M. Filippi, and J.S. Wolinsky, *European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group.* Annals of neurology, 2001. **49**(3): p. 290-297.
113. Naismith, R.T., et al., *Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study.* CNS Drugs, 2020. **34**(2): p. 185-196.
114. Schwid, S.R., Panitch, H.S., *Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: A multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon ÃŸ-1a for relapsi.* Clinical Therapeutics, 2007. **29**(9): p. 2031-2048.
115. Khan, O., et al., *Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis.* 2013. **73**(6): p. 705-713.
116. Cohen, J., et al., *Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial.* 2015. **72**(12): p. 1433-1441.
117. Duquette, P., Girard, M., Despault, L., DuBois, R., Knobler, R.L., Lublin, F.D., Kelley, L., Francis, G.S., Lapierre, Y., Antel, J., Freedman, M., Hum, S., Greenstein, J.I., Mishra, B., Muldoon, J., Whitaker, J.N., Evans, B.K., Layton, B., Sibley, W.A., *Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial.* Neurology, 1993. **42**(4): p. 655-661.
118. Stefano, N., et al., *Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study.* Journal of the neurological sciences 2012. **312**(24): p. 97-101.
119. Durelli, L., Verdun, E., Barbero, P., Bergui, M., Versino, E., Ghezzi, A., Montanari, E., Zaffaroni, M., *Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: Results of a 2-year prospective randomised multicentre study (INCOMIN).* Lancet, 2002. **359**(9316): p. 1453-1460.
120. Kappos, L., et al., *Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial.* Lancet, 2011. **378**(9805): p. 1779-87.
121. Knobler, R.L., Greenstein, J.I., Johnson, K.P., Lublin, F.D., Panitch, H.S., Conway, K., Grant-Gorsen, S.V., Muldoon, J., Marcus, S.G., Wallenberg, J.C., Williams, G.J., Yoshizawa, C.N., *Systemic recombinant human interferon-ÃŸ treatment of relapsing-remitting multiple sclerosis: Pilot study analysis and six-year follow-up.* Journal of Interferon Research, 1993. **13**(5): p. 333-340.
122. Montalban, X., et al., *Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis.* N Engl J Med, 2019. **380**(25): p. 2406-2417.

123. Jacobs LD, C.D., *Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG).* Annals of neurology, 1996. **39**(3): p. 285-294.
124. O`Connor, P.W., Li, D., Freedman, M.S., Bar-Or, A., Rice, G.P.A., Confavreux, C., Paty, D.W., Stewart, J.A., Scheyer, R., *A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses.* Neurology, 2006. **66**(6): p. 894-900.
125. Hauser, S.L., et al., *Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis.* N Engl J Med, 2017. **376**(3): p. 221-234.
126. Kappos, L., et al., *Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial.* JAMA Neurol, 2021. **78**(5): p. 558-567.
127. Singer, B., et al., *Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonβ-1a versus subcutaneous interferonβ-1b: results of the randomized, multicenter, Phase IIIb REFORMS study.* 2012. **12**: p. 1-11.
128. Mikol, D.D., et al., *Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial.* 2008. **7**(10): p. 903-914.
129. O'Connor, P., et al., *Randomized trial of oral teriflunomide for relapsing multiple sclerosis.* 2011. **365**(14): p. 1293-1303.
130. Vermersch, P., et al., *Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial.* 2014. **20**(6): p. 705-716.
131. Confavreux, C., et al., *Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial.* 2014. **13**(3): p. 247-256.
132. National Institute for Health and Care Excellence, *Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527)*. 2018.
133. Vartanian, T., *An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis.* Clin Ther, 2003. **25**(1): p. 105-18.
134. European Medicines Agency, *CHMP assessment report for MAVENCLAD. Data on file.* 2017.
135. Cook, S., et al., *Safety of cladribine tablets in the treatment of patients with multiple sclerosis: An integrated analysis.* Mult Scler Relat Disord, 2019. **29**: p. 157-167.
136. European Medicines Agency, *Ponesimod tablets SmPC*. 2024.
137. European Medicines Agency, *Ofatumumab solution SmPC*. 2024.
138. European Medicines Agency, *Ocrelizumab solution SmCP*. 2024.
139. Brochet, B., et al., *Improvements in quality of life over 2 years with cladribine tablets in people with relapsing multiple sclerosis: The CLARIFY-MS study.* Mult Scler, 2023. **29**(14): p. 1808-1818.
140. De Stefano N et al, *(Data on file) Early Onset of Action and Sustained Efficacy of MRI Outcomes during Cladribine Tablets Treatment in Highly Active Relapsing Multiple Sclerosis: Results of the 2-year MAGNIFY-MS Study. ECTRIMS*. 2022.
141. Bell Gorrod, H., et al., *Adjusting for Treatment Switching in the Relapsing-Remitting Multiple Sclerosis Clarity Trial and the Clarity Extension Study.* Value in Health, 2017. **20**(9): p. A718.
142. National Institute for Health and Care Excellence, *Guide to the methods of technology appraisal 2013, NICE process and methods [PMG9]*. 2013.
143. Montgomery, S.M., et al., *A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK.* J Med Econ, 2017. **20**(5): p. 474-482.
144. Montgomery, S.M., et al., *Costs and effectiveness of fingolimod versus alemtuzumab in the treatment of highly active relapsing-remitting multiple sclerosis in the UK: re-treatment, discount, and disutility.* J Med Econ, 2017. **20**(9): p. 962-973.

145. Rog, D., et al., *Alemtuzumab Is The Most Cost-Effective Option In Comparison To Available Therapies In The Treatment of Rrms From The UK NHS Perspective.* Value in Health, 2017. **20**(9): p. A723.
146. Hettle, R., G. Harty, and S.L. Wong, *Cost-effectiveness of cladribine tablets, alemtuzumab, and natalizumab in the treatment of relapsing-remitting multiple sclerosis with high disease activity in England.* J Med Econ, 2018. **21**(7): p. 676-686.
147. Harty, G., et al., *PND71 - A COST MINIMISATION ANALYSIS OF CLADRIBINE TABLETS VERSUS ALTERNATIVE HIGH EFFICACY TREATMENTS FOR RELAPSING MULTIPLE SCLEROSIS (RMS) IN THE UNIED KINGDOM.* Value in Health, 2018. **21**: p. S341.
148. Phelps, H., et al., *PND73 - THE IMPACT OF MODELLING SUBSEQUENT TREATMENT ON ESTIMATES OF COST-EFFECTIVENESS: AN ANALYSIS OF DISEASE-MODIFYING TREATMENTS FOR RELAPSING-REMITTING MULTIPLE SCLEROSIS IN THE UNITED KINGDOM.* Value in Health, 2018. **21**: p. S341.
149. Rock, M., et al., *PND19 CLINICAL AND ECONOMIC IMPACT OF INITIATING DIMETHYL FUMARATE VERSUS GLATIRAMER ACETATE IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS IN EUROPE.* Value in Health, 2019. **22**: p. S273.
150. Giovannoni, G., et al., *Glatiramer acetate as a clinically and cost-effective treatment of relapsing multiple sclerosis over 10 years of use within the National Health Service: Final results from the UK Risk Sharing Scheme.* Mult Scler J Exp Transl Clin, 2019. **5**(4): p. 2055217319893103.
151. Di Maio, D., et al., *PND47 Socioeconomic Value of Ocrelizumab in the Treatment of Patients with Relapsing Forms of Multiple Sclerosis.* Value in Health, 2020. **23**: p. S631.
152. Spelman, T., et al., *Comparative Effectiveness and Cost-Effectiveness of Natalizumab and Fingolimod in Patients with Inadequate Response to Disease-Modifying Therapies in Relapsing-Remitting Multiple Sclerosis in the United Kingdom.* Pharmacoeconomics, 2022. **40**(3): p. 323-339.
153. Spelman, T., et al., *Comparative effectiveness and cost-effectiveness of natalizumab and fingolimod in rapidly evolving severe relapsing-remitting multiple sclerosis in the United Kingdom.* J Med Econ, 2024. **27**(1): p. 109-125.
154. Palace, J., et al., *UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model.* BMJ Open, 2014. **4**(1): p. e004073.
155. Hawton, A. and C. Green, *Health Utilities for Multiple Sclerosis.* Value Health, 2016. **19**(4): p. 460-8.
156. Heather, A., et al., *Multiple sclerosis health-related quality of life utility values from the UK MS register.* Mult Scler J Exp Transl Clin, 2023. **9**(2): p. 20552173231178441.
157. Tappenden, P., Chilcott J., O'Hagan T., McCabe, C., Cooper, N., Abrams, K., Ebers, K., Fenwick, L., McNamee, P., Parkin, D., Sculpher, M., , *Cost effectiveness of beta interferons and glatiramer acetate in the management of multiple sclerosis - Final Report to the National Institute for Clinical Excellence* 2001.
158. Tappenden, P., et al., *Cost-effectiveness of disease-modifying therapies in the management of multiple sclerosis for the Medicare population.* Value Health, 2009. **12**(5): p. 657-65.
159. Peninsula Technology Assessment Group (PenTAG), *The effectiveness and cost-effectiveness of natalizumab for multiple sclerosis: An evidence review of the submission from Biogen*. 2007.
160. Palace, J., et al., *Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator.* The Lancet Neurology, 2015. **14**(5): p. 497-505.
161. Gani, R., et al., *Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK.* Pharmacoeconomics, 2008. **26**(7): p. 617-27.

162. Chilcott, J., et al., *Modelling the cost effectiveness of interferon beta and glatiramer acetate in the management of multiple sclerosisCommentary: Evaluating disease modifying treatments in multiple sclerosis.* BMJ, 2003. **326**(7388): p. 522.
163. Gold, R., et al., *Evolving expectations around early management of multiple sclerosis.* Ther Adv Neurol Disord, 2010. **3**(6): p. 351-67.
164. Kappos, L., et al., *A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis.* N Engl J Med, 2010. **362**(5): p. 387-401.
165. Duddy, M., et al., *The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies.* Mult Scler Relat Disord, 2014. **3**(4): p. 450-6.
166. Ruutiainen, J., et al., *Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis.* J Med Econ, 2016. **19**(1): p. 21-33.
167. National Institute for Health and Care Excellence, *Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303)*. 2014.
168. National Institute for Health and Care Excellence, *Alemtuzumab for treating highly active relapsing–remitting multiple sclerosis (TA312)*. 2014.
169. National Institute for Health and Care Excellence, *Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320)*. 2014.
170. European Medicines Agency, *Teriflunomide tablets SmPC*. 2023.
171. National Institute for Health and Care Excellence, *Diroximel fumarate for treating relapsing–remitting multiple sclerosis (TA794)*. 2022.
172. NHS England, *Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). Reference: NHS ENGLAND/ D04/P/b*. 2014.
173. Merck Group, *CLARITY GEVD Re-Analysis - Weight EDSS status. Data on file*. 2017,.
174. Steinvorth, S.M., et al., *Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression.* Mult Scler, 2013. **19**(12): p. 1580-6.
175. Tremlett, H., et al., *New perspectives in the natural history of multiple sclerosis.* Neurology, 2010. **74**(24): p. 2004-15.
176. Tremlett, H., et al., *Relapses in multiple sclerosis are age- and time-dependent.* Journal of Neurology, Neurosurgery & Psychiatry, 2008. **79**(12): p. 1368-1374.
177. Merck Group, *CLARITY GEVD Re-Analysis. Relapses Duration by Hospitalization Status. Data on file.* 2017.
178. Ebers, G.C., *Natural history of multiple sclerosis.* J Neurol Neurosurg Psychiatry, 2001. **71 Suppl 2**(Suppl 2): p. ii16-9.
179. Briggs, A., K. Claxton, and M. Sculpher, *Decision modelling for health economic evaluation.* 2006: Oxford University Press.
180. Manouchehrinia, A., et al., *Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios.* J Neurol Neurosurg Psychiatry, 2016. **87**(3): p. 324-31.
181. Jick, S.S., et al., *Mortality of patients with multiple sclerosis: a cohort study in UK primary care.* J Neurol, 2014. **261**(8): p. 1508-17.
182. Lalmohamed, A., et al., *Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study.* Eur J Neurol, 2012. **19**(7): p. 1007-14.
183. Pokorski, R.J., *Long-term survival experience of patients with multiple sclerosis.* J Insur Med, 1997. **29**(2): p. 101-6.
184. Sadovnick, A.D., et al., *Life expectancy in patients attending multiple sclerosis clinics.* Neurology, 1992. **42**(5): p. 991-4.
185. Brønnum-Hansen, H., N. Koch-Henriksen, and E. Stenager, *Trends in survival and cause of death in Danish patients with multiple sclerosis.* Brain, 2004. **127**(Pt 4): p. 844-50.
186. Pakpoor, J., et al., *No evidence for higher risk of cancer in patients with multiple sclerosis taking cladribine.* Neurol Neuroimmunol Neuroinflamm, 2015. **2**(6): p. e158.

187. Acaster, S., et al., *A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis.* BMC Health Serv Res, 2013. **13**: p. 346.
188. Boye, K.S., et al., *Utilities and disutilities for attributes of injectable treatments for type 2 diabetes.* Eur J Health Econ, 2011. **12**(3): p. 219-30.
189. Shingler, S., et al., *Utilities for treatment-related adverse events in type 2 diabetes.* J Med Econ, 2015. **18**(1): p. 45-55.
190. Phillips, J.T., et al., *Clinical Significance of Gastrointestinal and Flushing Events in Patients with Multiple Sclerosis Treated with Delayed-Release Dimethyl Fumarate.* Int J MS Care, 2015. **17**(5): p. 236-43.
191. Matza, L.S., et al., *Health state utilities associated with attributes of treatments for hepatitis C.* Eur J Health Econ, 2015. **16**(9): p. 1005-18.
192. Trogdon, J.G., et al., *Breast Cancer in Young Women: Health State Utility Impacts by Race/Ethnicity.* Am J Prev Med, 2016. **50**(2): p. 262-9.
193. National Institute for Health and Care Excellence, *NICE health technology evaluations: the manual* 2023.
194. Hernández Alava, M., S. Pudney, and A. Wailoo, *Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study.* Pharmacoeconomics, 2023. **41**(2): p. 199-207.
195. Department of Health, *National Schedule of Reference Costs, 2019-20 - NHS trusts and NHS foundation trusts.* 2020.
196. Office of National Statistics. *Consumer price inflation time series (MM23)*. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/dkc3/mm23.
197. Department of Health, *Drugs and pharmaceutical electronic market information (eMit). Pharmex data for the period 1 July 2022 to 30 June 2023, for Pharmex products shown as Generic in the period 1 January 2023 to 30 June 2023*. 2022.
198. Curtis, L. and A. Burns. *Unit Costs of Health & Social Care 2020*. 2020; Available from: https://kar.kent.ac.uk/84818/.
199. Northern Devon Healthcare NHS trust pathology department, *Information on the Number and Cost of Diagnostic Test Services - PRIMARY CARE ONLY*. 2016.
200. National Institute for Health and Care Excellence. *NICE guideline for Tuberculosis (NG33)*

Appendix H: Warwick Evidence Diagnosis of LTBI. . 2015 [cited 2024; Available from: https://www.nice.org.uk/guidance/ng33/documents/tuberculosis-update-appendix-h2.

201. Shepherd, J., Jones, J., Hartwell, D., Davidson, P., Price, A., Waugh, N.,, *Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.* Health Technology Assessment, 2007. **11**(11).
202. Hawton, A.J. and C. Green, *Multiple sclerosis: relapses, resource use, and costs.* The European Journal of Health Economics, 2016. **17**(7): p. 875-884.
203. Tyas, D., et al., *The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity?* Value Health, 2007. **10**(5): p. 386-9.
204. Perard, R. and L. Parkes, *PND11 NURSE COSTING SURVEY FOR THE MANAGEMENT OF ADVERSE EVENTS IN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH DISEASE-MODIFYING DRUGS IN THE UK.* Value in Health, 2010. **13**(7): p. A389.
205. McCrone, P., et al., *Multiple sclerosis in the UK: service use, costs, quality of life and disability.* Pharmacoeconomics, 2008. **26**(10): p. 847-60.
206. Schneider et al. *QALY Shortfall Calculator*. 2021; Available from: https://shiny.york.ac.uk/shortfall/.

HTAI PCIG project:

Summary of Information for Patients (SIP):

International SIP template

Introduction for patient organisations:

Background:

Understanding the experiences of patients, their families and carers, is becoming widely recognised as an important component in any Health Technology Assessment (HTA). Patients and patient organisations can help to provide this information through their engagement with the HTA process, and it is now becoming standard practice for HTA bodies to request input during the assessment process. It is therefore important that relevant patient representative have an informed and appropriate understanding of the medicine under review to optimise their input.

Why should I use a SIP?

This *Summary of Information for Patients (SIP) Version 1* is a supporting document that has been developed to provide you with relevant background information about the medicine under review. We hope it will help you / your organisation to structure a response to the HTA body, and comment on where you see the medicine adding most value to the patient community. Production of the SIP has been in response to patient organisations requesting this information. However, using the SIP template is optional.

The information within this template has been provided by the pharmaceutical company that is developing the medicine, and sent to you by your HTA agency assessing the medicine. This has been reviewed by the HTA body to ensure that the content is not commercial in any way. **(NOTE TO HTA: Please delete last sentence if HTA body is not reviewing the industry content for accuracy and balance).**

It is important that the information included within this template is used as background reading to inform and support your input into the ongoing HTA assessment. Patient groups are requested to kindly not copy statements directly into their responses when providing input into the HTA review.

To help you navigate the SIP it has been divided into four sections:

- **SECTION 1: Submission summary.** This includes a summary about the medicine, the pharmaceutical company that makes it and the HTA body undertaking the assessment of the medicine.

- **SECTION 2: Current landscape.** This section has details about the condition, how it is diagnosed and currently treated. Patient-based evidence about the condition may be included here to help set the scene as to where the medicine will potentially fit in and provide benefit to patients.

- **SECTION 3: The medicine.** This is where all of the details about the medicine can be found, such as how it works, how it is given or taken, and its key attributes.

- **SECTION 4: Further information, glossary and references.**

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the guidance included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers.

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the medicine. Please outline the main patient population it is proposed to treat:

Response:

Cladribine tablets are a type of disease modifying therapy (DMT) used to treat multiple sclerosis (MS). The way that cladribine tablets manage MS is not fully understood, however it is known that they work by targeting parts of the immune system that are associated with disease progression.

There are different types of MS and cladribine tablets are currently used to treat a more aggressive type of MS known as highly active relapsing-remitting multiple sclerosis (RRMS) which manifests in periods when a patient's symptoms flare up aggressively (relapses), followed by periods of good or complete recovery (remission). Patients taking cladribine tablets should experience fewer relapses, and potential slower disability progression, than those not on treatment.

Evidence has shown that cladribine tablets can also be beneficial for patients with less severe RRMS (known as active RRMS). The purpose of this appraisal to the National Institute for Health and Care Excellence (NICE), is to consider whether cladribine tablets should also be made available as a treatment option for patients with active RRMS.

A range of different treatment options exist for active RRMS, which vary in terms of how frequently they are taken by patients, and whether they are taken as a tablet, injection or infusion.

Cladribine tablets are taken orally (swallowed as a tablet) and are taken for only two weeks per year for two years. Due to the way that cladribine tablets work on the immune system, the effect of the medicine continues after the patient has taken the tablets.

1b) Name of the medicine (generic and brand name):

Response:

Generic name: Cladribine tablets
Brand name: MAVENCLAD®

1c) Authorisation: Please provide marketing authorisation information and link to the regulatory agency approval:

Response:

On 22 March 2024, cladribine tablets were approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for active RRMS. This is an extension to the previous indication for cladribine tablets which was in a subset of RRMS patients with a more aggressive type of RRMS (known as highly active RRMS).

Links to regulatory approvals:

MHRA Products | Product results
Mavenclad | European Medicines Agency (europa.eu)

1d) Name, address and contact details of SIP author at the pharmaceutical company making the submission. Please provide this for patients/patient groups should they require additional information. In some countries, this section may be removed depending on local compliance regulations:

- Company name and address:
  Merck Serono Limited
  5 New Square
  Bedfont Lakes Business Park
  Feltham
  Middlesex
  TW14 8HA
  Telephone: 0208 818 7373 (medical information)
  Email: medinfo.uk@merckgroup.com

- Representative name and title:

  Alice Galbraith, Market Access and Government & Public Affairs Lead

- Representative contact details (email/phone):

  alice.galbraith@merckgroup.com

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

Merck UK has existing collaborative relationships with MS Together, MS Society, Shift.MS, MS Trust, and Neurological Alliance including financial support.

Section 1f to be completed by the HTA organisation

1f) Health Technology Assessment (HTA) organisation:

- HTA organisation name and address:
- Representative name and title:
- Representative contact details (email/phone):
- Submission date:
- If known, please also include an indication of the overall timelines for this health technology assessment:

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation may wish to add country-level information where needed to provide local country-level context.

Please focus this submission on the **target indication** rather than sub-groups, as this could distract from the focus of the SIP and the HTA review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition

Please provide a few sentences to describe the main condition that the medicine is planned to treat.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available.

Response:

MS is a chronic autoimmune disease of the central nervous system that can cause damage to the nerves of the brain and spinal cord. The immune system of patients with MS mistakenly attacks the layer that surrounds and protects the brain and/or spinal cord nerves called the myelin sheath. As the nerves control the functions of the whole body, damage to these nerves can cause various symptoms that may vary from person to person, and from day to day. The reason why the immune system of some people acts this way is unclear. However, experts believe that it might be due to a combination of genetic and environmental factors [1, 2].

Most common symptoms of MS include fatigue (a type of exhaustion that is out of proportion to the task undertaken), unusual feelings in the skin such as pins and needles, numbness or burning, problems with their vision and walking difficulties [1, 2]. However, symptoms can greatly vary in type, range, and severity.

MS can be broadly categorised in four different types [3, 2, 4, 5, 6, 7]:

1) Relapsing-remitting MS (RRMS) is the most common type of MS affecting 85% of MS patients. Patients with RRMS have periods when symptoms flare up aggressively, (known as relapses), followed by periods of good or complete recovery, (known as remission).
2) Secondary progressive MS (SPMS) occurs in almost 50% of people who were initially diagnosed with RRMS and is characterised by disability which gets worse over time with fewer or no relapses.
3) Primary progressive MS (PPMS) occurs in 10-15% of the patients for whom despite disease progression, it is rare to have relapses and the cause of nerve damage is not yet fully understood.
4) Clinically isolated syndrome (CIS) is also considered a type of MS, and it refers to someone's first episode of neurological symptoms, noting this as the potential first sign of MS.

It is estimated that more than 150,000 people in the UK have MS and over 7,000 people are newly diagnosed each year [2, 4]. MS is more common in women than in men, and it is usually diagnosed in people in their 30s and 40s [2, 4]. Among young adults, MS is the most common debilitating neurological disease and the leading cause of disability (not related to trauma) in many countries including the UK [1, 4]. Compared with the general population, the life expectancy of patients with MS is reduced by approximately 10 years and patients are more likely to die of another condition that is simultaneously present with MS in a patient, known as a comorbidity [8, 9, 10]. Specifically in the UK, patients with MS experience cardiovascular comorbidities, psychological conditions (e.g., depression, anxiety, bipolar disorder), epilepsy, restless leg syndrome, migraines, pulmonary

diseases (e.g., asthma), autoimmune conditions, cancer, and metabolic disorders (e.g., dyslipidaemia, diabetes) [11].

Overall, the unpredictability of MS, the burden of disability and comorbidities experienced by patients with MS and symptoms, such as fatigue and pain, have a detrimental effect on a patient's quality of life (QoL) and their ability to perform routine daily activities, often eventually leading to the need of a caregiver [12, 13, 14, 15].

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

If relevant to the medicine submission, please briefly explain how the condition is diagnosed and how this impacts patients:

Response:

MS is usually difficult to diagnose as most of the symptoms can be confused with other health conditions. [1, 2]. In addition, there is no single test that can diagnose MS with certainty [1, 2].

If a GP thinks a patient might have MS, a referral to a neurologist is provided. Neurologists will perform multiple diagnostic steps and use their experience to decide if a patient has MS or not.

There are a number of simple tests that a neurologist can first carry out that can suggest, or rule out, MS as the cause of symptoms. These include checks on a patient's movement, coordination, vision, balance and reflexes. Typically, the neurologist will request one or more additional tests to look for evidence of MS which include the following [1, 2]:

- Magnetic resonance imaging (MRI) is the most common test performed to detect whether there are scars caused by MS on the brain and/or spinal cord of a patient.
- Evoked potential test involves putting small electrodes on the patient's head, arms or legs to measure the speed of messages travelling along their nerves from their eyes, ears or skin on their limbs.
- Lumbar puncture is a procedure performed under local anaesthetic and removes a sample of the spinal fluid to be analysed for any unusual antibodies, fragmented myelin nerve coating, or an unusual amount of white blood cells that may indicate MS.
- Blood tests cannot diagnose MS. However, they might be performed to rule out other causes/diseases of the patients' symptoms.

Once MS has been diagnosed, neurologists can identity the type of MS by looking at the patterns of a patient's symptoms and the results of the MRI scan [1]. However, diagnosing the type of MS might be challenging at the beginning due to the unpredictability and variations of MS symptoms [1].

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is considered the standard of care for this condition? Please give emphasis to the specific setting and condition being considered by the HTA body in this review

- Please also consider:
    - Are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are
    - What are the short- and long-term implications of using current medicines?
- Please reference current treatment guidelines where needed
- Please conclude by stating how you feel the medicine will potentially address the unmet needs of patients

Response:

Currently there is no cure for MS, however, existing therapies can manage symptoms or control the condition. Due to its chronic nature, patients with MS require long-term treatment.
Two main treatment approaches exist:

(i) Symptomatic treatments only manage individual symptoms of MS which are either physical or mental. These treatments do not treat the underlying cause of MS or change the course of the condition. They are available to patients regardless of the type of MS [2].

(ii) Disease modifying therapies (DMTs) can reduce the number and impact of relapses and reduce the build-up of disability. DMTs work on different parts of the immune system to reduce the inflammation caused by MS to the nerve cells in the brain and spinal cord. This helps reduce the number and severity of relapses patients experience. Due to the nature of their mechanism of action, most DMTs are used for people with RRMS.
There are different types of DMTs available, including low-to-moderate efficacy DMTs and high-efficacy DMTs. The different types are based on how well they control the disease. In England, there are nine DMTs for the treatment of RRMS (three high-efficacy DMTs and six low-to-moderate efficacy DMTs) and the way they are administered varies including injections, infusions or pills.

Treatment for MS may also include therapies, such as physiotherapy, and self-management techniques.

Even though many DMTs are available and provide health benefits to patients with RRMS, some patients find it difficult to continue using DMTs due to the method and frequency of their administration, as well as the medical observation required after their use. For example, the only currently approved oral high-efficacy DMT must be taken daily. Other high-efficacy DMTs are infusions or injectables and require frequent administration, monitoring and management of side effects [16, 17, 18, 19, 20, 21].

Cladribine tablets have a unique short-term treatment schedule, providing a treatment option that is convenient to use with low treatment burden for patients. Specifically, they allow patients to take oral medication for only two weeks per year in Years 1 and 2 to achieve a sustained clinical benefit that lasts four years, even when patients are not receiving treatment.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might include outputs from patient preference studies,

when conducted in order to show what matters most to patients and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE evidence that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Any such evidence included in the SIP should be formally referenced wherever possible.

Response:

The quality of life of patients with MS is an important aspect to consider, particularly as current treatments may not cure MS and patients might experience relapses in their disease.

Patients with MS experience a greater level of emotional, cognitive, and physiological comorbidities than the general population. Evidence has shown that patients with MS have a lower quality of life than patients with many other chronic conditions including ischaemic heart disease, Type 2 diabetes, and Crohn's disease [22]. In addition, a study conducted across MS patients in the UK, Germany, France, Italy and Spain suggests that patients become worse at performing daily activities as their MS becomes more severe [23].

Patient preferences have also been documented in a study in England and Germany which looked at which DMTs patients prefer. The study reported that patients in the UK (n=799) and in Germany (n=363) prefer orally administered DMTs (42%) compared to injectable (16%) or infusion administered (38%) DMTs [24].

The combination of MS symptoms, together with social and financial consequences of the disease present a great burden on MS patients' quality of life.

SECTION 3: The medicine

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used if they will help to convey information more clearly.

3a) How does the medicine work?

What are the important features of this medicine?

Please outline as clearly as possible important details relating to the mechanism of action and how the medicine interacts with the body that you consider relevant to patient groups.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

Response:

Cladribine tablets work by targeting certain cells in the immune system which are associated with the progression of MS. Specifically, they mostly act on certain types of lymphocytes, which are a type of white blood cell in the immune system that play an important role in various processes including inflammation [25, 26].

Within these cells, signalling pathways exist that trigger the death of the cell when it needs replacing. Cladribine tablets act by causing the cells they target to initiate one of these signalling pathways, resulting in the death of the cell.

Overall, this causes a reduction in the number of lymphocytes in the immune system and the suppression of immune system processes. The ways in which this helps to reduce disease progression in MS are not known, but the prolonged reduction in the inflammation of the central nervous system is considered an important part of how cladribine tablets reduce flare-ups of MS symptoms and slow down the progression of disability [26, 25, 27].

The effect of cladribine tablets is long-lasting, meaning that although they are administered as one 2-week course a year for two years, their effect continues after patients have finished their treatment.

In contrast to other treatments for MS, cladribine tablets do not supress the immune system continuously, meaning that over time lymphocytes will return, gradually increasing back to normal levels.

Cladribine tablets give patients with RRMS the opportunity to adhere to an easy treatment regimen and continue with their normal daily activities. Considering the current alternative DMTs which require frequent administration, monitoring and management of side effects, cladribine tablets provide a much-needed advancement in the treatment of MS.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes? / No?

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination medicine, please ensure the sections on efficacy (3d), QoL (3e) and safety/side effects (3f) focus on data that relate to the combination, rather than the individual medicine.

Response:

No.

However, cladribine tablets contain a substance (hydroxypropylbetadex) which may be available in other medicines. Therefore, it is recommended that patients who take any other oral medicine do so at least 3 hours before or after taking cladribine tablets in the days they take cladribine tablets [25].

3c) Administration and dosing

How and where is the medicine given or taken? Please include the amount and how often the medicine should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Before a patient with MS start a treatment course with cladribine tablets, their doctor will do a blood test to check that the levels of lymphocytes (a type of white blood cell) are in an acceptable range to receive the treatment. Before and during treatment patients will also receive blood tests to check that their liver is functioning correctly, as in the event of liver injury it may not be suitable for a patient to start or continue treatment.

Cladribine tablets are administered orally and the dose of cladribine tablets depend on the weight of the patient (3.5 mg/kg body weight over 2 years or 1.75 mg/kg per year). Cladribine tablets are given to patients in two treatment courses. The first course is taken in Year 1 and the second taken in Year 2 of treatment.

Each treatment course consists of two treatment weeks: one at the beginning of the first month and one at the beginning of the second month in Years 1 and 2 of treatment.
Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single dose per day, depending on body weight. For example, if a patient weighs 85 kg and is about to start treatment week 1, they will be given 8 tablets. No further treatment is required in Years 3 and 4.

The tablets should be taken at the same time each day and can be taken with or between meals.
Care should be taken with limiting contact of the tablets with skin and other surfaces, further information about this is provided to patients in the Patient Information Leaflet, supplied with the medicine.

If a daily dose is missed, it cannot be taken with the next dose. However, the missed dose can be taken on the next day and patients can extend the number of days they take cladribine tablets in that treatment week [26, 25].

The convenient, ready-to-use oral tablet formulation means that patients can take cladribine tablets at home without the need of frequent hospital visits or intravenous treatments. Cladribine tablets do not require any special storage conditions.

3d) Efficacy

Efficacy is the measure of how well a medicine works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the medicine is at treating the main condition outlined in section 2a. If there are data available, please also describe how it is different to other medicines available outlined in section 2c?

Response:

CLARITY and CLARITY-EXT studies are the main clinical studies that tested how effective and safe cladribine tablets are for the treatment of patients with RRMS. Both studies are phase 3 and have now been completed [28, 29, 30].

The CLARITY study included 1,290 patients with RRMS and compared cladribine tablets with a placebo over 96 weeks. CLARITY-EXT was a subsequent 2-year extension study, where patients from the CLARITY study were further assessed to test whether cladribine tablets continued to provide a clinical benefit, two years after completing treatment. The CLARITY-EXT study included 1,326 patients with RRMS and did not compare cladribine tablets with any other treatment [28, 29, 30].

Both studies tested the average number of relapses patients had in one year; whether patients' disability got worse; whether there was evidence of disease activity; whether patients experienced side effects; whether patients were able to tolerate treatment; and how cladribine tablets affected their quality of life [28, 29, 30].

The CLARITY study showed that cladribine tablets were more effective than placebo. The CLARITY-EXT study showed that cladribine tablets have long-term effectiveness and safety over a 4-year period [28, 29, 30].

CLASSIC-MS is another study that tested the clinical benefit of cladribine tablets and showed that patients who received cladribine tablets had a sustained long-term ability to move or walk around freely, benefited from reduced disability and had a lower risk of their disease getting worse for almost 11 years compared with patients who never received cladribine tablets. [31].

Currently, there are no further ongoing studies that compare cladribine tablets directly with other available DMTs.

3e) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand the trade-offs and willingness to accept benefit/risk by patients. Please include all references as required.

Response:

MS patients' quality of life can be negatively impacted by a variety of symptoms, including fatigue and pain. In the CLARITY study, patient-reported outcomes were collected via a series of surveys. Patient reported outcomes relevant to the physical limitations caused by MS did not reveal a

significant difference between patients who received cladribine tablets or placebo. However, when looking at patients' health distress (emotional, social, spiritual, physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious, or lonely), patients experienced better outcomes with cladribine tablets than placebo [29].

3f) Safety of the medicine and side effects

When a regulatory or HTA body makes a decision about a medicine, it will pay close attention to the benefits of the medicine in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this medicine, and include benefit/risk assessment details where possible. This will support patient group reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen and how they could potentially be managed. Where appropriate and relevant to patients, please also highlight risk reduction comparisons with other treatments.

Where it will add value or context for patient readers please included references to the Summary of Product Characteristics from regulatory agencies etc.

Response [26, 25]:

Like all medicines, cladribine tablets can cause side effects, although not everybody gets them. In case of side effects, patients are advised to talk to their doctors, pharmacists or nurses.

The most common side effect of cladribine tablets (may affect more than 1 in 10 people), which may be severe, is having an abnormally low number of white blood cells called lymphocytes (lymphopenia).
Lymphopenia may increase the risk of getting an infection. An infection commonly seen with cladribine tablets is shingles.
Patients should tell their doctor immediately if they have symptoms of shingles such as a 'band' of severe pain and blistering rash, typically on one side of the upper body or the face. Other symptoms may include headache, burning, tingling, numbness or itchiness of the skin in the affected area and feeling generally unwell or feverish in the early stages of infection.
In case a patient has shingles, it will need to be treated. Treatment with cladribine tablets may need to be stopped until the infection is cleared.

Patients who start or continue a treatment course with cladribine tablets will need to do a blood test for their doctors to check that the levels of lymphocytes (a type of white blood cell) are in an acceptable range.
If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the patient should not receive cladribine tablets anymore.

Other common side effects of cladribine tablets (may affect up to 1 in 10 people) are:

- Cold sore (oral herpes)
- Rash
- Hair loss
- Reduction in the number of certain white blood cells (neutrophils)
- Allergic reactions, including itching, hives, rash and swelling of the lips, tongue or face

Very rare side effects of cladribine tablets (may affect up to 1 in 10,000 people) are:

- Tuberculosis

Women of childbearing potential must prevent pregnancy by use of effective contraception during treatment with cladribine tablets and for at least 6 months after the last dose. Male patients must

take precautions to prevent pregnancy of their female partner during treatment with cladribine tablets and for at least 6 months after the last dose.

3g) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the medicine. Please provide a top-level summary for each, such as title, location, patient group size, completion dates etc.

Response:

There are no ongoing studies with cladribine tablets in patients with RRMS.

3h) Summary of key benefits to patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the medicine for patients, caregivers and their communities when compared with current medicines
- Please outline any data from the clinical trials listed above that support this
- This should inform any relevant cost or value considerations in the following section (3j)

Response:

Cladribine tablets as an option for the treatments of RRMS could provide the following benefits to patients:

- Better treatment adherence as less frequent dosing of cladribine tablets will provide advantages over other DMTs by reducing the treatment burden and treatment fatigue for patients [32, 33, 34, 35].
- Improve short and long-term clinical benefits to patients in a minimally disruptive way to their everyday lives due to the short-course oral treatment.
- Avoid irreversible disability, early disease progression and progression to a more severe type of MS due to early intensive treatment [36, 37, 38, 39, 40, 41].
- Allow access to treatment without the need for hospital visits or regular appointments for administration and/or monitoring purposes.
- Provide an alternative treatment option for patients who would like to plan for a pregnancy [4].

3i) Value and economic considerations

Introduction for patient groups:

Health services want to get the most value from their budget and therefore needs to decide whether a new medicine provides good value compared with other medicines. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the medicines already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the HTA appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g. whether you feel these are the relevant endpoints, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or adverse events of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g.

travel costs, time-off work)?

Instructions to manufacturer: This is intended as a single-page summary for patient groups and needs to be completed in non-technical language. Focus should be on a summary of the key costs/drivers used in any models, the value afforded by the medicine, and any financial implications that may be of relevance to patients/patient groups, rather than a detailed health economic justification (cost/QALY, for example).

- What were the important improvements in health from the medicine compared with the medicines already in use that support its value offering (e.g. longer survival times or reduction in severity or frequency of symptoms)? Were there important side effect differences between the medicines that support the value of the medicine?
- Would the medicine lead to any cost implications (positive or negative) for the health service (e.g. number of days in hospital)?
- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g. where it is given or the monitoring that is needed)?

Response:

As part of the submission to NICE, the manufacturer built a cost-effectiveness model to assess whether the benefits of treating patients with cladribine tablets outweighed the associated costs to the NHS in comparison to other available DMTs.

There were several factors to justify why cladribine tablets could have a positive impact on the NHS, as outlined below:

Fewer relapses within a year

When cladribine tablets were compared indirectly with other available DMTs for the treatment of RRMS, they showed that patients had fewer relapses within a year compared to other available therapies and patients were less likely to stop their treatment compared to patients who were treated with other DMTs. Cladribine tablets were also shown to be as effective as other DMTs when looking at whether patients' disability progressed over time.

Oral administration and treatment regimen

Cladribine tablets are an oral treatment and its treatment course lasts for only two weeks in Year 1 and 2. Contrary to other available DMTs that require continuous treatment and may require additional costs and NHS resources (i.e., hospital admissions for infusions, additional medications provided alongside therapy, and any additional nurse or neurologist visits to support drug administration as well as monitoring costs), cladribine tablets do not require these.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patient groups would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the HTA assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Further information on HTA and the role of patient groups**:**

- EUPATI guidance on patient involvement in HTA: Guidance for patient involvement in HTA - EUPATI Toolbox

- EFPIA – Working together with patient groups: working-together-with-patient-groups-23102017.pdf (efpia.eu)
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: The International Network of Agencies for Health Technology Assessment (inahta.org)

4b) Glossary of terms

Response:

- CIS – Clinically isolated syndrome
- Comorbidity – A disease that is simultaneously present with another (or others) in a patient.
- Cost-effectiveness model – A way to examine the relationship between the costs and health outcomes of one or more treatments.
- Debilitating disease – When the patient is very weak and infirm.
- Disability – The loss of abilities that results from damage to the central nervous system.
- DMT– Disease modifying therapy
- Fatigue – A type of exhaustion that is out of proportion to the task undertaken.
- Health distress – Emotional, social, spiritual, or physical pain or suffering that may cause a person to feel sad, afraid, depressed, anxious, or lonely.
- HRQoL– Health-related quality of life
- Infusion – Administering medicine directly into a patient's vein (sometimes referred to as intravenous infusion).
- Lymphopenia – A reduction in the number of white blood cells called lymphocytes.
- MRI – Magnetic resonance imaging
- MS – Multiple sclerosis
- Myelin sheath – The layer that surrounds and protects the brain and/or spinal cord nerves.
- NICE –National Institute for Health and Care Excellence
- Nucleoside analogue – A pharmacological class of compounds with cytotoxic, immunosuppressive, and antiviral properties.
- Placebo – An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested in a clinical study.
- PPMS – Primary progressive multiple sclerosis
- QoL– Quality of life
- Relapse – Periods when multiple sclerosis symptoms flare up aggressively.
- Remission – Periods of good or complete recovery
- RRMS – Relapse Remitting Multiple Sclerosis
- SPMS – Secondary progressive multiple sclerosis

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

[1] NHS, “Multiple Sclerosis Overview,” 2022. [Online]. Available: https://www.nhs.uk/conditions/multiple-sclerosis/#:~:text=Multiple%20sclerosis%20(MS)%20is%20a,it%20can%20occasionally%20be%20mild..

[2] Multiple Sclerosis Trust, “MS information and support,” 2022. [Online]. Available: Available from: https://mstrust.org.uk/information-support/about-ms/what-is-ms.

[3] Zuvich et al, “Genetics and pathogenesis of multiple sclerosis.,” *Semin Immunol,* pp. 21(6): p. 328-33, 2009.

[4] Walton et al, “Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition.,” *Mult Scler,* pp. 26(14): p. 1816-1821, 2020.

[5] World Health Organization, “Atlas of multiple sclerosis,” 2013. [Online]. Available: http://www.msif. org/includes/documents/cm_docs/2013/m/msif-atlas-of-ms-2013-report. pdf?f=1, 2013.

[6] Montalban et al, “ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis.,” *Mult Scler,* pp. 24(2): p. 96-120., 2018.

[7] Scolding et al, “Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis,” *Pract. Neurol,* pp. 15(4): p. 273-279., 2015.

[8] Ragonese et al, “Mortality in multiple sclerosis: a review.,” *Eur. J Neurol,* pp. 15(2): p. 123-127, 2008.

[9] Confavreux and Vukusic, “The clinical course of multiple sclerosis. Handb.,” *Clin. Neurol,* pp. 122: p. 343-369., 2014.

[10] Marrie et al, “Effect of comorbidity on mortality in multiple sclerosis.,” *Neurology,* 2015.

[11] Hauer, Perneczky and Sellner, “A global view of comorbidity in multiple sclerosis: a systematic review with a focus on regional differences, methodology, and clinical implications.,” *Journal of Neurology,* pp. 268(11): p. 4066-4077., 2021.

[12] Merck Group, “Great Britain is first across Europe to get regulatory approval of MAVENCLAD® (cladribine tablets) as the only short course oral treatment for active Relapsing Multiple Sclerosis patients.,” 23 April 2024. [Online]. Available: https://www.merckgroup.com/uk-en/press-releases/GB-Mavenclad-27-Mar-2024-Local-Press-Materials-for-Announcements-press-release-for-the-label-expansion.pdf..

[13] Ramirez et al, “Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review.,” *BMC Neurology,* p. 21(1): p. 468., 2021.

[14] H. e. a. Moore, “Fatigue in multiple sclerosis: A UK MS-register based study.,” *Multiple Sclerosis and Related Disorders,* p. 64, 2022.

[15] Moore et al, “Fatigue in multiple sclerosis: A UK MS-register based study.,” *Multiple Sclerosis and Related Disorders,* p. 64, 2022.

[16] Mayer et al, “Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies.,” *Multiple Sclerosis and Related Disorders,* p. 30: p. 2, 2019.

[17] Simpson, Mowry and Newsome, “Early Aggressive Treatment Approaches for Multiple Sclerosis.,” *Current Treatment Options in Neurology,* p. 23(7): p. 19, 2021.

[18] Croft et al, “MS Forward View: a consensus for the future of MS services.,” *Mult Scler Trust,* pp. 9: p. S5-S48., 2016.

[19] Mynors, Bowen and Doncaster, “MS Specialist Nursing in the UK 2016: Report on progress towards equitable provision.,” *Mult Scler Trust,* 2016.

[20] Costello and Halper, “Multiple Sclerosis: Key Issues in Nursing Management.,” 2004.

[21] Rog et al, “Understanding the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis.,” *Journal of Neurology, Neurosurgery & Psychiatry,,* p. 93(9): p. e2., 2022.

[22] Orme et al, “The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK.,” *Value in Health,* pp. 10(1): p. 54-60., 2007.

[23] Karampampa et al, “Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries,” *Mult. Scler,* pp. 18(2 Suppl): p. 7-15., 2012.

[24] Jonker et al, “Summarizing Patient Preferences for the Competitive Landscape of Multiple Sclerosis Treatment Options.,” *Med Decis Making,* pp. 40(2): p. 198-211., 2020.

[25] MHRA, “Summary of product characteristics: Cladrine tablets,” 2024. [Online]. Available: Microsoft Word - 156867037728575770_spc-doc.doc (mhraproducts4853.blob.core.windows.net).

[26] MHRA, “Patient Infromation Leaflet: Cladribine tablets,” 2023. [Online]. Available: b566a40253c1562cc6df002f85ccb2139a2d94c5 (mhraproducts4853.blob.core.windows.net).

[27] Leist and Weissert, “Cladribine: mode of action and implications for treatment of multiple sclerosis.,” *Clin Neuropharmacol,* pp. 34(1): p. 28-35, 2011.

[28] Giovannoni et al, “A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.,” *N Engl J Med,* pp. 362(5): p. 416-26., 2010.

[29] Giovannoni et al, “Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study,” *Mult Scler,* pp. 24(12): p. 1594-1604, 2018.

[30] National Institute for Health and Care Excellence, “Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA493),” 2017.

[31] Giovannoni et al, “Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study.,” *Mult Scler,* pp. 29(6): p. 719-730, 2023.

[32] Treadaway et al, “Factors that influence adherence with disease-modifying therapy in MS,” *J Neurol,* pp. 256(4): p. 568-576., 2009.

[33] Devonshire et al, “The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis,” *Eur. J Neurol,* pp. 18(1): p. 69-77., 2011.

[34] Menzin et al, “Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis,” *J Manag. Care Pharm,* pp. 19(1 Suppl A): p. S24-S40., 2013.

[35] Wicks et al, “Preferred features of oral treatments and predictors of non-adherence: two web-based choice experiments in multiple sclerosis patients.,” *Interact. J Med. Res,* p. 4(1): p. e6., 2015.

[36] Filippi et al, “Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis,” *J Neurol, 2022,* pp. 269(3): p. 1670-1677, 2022.

[37] Casanova et al, “Escalation vs. Early Intense Therapy in Multiple Sclerosis,” *J Pers Med,* p. 12(1), 2022.

[38] Pipek et al, “Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis,” *Mult Scler Relat Disord,* p. 71: p. 104581, 2023.

[39] Harding et al, “Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis,” *JAMA Neurol,* pp. 76(5): p. 536-541., 2019.

[40] Prosperini et al, “Induction Versus Escalation in Multiple Sclerosis: A 10-Year Real World Study,” *Neurotherapeutics,* pp. 17(3): p. 994-1004., 2020.

[41] Freeman et al, “High-Efficacy Therapies for Treatment-Naïve Individuals with Relapsing–Remitting Multiple Sclerosis.,” *CNS Drugs,* pp. 36(12): p. 1285-1299., 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID6263]

Clarification questions

August 2024

File name	Version	Contains confidential information	Date
ID6263 Cladribine for RRMS	**1**	**Yes**	**02.08.2024**

Section A: Clarification on clinical effectiveness data

A1. Endpoints

1. **Please clarify the definition of the primary endpoint annualised relapse rate (ARR)?**

In the CLARITY trial, ARR was defined as an increase of 2 points in at least one functional system of the Kurtzke Functional Systems (KFS), also known as Expanded Disability Status Scale (EDSS), or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement [1]. The definition is provided in the CS, Document B, Table 7.

2. **CDP 6 months was included as part of post-hoc analyses, why was this not part of a pre-specified analysis? Can you please provide a rational.**

At the time of the CLARITY trial initiation, 3-month confirmed disability progression (CDP) was the recommended endpoint to measure disease progression. All older studies evaluating the efficacy of disease-modifying therapies (DMTs) for the treatment of patients with relapsing, remitting multiple sclerosis (RRMS) report 3-month progression data only. Since then, there have been developments in the definition of sustained accumulation of disability (3-month versus 6-month CDP) and assumptions on the durability and magnitude of treatment benefit beyond the duration of a clinical trial. This has led the European Medicines Agency (EMA) to release guidance recommending the use of the 6-month definition of CDP:

“An accurate and reliable definition of confirmed progression is important and should include two consecutive examinations carried out by the same physician at least 6 months apart.” [2].

In line with the EMA guidance, Merck conducted post-hoc analyses for 6-month CDP and presented them alongside 3-month CDP analyses, which were pre-specified.

The above explanation was provided by Merck in the clarification letter in 2017 in response to the same question, which was asked by the EAG committee in the 2017 cladribine NICE submission.

A2. Section B1.2.2, page 20, document B: it was stated that the treatment initiation time depends on lymphocyte count and platelet counts, however, there was no details on this specific group of patient (for instance who started late for yr 1/yr 2 treatment), including the number of patients, how blinding retained, and time of endpoint calculation. Could you please clarify?

The following statement on page 20 of Document B is the method of administration from cladribine EMA Summary of Product Characteristics (SmPC): “Lymphocyte counts must be normal before initiation of cladribine tablets in Year 1, and patients should have at least 800 cells/mm^3 before initiation of cladribine tablets in Year 2. In the absence of this, a treatment course could be delayed for up to 6 months to allow lymphocyte counts to recover [3].”

Overall, in the CLARITY trial, a total of four patients required a delay in the treatment course: two patients in the placebo arm and two patients in the 5.25 mg/kg cladribine tablets arm (patients in the 5.25 mg/kg cladribine tablets arm are not relevant for this submission) [4]. No delays in the treatment course were reported for patients receiving cladribine tablets 3.5 mg/kg. Therefore, the blinding was retained and no issues on the time of endpoint calculation were reported.

The two patients in the placebo arm required a delay in the treatment administration due to relapses, for which they both received rescue treatment (steroids). One patient received no further courses of treatment because of disease progression and was placed on rescue medication but remained in the study for follow-up and completed all of the study assessments through Week 96. The other patient receiving placebo reported for two follow-up visits after completing the initial four courses and then was withdrawn from the study because of a protocol violation, i.e., the patient was not attending study visits [4].

A3. Could you please clarify the methods of the SLR and the NMA?

SLR methods

The systematic literature review (SLR) reviewed published evidence using a reproducible and validated comprehensive search strategy comprised of disease terms, a study design filter and approved intervention terms, to assess the comparative efficacy, safety, and tolerability associated with key interventions in the treatment of RRMS. The study design filter was adapted from the Scottish Intercollegiate Guidelines Network guidelines to identify randomised clinical trials (RCTs) using a combination of Emtree/Medical Subject Headings

(MeSH) and free text terms for Embase and Medline, Medline in process, and Cochrane (Appendix D Table 1-3).

Studies identified in the literature search had to meet pre-defined eligibility criteria in order to be included in the review (Document B, Table 6). Abstracts of citations identified through the searches were reviewed for inclusion based on title and abstract alone by two independent reviewers; any discrepancies were reconciled by a third reviewer. Full-text copies of studies that met the screening criteria were obtained and screened by two independent reviewers; any discrepancies were reconciled by a third reviewer. Data from each study was extracted by two independent reviewers and any discrepancies were reconciled by a third independent reviewer. A critical appraisal of the study, using the assessment criteria recommended in the NICE manufacturer's template, was also conducted in a similar manner.

Original searches were conducted on 5 February 2016, with further updates conducted on 4 January 2017 (to support the previous NICE submission for cladribine tablets, TA493), as well as updates conducted on 16 April 2023, and on 6 February 2024 to ensure all contemporary evidence from database inception until 6 February 2024 was included to support the present submission.

NMA methods

RCTs identified in the SLR (detailed in Section B.2.1 and Appendix D) informed the NMA to establish the comparative effectiveness of cladribine tablets against DMTs listed in the NICE final scope in patients with active RRMS. The NMA included DMTs recommended by NICE in patients with active RRMS. All other studies were removed from the NMA if the intervention or comparator arms were not of interest (i.e., unlicenced in the UK, not in NICE scope). As per the review inclusion criteria, the selected trials for the NMA were composed of adult patients (≥18 years) with a confirmed diagnosis of RRMS. Nonetheless, although some studies specified RRMS as an inclusion criterion, they also included a small number of patients with progressive disease. If that was the case, trials with more than 20% of progressive patients were excluded, consequently stipulating a minimum of 80% of patients with RRMS for studies that were included. A similar approach was taken in the previous NICE submissions for cladribine tablets (TA493/TA616) [5, 6] and ponesimod (TA767) [7].

The NMA was conducted with a set of Bayesian Markov Chain Monte Carlo techniques using the statistical package WinBUGS. The code for the NMA was based on that recommended by the NICE Decision Support Unit Technical Support Document (NICE DSU

TSD 2) [8]. Vague or non-informative priors were used. Three chains were run for each model. ConvEAGence and lack of auto-correlation were confirmed with autocorrelation plots after a 100,000-simulation burn-in phase.

Both fixed and random effects models were considered as part of this analysis. In the fixed effects model, it was assumed that each study in the network is generating a common true effect, with between study variations in effect arising from sampling error. In the random effects model, the effect of treatment in each study was assumed to come from a common distribution of effects, with between study variation in effect arising from sampling error and heterogeneity between the studies.

The choice of random versus fixed effects model was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC). The model with lowest DIC and/or the closest total residual deviance to the number of data points in the model were considered the best fitting model. In deciding the choice of fixed versus random effects models heterogeneity of trial designs, populations and evidence sources was also taken into account.

The NMA model estimates the HR for treatment discontinuation and disability progression assuming an exponential distribution and relative ARR, and a Poisson distribution for the number of relapses within one study arm.

During the discussion with the EAG during the Clarification call on 25th July (12:00pm), the EAG asked for a reason for using the arm-based approach. For meta-analysis, arm-based summaries are the preferred format. This approach allows for the definition of an exact likelihood for each trial arm and eliminates the need for adjustments. Additionally, only in the case of continuous data, contrast-based models can be employed using the normality assumption. For our analysis, the Annualised Relapse Rate (ARR) data was presented as person-time and number of relapses, while proportional data at specific time points was available for disability progression and treatment discontinuation. Given the nature of these data types, an arm-wise analysis was the appropriate approach.

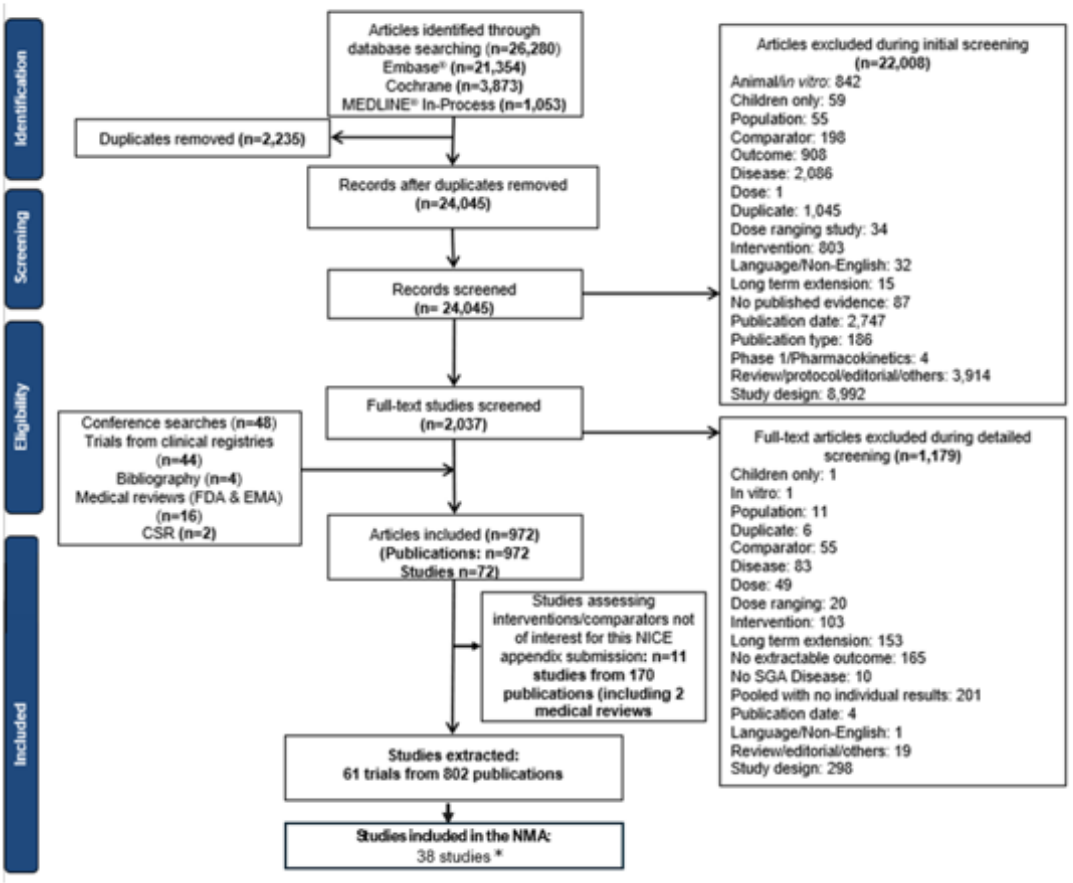
A4. Appendix D; Could you please look into the PRISMA study flow diagram, 61 trials were published in 802 publications (Appendix D, Figure 1 and table 7). Could you please clarify the PRISMA for both the SLR and NMA separately?

In the PRISMA study flow diagram (Appendix D, Figure 1 and Table 7), a total of 61 trials were published across 802 publications for the SLR, while the NMA included 38 studies. To clarify the PRISMA for both the SLR and NMA: both follow the same methodology for

identification, screening, and inclusion; however, the NMA only includes studies which passed the feasibility assessment, resulting in the total of 38 studies.

Please note, one study (Mokhber 2014) was mistakenly included in the list of studies included in the NMA. This has been now corrected, therefore, the number of studies in the NMA is 38 (not 39 as initially stated). All necessary changes were introduced in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

Figure 1: Flow of studies through the systematic review process



Note: *Of the 61 trials identified in the SLR, following the feasibility analysis, 38 studies were selected for inclusion in the NMA

CSR: Clinical study report; EMA: European Medicines Agency; FDA: Food and Drug Administration; NMA: Network meat-analysis; SGA: Sub-group analysis

A5. Appendix D, the quality assessment include 61 studies, could you please confirm the correct number of included studies?

The quality assessment was conducted for all 61 trials identified in the SLR. However, the total number of publications were 802. For your reference, please see the supplementary Excel file named: *Merck_Clinical_NICE quality assessment.*

Of the 61 studies identified in the SLR, 38 were included in the NMA.

A6. Document B, page 35: Could you clarify how the safety evidence trials were identified, such as ORACLE MS, PREMIERE?

The ORACLE MS and the PREMIERE studies were conducted by Merck, and form the evidence base for oral cladribine tablets. Whilst ORACLE MS and PREMIERE did not meet the pre-specified inclusion criteria for the clinical SLR, both studies report safety outcomes of relevance to this submission and so were included as additional evidence.

A7. Could you clarify the randomisation methods of the CLARITY-EXT study?

Randomisation in the CLARITY-EXT trial was conducted using the same procedures used in the CLARITY study [9].

In the CLARITY-EXT trial, randomisation was performed with the use of a central system and a computer-generated treatment randomisation code. Patients were assigned a unique 12-digit identification number, with the first five digits comprising the trial number, the next three digits the site number, and the final four digits the sequential subject number. For the purposes of this trial, patients retained the same last seven digits that had been assigned to them in CLARITY, and only the five-digit trial number prefix was changed. In addition to obtaining the patient identification number from the electronic case report form, the trial personnel had to register the patient in the central randomisation system by completing a screening form [10].

Overall, treatment allocation over the first 96 weeks of the CLARITY-EXT trial depended on the initial treatment randomisation in the CLARITY trial, as follows (Figure 1):

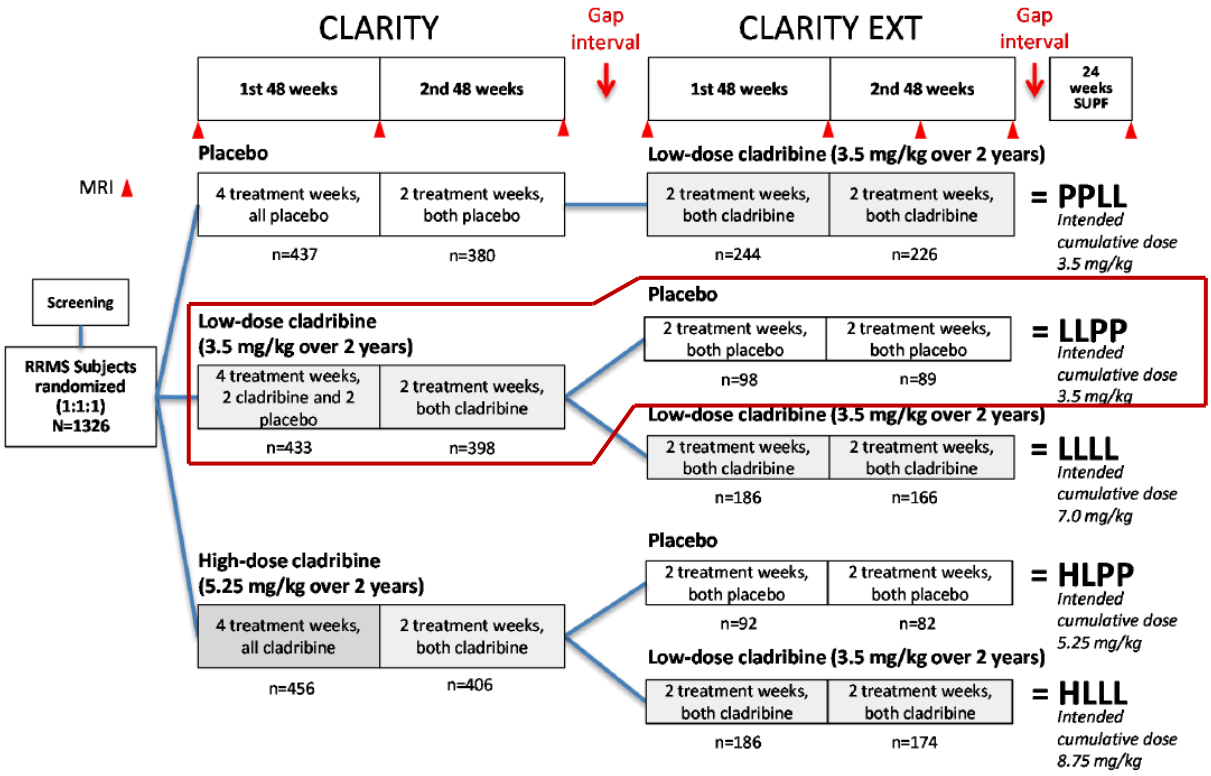
- Subjects randomised to placebo during CLARITY were assigned to low-dose oral cladribine in the 96-week extension study (a total cumulative dose of 3.5 mg/kg by body weight over 2 years).

- Subjects randomised to low-dose oral cladribine during CLARITY were re-randomized in a 2:1 ratio to receive either low-dose oral cladribine or placebo in the 96-week extension study.

- Subjects randomised to high-dose oral cladribine during CLARITY were re-randomized in a 2:1 ratio to receive either low-dose oral cladribine or placebo in the 96-week extension study.

Double-blinding was also conducted using the same procedures used in the CLARITY study [9]. The double-blinded nature of CLARITY-EXT was as follows: a treating physician, blinded to treatment, was responsible for supervision of study medication administration, monitoring of safety assessments, and the recording and treatment of adverse events (AEs) and relapses. The blinding was maintained from the CLARITY trial in all treatment arms during the CLARITY-EXT trial [10].

Figure 1. Design of the CLARITY and the CLARITY-EXT trials



Source: [1, 9]

NOTE: Red box indicates the licensed dose of cladribine tablets (cumulative 3.5 mg/kg)

HLLL: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4; HLPP: cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4; LLLL: cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4; LLPP: cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4; PPLL: Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4; RRMS: Relapsing-remitting multiple sclerosis; SUPF: Supplemental follow-up

A8. Can you provide the detailed critical appraisal table for CLARITY-EXT?

The CLARITY-EXT trial is a secondary publication of the CLARITY trial. Critical appraisal for the CLARITY trial was performed and presented in the CS (Document B, Table 11 and Appendix D.1.3, Table 18), as well as in the supplementary Excel file named *"Merck_Clinical_NICE quality assessment".* Additionally, the extraction for the CLARITY-EXT was also performed and is presented in the data extraction workbook mentioned below, however since both studies are linked and share the same methodology, the critical appraisal is performed for only the primary study (which in this case is CLARITY trial). Detailed critical appraisal of CLARITY-EXT was not added to Table 18 (Appendix D.1.3), as Table 18 focuses only on trials identified in the SLR.

For your reference, please see the supplementary Excel files named: "*Merck_Clinical_Data Extraction Grid_inception-2024"* and *"Merck_Clinical_NICE quality assessment".*

A9. The outcome specified for NMA 'Treatment discontinuation' (Document B, Figure 16) corresponds to which of the following outcome specified in Appendix D (Table 6): 'All-cause study withdrawals', 'Study withdrawals due to AEs', 'All-cause treatment withdrawals' or 'Treatment withdrawals due to AEs'?

The treatment discontinuation outcome specified in NMA (Document B, Section B.2.9.3.4, Figure 16) corresponds to all-cause treatment withdrawals.

Please note, the clarification was introduced in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

A10. When was the NMA outcomes 3-month and 6-month CDP (Document B, Figures 13 and 15) measured? at 12 or 24 months of follow-up?

The NMA outcomes, 3-month and 6-month CDP, in Document B (Figures 13 and 15) were measured at 24-months of follow-up.

Please note, the clarification was introduced in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

A11. Could you clarify if an apriori selected set of TEMs (treatment effect modifiers) were used for the NMA?

The list of covariates was identified prior to running of analyses. The selected set of covariates were: mean EDSS score at baseline, proportion of female participants in each trial, disease duration, mean age at baseline, race, one relapse in previous year and mean number of relapses in two years.

To address some of the concerns raised by the EAG, there are two points that Merck would like to highlight.

Firstly, while there is a lack of evidence for TEMs in RRMS and lack of consensus on the definite list of TEMs that should be applied when assessing effectiveness of DMTs, it is known that treatment efficacy varies widely between individuals, and how they respond to a treatment or whether they discontinue a treatment is influenced by patients' baseline characteristics (previous treatment history, and several demographic, radiological and clinical characteristics) [11]. Overall, the covariates chosen for the present NMA are broadly in line with TEMs described in the literature as relevant when considering DMT treatment outcomes [12].

Secondly, this is not a unique issue observed only for cladribine tablets as all recent NICE MS appraisals in active RRMS have faced a similar challenge in regards to TEMs selection, including ponesimod (TA767), ofatumumab (TA699) and ocrelizumab (TA533). In the committee papers for ponesimod appraisal, the EAG acknowledged that *"these discrepancies in opinion may be inevitable in a disease where population definitions are not standardised, and where there is a lack of evidence for treatment effect modifiers."* [13] and further in the ofatumumab appraisal EAG noted that *"baseline characteristics such as time since first MS symptoms and proportion of patients with prior DMTs could be potential treatment effect modifiers"* [14].

Results for meta regression based on mean EDSS score at baseline, proportion of female participants, disease duration and mean age at baseline are shared separately in the supplementary Excel file named: *“Merck_Meta-Regression-Meta Analysis and Inconsistency”.*

A12. Can you please address and assess if the NMA met important assumptions of homogeneity, transitivity, and consistency to ensure the credibility of its results? There are established methods for assessing these

assumptions besides qualitative comparisons of inclusion/exclusion criteria, baseline characteristics, and definitions of the outcome.

Tests for inconsistency and heterogeneity were carried out and reported as forest plots for ARR, CDP3M, CDP6M and treatment discontinuations. Additionally, a meta-analysis to identify and compare heterogeneity in placebo-controlled trials as well as DMT vs. DMT trials was carried out. Test for inconsistency between multiple closed loops are suggestive of low likelihood of inconsistency across the pairwise comparison. The significance of the pre-specified TEMs and/or covariates (as outlined in question A11) across different outcomes obtained via network meta-regression is shown below (Table 1). The only significant beta estimate across all the covariates across the outcomes was the covariate of age for the outcome 6-month CDP. However, the results of meta-regression were similar to the results of the NMA. For your reference, please see the supplementary Excel file named: *"Merck_Meta-Regression-Meta Analysis and Inconsistency*

Table 1. Posterior beta estimates for different outcomes

Outcome	Covariate	95% LCrI	Median	95% UCrI	Comments
3-month CDP	EDSS	[redacted]	[redacted]	[redacted]	[redacted]
	Gender	[redacted]	[redacted]	[redacted]	[redacted]
	Disease duration	[redacted]	[redacted]	[redacted]	[redacted]
	Age	[redacted]	[redacted]	[redacted]	[redacted]
6-month CDP	EDSS	[redacted]	[redacted]	[redacted]	[redacted]
	Gender	[redacted]	[redacted]	[redacted]	[redacted]
	Disease duration	[redacted]	[redacted]	[redacted]	[redacted]
	Age	[redacted]	[redacted]	[redacted]	[redacted]
Treatment discontinuation	EDSS	[redacted]	[redacted]	[redacted]	[redacted]
	Gender	[redacted]	[redacted]	[redacted]	[redacted]
	Disease duration	[redacted]	[redacted]	[redacted]	[redacted]
	Age	[redacted]	[redacted]	[redacted]	[redacted]
ARR	EDSS	[redacted]	[redacted]	[redacted]	[redacted]
	Gender	[redacted]	[redacted]	[redacted]	[redacted]
	Disease duration	[redacted]	[redacted]	[redacted]	[redacted]
	Age	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ARR: Annualised relapse rate; CDP: Confirmed disability progression; EDSS: Expanded Disability Status Scale; LCrI: Lower credible interval; UCrI: Upper credible interval

Finally, the transitivity was evaluated by comparison of the distribution of TEMs, which was done by reviewing the inclusion/exclusion criteria, baseline characteristics and outcome definitions. Additionally, to evaluate the potential impact of TEMs to check the transitivity, we assessed the meta-regression analyses.

A13. Can you please explain how connectivity of NMA nodes were assessed? What were the criteria for the connection of any given treatment node? What was the anchor for connecting the network of disease-modifying therapies (DMT)? Some of these criteria may be the same or similar DMT dose, frequency, mode of administration, similar outcome definition, etc. How did the company operationalize this process?

For DMTs where different doses were available for the same treatment, for example IFN30 and IFN40, the different doses were treated as different comparators. The mode of administration and dosing for the placebo arm varies with the intervention arm but was considered the same. The definitions for outcomes were compared across the different studies to ensure consistency and accuracy in groupings.

The differences in outcome definitions across the studies (especially for CDP outcomes) are one of the limitations of the NMA, as they can introduce additional heterogeneity and potential bias into the NMAs. However, this is not a unique issue observed only for cladribine tablets as the NMAs conducted for all recent NICE MS appraisals in active RRMS have faced a similar challenge in regards to heterogeneity of the outcomes definitions, including ponesimod (TA767), ofatumumab (TA699) and ocrelizumab (TA533).

A14. Can you please clarify how the pair-wise direct comparison meta-analysis for pooling the trials included in NMA with the same treatments was performed. Provision of forest plots with study names and necessary statistics including individual trial and pooled estimates with variability, I-square values would be helpful. This would help to assess the homogeneity assumption.

All pairwise comparison results are shared for each outcome to help assess heterogeneity. For detail, please find the supplementary Excel file named: "*Merck_Meta-Regression-Meta Analysis and Inconsistency*", Sheets named: *"Meta-Analysis_CDP3M", "Meta-Analysis_CDP6M" , "Meta-Analysis_ARR" and "Meta Analysis_Txt Disc".*

A15. For transitivity assumption, did the company use meta-regression model to evaluate and adjust (if needed) for the imbalanced TEMs, if there was any? Moreover, it would be very useful if the company could examine the rate of NMA outcomes (e.g., annualized relapse rate, treatment discontinuation) in the placebo groups of trials included in the NMA. This would add to the credibility of the NMA meeting transitivity assumption if these rates are similar. For

annualized relapse rate (ARR) did the company consider the assessment time? Were there adjustments if the time of assessment differed across trials? Was the uniformity of the anchor treatment, I.e., placebo looked at across the trials in terms of mode of administration, frequency? This would impact the connectivity of network nodes for placebo.

We performed network meta-regression for all four outcomes (ARR, 6-month CDP, 3-month CDP, and all-cause treatment discontinuation) based on four covariates (mean EDSS score at baseline, the proportion of female participant across studies, mean disease duration, and mean age at baseline). Except for mean age at baseline for the 6-month CDP outcome, none of the other TEMs were significant. The results of meta-regression were similar to those of the NMA.

Additionally, we carried out the baseline risk-adjusted NMA to understand the differences in the outcomes in the placebo arm. This analysis showed that either the results of baseline risk-adjusted NMA are similar to conventional NMA or there was no significant difference in posterior beta values. We have compared rates in the placebo arm for all the outcomes, which are presented separately in the supplementary Excel file named: "*Merck_Meta-Regression-Meta Analysis and Inconsistency*", sheet named:"*Beta_result_metaregression*".

For the ARR outcome, the time of assessment was not considered. Instead, the total number of relapses observed within a treatment group and the total number of person-years of follow-up for that treatment group as the input data were considered; this is in line with ARR analyses conducted in the NMA for the previous NICE submission for cladribine tablets (TA493) and was considered as appropriate by the EAG at the time (as described in committee papers, page 467, Table 28: *"The EAG considers that the modelling of each outcome in NMA was appropriate"*) [15].

A16. Could you please provide the table (or forest plot) indicating closed triangular loops where both direct and indirect comparisons were pooled as 'mixed treatment' evidence and show the consistency between indirect and direct effect estimates for the treatment comparison using a statistical test and presenting inconsistency factor (IF statistic) and 95% CI. For this, could you present direct, indirect, and combined mixed estimates separately (if

applicable). This is a local loop-specific test. There is also a global test for an entire network.

The results are presented in the supplementary Excel file named: *"Merck_Meta-Regression-Meta Analysis and Inconsistency"* for each outcome. Inconsistency checks were performed with results comparing indirect, direct, and mixed estimates presented in the forest plots.

A17. Could you examine the hazard ratio (HR) proportionality assumption in individual studies? To provide KM curves for those HRs to check proportionality of hazard assumption.

There are no time-to-event data or KM curves available to check the proportionality assumption. The binomial model with cloglog link function was used, which gives hazard ratio instead of odds ratio.

A18. For each included trial in the NMA, how was discontinuation measures defined?

Please find below the definitions of treatment discontinuation for studies included in the NMA. All-cause treatment discontinuation was available in the 25 RCTs included in the NMA for the discontinuation outcome.

Study/RCT included in the discontinuation NMA	Definition of treatment discontinuations
APEX 2019 (Saida 2019)	Definition not reported; All-cause treatment discontinuation rates were reported
ASCLEPIOS I 2020 (Hauser 2020)	Definition not reported; All-cause treatment discontinuation rates were reported
ASCLEPIOS 2 2020 (Hauser 2020)	Definition not reported; All-cause treatment discontinuation rates were reported
Bornstein 1987	Definition not reported
Cadavid 2009 (BECOME trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Calabrese 2012	Definition not reported
Calabresi 2014 (ADVANCE trial)	Definition not reported
CLARITY trial	Definition not reported; All-cause treatment discontinuation rates were reported
Cohen 2015 (GATE study)	Definition not reported; All-cause treatment discontinuation rates were reported
Comi 2001 (European and Canadian Glatiramer trial)	Definition not reported
Confavreux 2014 (TOWER trial)	Patients were required to discontinue treatment in the event of confirmed increases in alanine aminotransferase concentrations greater than three times the upper limit of normal, or decreases in neutrophil count below 1 × 10^9/L. Patients who discontinued study treatment underwent an 11 day accelerated elimination procedure, receiving activated charcoal (50 g every 6 h) or cholestyramine (8 g every 8 h); All-cause treatment discontinuation rates were reported
Duquette 1993 (IFNB MS trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Durelli 2002 (INCOMIN trial)	The number of patients who discontinued because of persisting disease activity or progression was slightly higher (p=0·21) in interferon beta-1a-treated patients than in the other group; the number of patients who discontinued because of adverse events or laboratory abnormalities was higher (p=0·015) in interferon beta-1b-treated patients; All-cause treatment discontinuation rates were reported
Ebers 1998 (PRISM trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Etemadifar 2006	Definition not reported

Study/RCT included in the discontinuation NMA	Definition of treatment discontinuations
EVOLVE-MS 2 2020 (Naismith 2020)	Definition not reported; All-cause treatment discontinuation rates were reported
Fox 2012 (CONFIRM trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Gold 2012 (DEFINE)	Definition not reported; All-cause treatment discontinuation rates were reported
Jacobs 1996 (MSCRG trial)	Definition not reported
Johnson 1995 (Copolymer1 trial)	Definition not reported
Kappos 2011	Definition not reported
Khan 2013 (Gala trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Kira 2022	Definition not reported; All-cause treatment discontinuation rates were reported
Knobler 1993	Definition not reported
Lublin 2013 (CombiRx trial)	Definition not reported
Mikol 2008 (REGARD trial)	Definition not reported; All-cause treatment discontinuation rates were reported
MS200527-0086 (Montalban 2019)	Definition not reported; All-cause treatment discontinuation rates were reported
O'Connor 2006	Definition not reported; All-cause treatment discontinuation rates were reported
O'Connor 2009 (BEYOND trial)	Definition not reported; All-cause treatment discontinuation rates were reported
O'Connor 2011 (TEMSO trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Opera I trial	Definition not reported; All-cause treatment discontinuation rates were reported
Opera II trial	Definition not reported; All-cause treatment discontinuation rates were reported
OPTIMUM 2021 (Kappos 2021)	Definition not reported; All-cause treatment discontinuation rates were reported
Schwid 2007 (EVIDENCE trial)	Definition not reported
Singer 2012 (REFORMS trial)	Definition not reported; All-cause treatment discontinuation rates were reported
Stefano 2012 (IMPROVE trial)	Definition not reported
Vermersch 2014 (TENERE Trial)	Any patient with an ALT increase >3× the upper limit of normal (ULN; confirmed by retest within 48 hours) was required to discontinue treatment and undEAGo further monitoring until levels normalised. Any occurrence of ALT >8× ULN or potential Hy's Law (ALT >3× ULN and total bilirubin >2× ULN) was reported as a serious AE requiring discontinuation. Confirmed neutrophil counts <1000 cells/µl, with or without signs of infection, also necessitated treatment discontinuation, as did confirmed serum amylase or lipase values of >5× ULN, with or without clinical pancreatitis; All-cause treatment discontinuation rates were reported
Vollmer 2014 (BRAVO trial)	Definition not reported

A19. Can you please re-run the NMA including the GALA study that was excluded without a clear rational as we believe it is relevant.

The NMA presented in the CS has included GALA study for assessment of ARR (B.2.9.3.1, Figures 10 and 11) and for the assessment of discontinuation (B.2.9.3.4, Figures 16 and 17) [16]. However, 3-month and 6-month CDP data were not available in the GALA study publication [17], as these outcomes were not reported in the study [16]. For this reason, the NMA presented in the CS excluded GALA study for assessment of CDP outcomes.

This question has been discussed with the EAG in the Clarification call on 25th July (12:00pm). The above rationale was accepted by the EAG and it was agreed that there is no need to re-run the present NMA.

A20. Out of 61 trials, 39 were included in NMA, with 22 trials being excluded. What were the exclusion reasons for these 22 trials? Please tabulate.

From the clinical SLR, we have a total of 61 studies and out of which 23 have not reported any outcomes, remaining 38 studies were included in the analysis (Table 2). Additionally, the RADIANCE and the SUNBEAM trials (highlighted in yellow in the table below) were excluded as they report on ozanimod, which is not currently recommended by NICE for treatment of RRMS.

Table 2: Studies reporting data for NMA

Study Count	Study Name	ARR	3mCDP	6mCDP	Treatment Discontinuation	At least 1 outcome	NMA inclusion
1	APOLITOS	✓	×	×	✓	✓	✓
2	EVOLVE-MS 2	×	×	×	✓	✓	✓
3	ASSESS	×	×	×	×	×	×
4	RADIANCE	✓	✓	✓	✓	✓	×
5	AC-0588201	×	×	×	×	×	×
6	IR.MUI.REC.1396.3.786	×	×	×	×	×	×
7	APEX	✓	×	×	✓	✓	✓
8	Saida et.al	×	×	×	×	×	×
9	GOLDEN	×	×	×	×	×	×
10	OPTIMUM	✓	✓	✓	✓	✓	✓
11	ASCLEPIOS I	✓	✓	✓	✓	✓	✓
12	ASCLEPIOS II	✓	✓	✓	✓	✓	✓
13	SUNBEAM	✓	✓	✓	✓	✓	×
14	COGNITION	×	×	×	×	×	×
15	EPOC	×	×	×	×	×	×
16	2007-006338-32	×	×	×	×	×	×
17	2008-006786-92	×	×	×	×	×	×
18	Nabavi et.al	×	×	×	×	×	×
19	NCT02727907	×	×	×	×	×	×
20	NCT01006265	×	×	×	×	×	×
21	NCT02975349	✓	×	×	✓	✓	✓
22	RIFUND-MS	×	×	×	×	×	×
23	CLARITY	✓	✓	✓	✓	✓	✓
24	CONFIRM	✓	✓	✓	✓	✓	✓
25	DEFINE	✓	✓	✓	✓	✓	✓
26	ADVANCE	✓	×	✓	×	✓	✓
27	CARE-MS II	×	×	×	×	×	×
28	CARE MS I	×	×	×	×	×	×
29	CombiRx	✓	×	✓	×	✓	✓

Study Count	Study Name	ARR	3mCDP	6mCDP	Treatment Discontinuation	At least 1 outcome	NMA inclusion
30	GATE	✓	×	×	✓	✓	✓
31	Opera 1	✓	✓	✓	✓	✓	✓
32	Opera 2	✓	✓	✓	✓	✓	✓
33	TOWER	✓	✓	✓	✓	✓	✓
34	BECOME	✓	×	✓	✓	✓	✓
35	BRAVO	✓	✓	✓	×	✓	✓
36	GALA	✓	×	×	✓	✓	✓
37	REFORMS	✓	×	×	✓	✓	✓
38	TEMSO	✓	✓	✓	✓	✓	✓
39	TENERE	✓	×	×	✓	✓	✓
40	PRISMS	✓	✓	✓	✓	✓	✓
41	REGARD	✓	×	✓	✓	✓	✓
42	TRANSFORMS	×	×	×	×	×	×
43	CAMMS223	×	×	×	×	×	×
44	BEYOND	✓	✓	×	✓	✓	✓
45	Bornstein 1987	✓	✓	×	×	✓	✓
46	Calabrese 2011	✓	×	×	×	✓	✓
47	Copolymer 1 trial	✓	✓	×	×	✓	✓
48	DECIDE	×	×	×	×	×	×
49	Etemadifar 2006	✓	×	×	×	✓	✓
50	European and Canadian Glatiramer study	✓	×	×	×	✓	✓
51	EVIDENCE	✓	×	×	×	✓	✓
52	IFNB MS trial	✓	✓	×	✓	✓	✓
53	IMPROVE	✓	×	×	×	✓	✓
54	INCOMIN trial	✓	×	✓	✓	✓	✓
55	Knobler 1993	✓	×	×	×	✓	✓
56	Mokhber 2015	×	×	×	×	×	×
57	MSCRG	✓	×	✓	×	✓	✓
58	O'Connor 2006	✓	×	×	✓	✓	✓
59	RESTORE	×	×	×	×	×	×
60	Wroe 2005	×	×	×	×	×	×
61	Kappos 2011	✓	×	×	×	✓	✓
Total							**38/61**

A21. Can you please tabulate the effect estimates per individual trial included in NMA and provide pair-wise direct comparison meta analyses (DMT vs.

placebo and DMT-1 vs. DMT-2) for the four outcomes (ARR, 3-month CDP, 6-month CDP, and treatment discontinuation) in the trials included in NMA.

Pairwise meta-analysis were conducted for DMT vs. Placebo and DMT-1 vs. DMT-2 are presented for each outcome in the supplementary Excel file named: "*Merck_Meta-Regression-Meta Analysis and Inconsistency*".

A22. The league tables for ARR, 3-month CDP, 6-month CDP, and treatment discontinuation cannot be found.

The league tables for the assessed outcomes are provided below:

Figure 2. ARR league table – fixed effect model

Figure 3. ARR league table – random effect model

Figure 4. 3-month CDP league table – fixed effect model

Figure 5. 3-month CDP league table – random effect model

Figure 6. 6-month CDP (without INCOMIN) league table – fixed effect model

Figure 7. 6-month CDP (without INCOMIN) league table – random effect model

Figure 8. Treatment discontinuation league table – fixed effect model

Figure 9. Treatment discontinuation league table – random effect model

Please note, the above figures were added in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

A23. Can you provide surface under the cumulative ranking curve (SUCRA) curves for cladribine, comparator DMTs, and placebo?

The SUCRA plots for cladribine, comparator DMTs and placebo are provided below:

Figure 10. ARR SUCRA – fixed effect model

Figure 11. ARR SUCRA – random effect model

Figure 12. 3-month CDP SUCRA – fixed effect model

Figure 13. 3-month CDP SUCRA – random effect model

Figure 14. 6-month CDP (without INCOMIN) SUCRA – fixed effect model

Figure 15. 6-month CDP (without INCOMIN) SUCRA – random effect model

Figure 16. Treatment discontinuation SUCRA – fixed effect model

Figure 17. Treatment discontinuation SUCRA – random effect model

Please note, the above figures were added in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

A24. The treatment ranking for DMTs were not provided, can you please supply this?

The SUCRA-based ranking is provided below:

Figure 18: Treatment ranking and SUCRA for ARR – Random effects model

DMF: DMF, 240 mg, bid; Ofatu: Ofatumumab, 20 mg; Teriflu14: Teriflunomide, 14 mg, qd; GA20: GA, 20 mg, qd; IFN250: IFN beta-1b, 250 mcg, od; Clad: Cladribine, 3.5 mg/kg; DRF: Diroximel Fumarate; GA40: GA, 40 mg, tiw; IFN30: IFN beta-1a, 30 mcg, q1w; Teriflu7: Teriflunomide, 7 mg, qd; IFN44: IFN beta-1a, 44 mcg, tiw; Ocre: Ocrelizumab, 600 mg; Pones: Ponesimod, 20 mg, od; IFN22: IFN beta-1a, 22 mcg, tiw

Figure 19: Treatment ranking and SUCRA for 3-month CDP – Random effects model

DMF: DMF, 240 mg, bid; Ofatu: Ofatumumab, 20 mg; Teriflu14: Teriflunomide, 14 mg, qd; GA20: GA, 20 mg, qd; IFN250: IFN beta-1b, 250 mcg, od; Clad: Cladribine, 3.5 mg/kg; DRF: Diroximel Fumarate; GA40: GA, 40 mg, tiw; IFN30: IFN beta-1a, 30 mcg, q1w; Teriflu7: Teriflunomide, 7 mg, qd; IFN44: IFN beta-1a, 44 mcg, tiw; Ocre: Ocrelizumab, 600 mg; Pones: Ponesimod, 20 mg, od; IFN22: IFN beta-1a, 22 mcg, tiw

Figure 20: Treatment ranking and SUCRA for 6-month CDP – Random effects model

DMF: DMF, 240 mg, bid; Ofatu: Ofatumumab, 20 mg; Teriflu14: Teriflunomide, 14 mg, qd; GA20: GA, 20 mg, qd; IFN250: IFN beta-1b, 250 mcg, od; Clad: Cladribine, 3.5 mg/kg; DRF: Diroximel Fumarate; GA40: GA, 40 mg, tiw; IFN30: IFN beta-1a, 30 mcg, q1w; Teriflu7: Teriflunomide, 7 mg, qd; IFN44: IFN beta-1a, 44 mcg, tiw; Ocre: Ocrelizumab, 600 mg; Pones: Ponesimod, 20 mg, od; IFN22: IFN beta-1a, 22 mcg, tiw

Figure 21: Treatment ranking and SUCRA for treatment discontinuation – Random effects model

DMF: DMF, 240 mg, bid; Ofatu: Ofatumumab, 20 mg; Teriflu14: Teriflunomide, 14 mg, qd; GA20: GA, 20 mg, qd; IFN250: IFN beta-1b, 250 mcg, od; Clad: Cladribine, 3.5 mg/kg; DRF: Diroximel Fumarate; GA40: GA, 40 mg, tiw; IFN30: IFN beta-1a, 30 mcg, q1w; Teriflu7: Teriflunomide, 7 mg, qd; IFN44: IFN beta-1a, 44 mcg, tiw; Ocre: Ocrelizumab, 600 mg; Pones: Ponesimod, 20 mg, od; IFN22: IFN beta-1a, 22 mcg, tiw

A25. Can you conduct a sensitivity analysis for the NMA's main findings by the age of trials (older vs. newer trials). Is the risk of bias comparable or different in older vs. newer trials included in NMA?

There are six studies/trials, which were published before the year 2000 – Prism trial (comparing IFN beta 22 µg, IFN beta 44 µg, and placebo), Knobler 1993 (comparing IFN beta 250 µg and placebo), IFNB MS trial (comparing IFN beta 250 µg with placebo), Bornstein 1987 (comparing GA 20 mg with placebo), Copolymer1 trial (comparing GA 20 mg with placebo), and MSCRG trial (comparing IFN beta 30 µg with placebo). For the previous NICE submission (TA493), a sensitivity analysis was performed for the RRMS population by removing these studies in response to the EAG clarification questions; the results were similar for all the outcomes assessed, therefore the analysis was not performed

again. This sensitivity analysis is provided in the supplementary Word file named: "*Merck_A25_sensitivity analysis by year of publication*". Therefore, this analysis was not performed again. Except for IFN beta 22 µg, all other interventions were included in new studies as well. By removing these trials, we will lose IFN beta 22 µg only.

Section B: Clarification on cost-effectiveness data

B1. The modelled patient population characteristics is based on characteristics of the distribution in the CLARITY trial population. Could you comment on how generalizable the CLARITY trial population is to the UK RRMS patient population with respect to the following: age, sex, EDSS state, body weight, disease duration and relapse in prior 12 months.

As outlined in the CS (Document B, Section B.3.3.1) *"The ITT population in the CLARITY trial is considered generalisable to the population with MS in clinical practice in England, given that the profile of the active RRMS group in the CLARITY trial (e.g., intention to treat) is similar to that of patients enrolled to the UK multiple sclerosis risk sharing scheme (age 39.4 years, relapses in the past 2 years [median=3], disease duration 8.8 years) [18].*" This is in line with the EAG critique's in the previous cladribine appraisal (TA493/TA616), which concluded that "*population included in the CLARITY trial representative of people with MS likely to be treated in* UK clinical practice" [15].

In addition, in the table below (Table 3), we provide information on the patient characteristics from the pivotal studies of other DMTs recently assessed by NICE which were considered as generally representative of those patients treated in the NHS as discussed in the respective guidance documents.

Table 3. Patient characteristics across studies used in recent RRMS TAs

		Ofatumumab TA699 [19]		Ocrelizumab TA533 [20]		Ponesimod TA767 [7]
Characteristic	**CLARITY**	**ASCLEPIOS I ofatumumab-teriflunomide**	**ASCLEPIOS II ofatumumab-teriflunomide**	**OPERA I ocrelizumab-IFNB-1a (Rebif)**	**OPERA II ocrelizumab - IFNB-1a (Rebif)**	**OPTIMUM (ITT)**
Age at treatment (years): mean (SE)	38.7 (0.474)	37.8-38.9	38.0-28.2	36.9-37.1	37.2-37.4	36.7
Female to male ratio	65.9%-68.8%	66-3%-68.6%	66-3%-67.3%	65.9%-66.2%	65.0%-67.0%	64.9%
Relapse in prior 12 months: mean (SE)	[redacted]	1.3 (0.7)	1.3 (0.7)	1.31 (0.65)-1.33(0.64)	1.32 (0.69)-1.34 (0.73)	1.3 (0.63)
Average patient weight (kg)	[redacted]	73.6	75.5	NR	NR	NR
Disease duration (years)	[redacted]	5.6-5.8	5.5-5.6	NR	NR	7.64*

		Ofatumumab TA699 [19]		Ocrelizumab TA533 [20]		Ponesimod TA767 [7]
EDSS mean	**2.8-2.9**	2.9-3	2.9	2.75- 2.86	2.78-2.84	2.56

*Time since first symptoms at randomisation

Please see the relevant sections in the three final guidance documents which describe generalisability of previous DMT clinical trials:

- Final guidance TA767: Section 3.5, pg. 9: Ponesimod for treating relapsing–remitting multiple sclerosis (nice.org.uk)
- Final guidance TA699: Section 3.5, pg. 8: Ofatumumab for treating relapsing multiple sclerosis (nice.org.uk)
- Final guidance TA533: Section 3.6, pg. 9-10: Ocrelizumab for treating relapsing–remitting multiple sclerosis (nice.org.uk)

B2. How were the hazard ratios generated from the NMA for treatment discontinuation (Table 17 of Appendix D) converted to annual probabilities of discontinuation (Table 37 of CS document B)

The placebo mean effect size (meanPla) and the precision (precPla) based on all the studies with placebo as one of the arms were calculated and then the two variables were passed in WINBUGS code below:

```
# with precision (1/variance) precA, over a time period timeA, where time A is 1 year
A ~ dnorm(meanPla,precPla)
for (k in 1:nt) {
cloglog(T[k]) <- log(timeA) + A + d[k]
}
```

Where T[k] is the annualised probabilities of discontinuation, nt: number of treatments and d[k]: is treatment effect for kth treatment vs placebo

B3. What constitutes Best Supportive Care (BSC) or how is BSC defined in the model?

BSC comprises all forms of supportive therapy given to treat the symptoms of MS, including drug therapy, physiotherapy and counselling. As assumed in previous NICE MS appraisals, BSC (i.e., largely symptom management) is assumed to incur zero cost as disease management costs are already considered in the model for all patients (i.e., EDSS health state costs) [7, 19].

B4. In the CLARITY trial, patients randomised to placebo, are they on any treatment or than a DMT for RRMS?

For all patients included in the CLARITY trial (those in cladribine tablets arms and in the placebo arm), corticosteroids were permitted for the treatment of acute relapses at the discretion of the Treating Physician. Steroid treatments for relapses were to consist of 1g IV solumedrol for three days. If not possible, oral steroids could be utilised for not more than fourteen days following a relapse.

Additionally, for all patients included in the CLARITY trial, any medications that were not excluded by the protocol, considered necessary for the patient's welfare and that would not interfere with the trial medication, may have been provided at the discretion of the Investigator [4].

Patients were not permitted to use any investigational drugs or any of the following therapies (as listed in the exclusion criteria) [4]:

- Immunomodulatory therapy (including but not limited to glatiramer acetate, interferons, or natalizumab; with the exception of Rebif, to be given as rescue medication at a dose of 44 µg three times per week)
- Immunosuppressive therapy (including but not limited to cyclophosphamide, mitoxantrone, cyclosporin, methotrexate, and azathioprine)
- Cladribine (outside of the current trial protocol), total lymphoid irradiation, myelosuppressive therapy, campath-1h, IVIG and plasmapheresis
- Cytokine or anti-cytokine therapy

The concomitant usage of medications that could affect GI motility and absorption of cladribine, including proton pump inhibitors, H2 antagonists, etc., were strongly discouraged and were to be discussed with the Sponsor Medical Responsible prior to use [4].

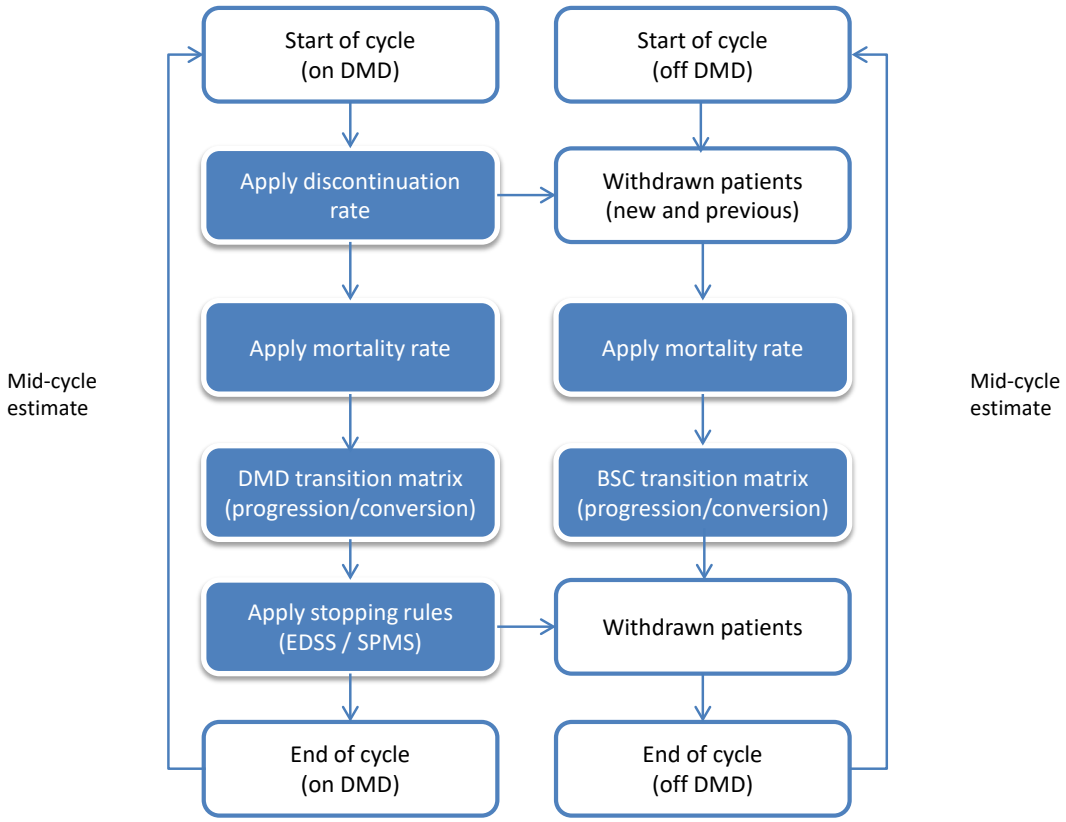
The use of any herbal/natural products or other unconventional remedies was discouraged [4].

B5. Could you clarify how the acquisition costs of other DMTs are applied with regard to mid-cycle occupancy and how this differs from the how the costs of cladribine tablets. A section of the report (section B.3.2.2.2) states that "In line with the approach in previous RRMS economic models (as mentioned in Table

28), the majority of costs are modelled based on the mid-cycle occupancy for each state, which is estimated from the average number of patients in each state at the start and end of each cycle (e.g., equivalent to half-cycle correction). The exceptions are the acquisition and administration costs for cladribine tablets, which are given at model entry and at the start of Year 1. These costs are applied to state occupancy at the start of each "treated" cycle. This is aligned with TA493/TA616 [25]."

To mitigate the risk of under- or over-estimating costs and effects, the model applies a half-cycle correction, with EDSS and drug-related costs and QALY being modelled based on midpoint estimates assuming that patients, on average, transition mid-way through the model cycle. Therefore, following the calculation process in Figure 22, the annual drug acquisition costs (length of the cycle period) of each DMT, except cladribine, are multiplied by the mid-cycle occupancy (i.e., the average of the number of patients starting each cycle and the number of patients at the end of each cycle after applying the discontinuation rate, mortality rate, EDSS progression and stopping rule).

Figure 22: Calculation process for DMD-treated patients



BSC: Best supportive care; DMD: Disease modifying drugs; EDSS: Kurtzke Expanded Disability Status Scale; SPMS: Secondary progressive multiple sclerosis

Unlike its comparators (i.e., continuously administered DMT), cladribine is a fixed course

treatment that has a unique posology that recommends two short treatment courses (i.e., only two weeks per year) administered over 2 years, with an interval of 12 months between the first and second courses. Thus, cladribine acquisition cost is accrued at the start of the model cycle as therapy is given as a fixed course at the beginning of each cycle period. A similar approach to calculating cladribine acquisition cost was used in the NICE submission for ofatumumab, and which was considered as appropriate by the EAG at the time (as described in committee papers for TA699, page 283: "*For alemtuzumab and cladribine, the full costs are incurred for those who discontinue treatment part way through the model cycle since these treatments are administered at the start of each treatment year. For all other DMTs, costs are calculated based on the half-cycle corrected state occupancies in the usual fashion; in effect this means half the annual cost is applied. All costs for each of the DMTs were checked by the EAG using the BNF online database and previous MS appraisals (e.g. TA6245, ongoing NICE appraisal of siponimod [ID1304]) and in general, the annual costs were believed to have been derived appropriately."*) [14].

B6. PRIORITY: Please clarify whether the discontinuation rates reported in the RCTs included in the NMA for discontinuation also encompass people who discontinue due to disease progression to SPMS. If so, this may result in double counting, as discontinuation due to progression is already included in the model. This is noted in the statement on page 105 of CS document B: "The modelling of discontinuation due to the onset of SPMS causing an inability to walk was captured through the transition of patients between EDSS states, and the application of a 'discontinuation rule' for patients who transition beyond a set EDSS level in the model. It was assumed that any patient transitioning to EDSS state 7.0 or greater would be considered SPMS and hence discontinued from therapy in line with previous appraisals [93-95, 98]. The modelling of discontinuations due to reasons unrelated to clinical diagnosis (e.g., tolerability) was captured through a separate annual discontinuation probability, based on the NMA, applied in each cycle; see Section B.3.3.3.5 for more detail." Please clarify that there is no double counting with respect to treatment discontinuation in the economic model.

The clinical discontinuation/stopping rules (i.e., stopping DMT at EDSS ≥7.0 and progression to SPMS) are in line with NHS guidance regarding treatment discontinuation for MS [21], and were applied in the majority of previous NICE MS appraisals including NICE-recommended DMTs for RRMS (TA254, TA303, TA312, TA320, TA533, TA624, TA699, TA767) [7, 19, 20,

22-26], and the 2017 cladribine NICE submission (TA493) [5]. Additionally, this approach was accepted by the EAG, as described in committee papers for TA493:[15]

- Page 519: *"The EAG considers that a more realistic approach to modelling discontinuation is, therefore, to use trial treatment discontinuation rates where available and then assume treatment would continue whilst the patient receives benefit, which, in the company model, is up until a patient reaches EDSS state 7"*

- Page 589: *"a more realistic approach is to use trial treatment discontinuation rates where available (i.e. for cladribine and alemtuzumab) & assume treatment would continue whilst the patient receives benefit for the other treatments (in the company model until a patient reaches EDSS state 7)"*

The stopping rule, however, can be removed from the model by applying it only to patients who progress to EDSS 10 (i.e., death) in the "*Clinical - treatment persist*" sheet. A scenario was performed where the stopping rule was not applied. In this scenario, cladribine remains cost-effective as shown in Table 4.

Table 4: Scenario analysis without stopping rule results for active RRMS at list price – Pairwise comparison (cladribine vs. comparator)

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine vs. comparator (£/QALY)
Cladribine Tablets	99,319	21.055	9.511	-	-	-	-
BSC	58,541	21.055	7.684	40,778	0.000	1.827	22,316
Peginterferon	91,797	21.055	8.414	7,522	0.000	1.096	6,860
Interferon beta-1a 30 µg	93,211	21.055	8.151	6,108	0.000	1.360	4,492
Interferon beta-1a 22 µg	93,291	21.055	8.040	6,028	0.000	1.471	4,097
Glatiramer acetate	95,170	21.055	8.138	4,149	0.000	1.373	3,023
Interferon beta-1a 44 µg	95,931	21.055	7.994	3,388	0.000	1.517	2,233
Interferon beta-1b 250 µg	105,947	21.055	8.709	-6,629	0.000	0.802	Cladribine tablets dominant
Ponesimod	123,112	21.055	8.188	-23,793	0.000	1.323	Cladribine tablets dominant
Teriflunomide	125,236	21.055	7.959	-25,917	0.000	1.552	Cladribine tablets dominant
Diroximel fumarate	155,824	21.055	8.279	-56,505	0.000	1.232	Cladribine tablets dominant
Dimethyl fumarate	160,994	21.055	8.302	-61,675	0.000	1.209	Cladribine tablets dominant
Ocrelizumab	163,623	21.055	8.654	-64,304	0.000	0.857	Cladribine tablets dominant
Ofatumumab	164,711	21.055	8.543	-65,392	0.000	0.968	Cladribine tablets dominant

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Please note, the necessary changes were introduced in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

B7. On page 106 of CS document B, the following sentence suggests a trend towards lower relapse rates in RRMS in recent years compared to the past: "By relating relapse rate to EDSS state, previous models incorporated an additional indirect effect of DMT on relapse rate through its effect on progression rate, which leads to double counting of the benefits of DMT when applying independent effects to both EDSS progression and relapse rate. This approach

also relies upon historical data from previous UK MS surveys dating back at least 10 years that may not accurately reflect relapse rates in contemporary practice given the trend towards lower annualised rates in the placebo arms of contemporary clinical trials [102, 128, 176]." Can the company provide a rationale or explanation for the observed trend of lower relapse rates in recent years, particularly in the placebo arms of RCTs? The EAG is concerned that this may be due to the selection of well-fit patients for RCTs and the enhanced care they receive as part of the RCT, which may result in lower relapse rates compared to those seen in clinical practice.

The observed trend for lower relapse rates in recent years is well known and has been described in several publications [27-34]. All recent NICE MS appraisals in active RRMS have faced a similar challenge. Therefore, this is not a unique issue observed only for cladribine tablets.

To address some of the concerns raised by the EAG, there are a few points that Merck would like to highlight.

The ARR in the model was assumed to be independent of EDSS. Relapse rate modelled as a function of EDSS state was explored in the sensitivity analysis presented in the CS (Document B, Table 61, Scenario S2). However, only results for cladribine tablets vs. ofatumumab, ocrelizumab and ponesimod were included, as they are the most relevant comparators given that they are high-efficacy DMTs used to treat active RRMS. To address concerns raised by the EAG, the same scenario was performed for all comparators. The results showed that cladribine was dominant vs. ponesimod, ocrelizumab, ofatumumab, dimethyl fumarate, diroximel fumarate, interferon beta-1b 250 µg and teriflunomide in the pairwise comparisons. In this alternative scenario, cladribine tablets also remained highly cost-effective (ICERs under £11.5k per QALY) vs. the other DMTs (interferons and glatiramer acetate) as shown in Table 5.

Table 5: Scenario analysis with relapse rate modelled based on EDSS state – Pairwise comparison (cladribine vs. comparator)

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine vs. comparator (£/QALY)
Cladribine Tablets	111,159	21.055	9.240	-	-	-	-
BSC	70,549	21.055	7.643	40,610	0.000	1.596	25,442
Interferon beta-1a 22 µg	101,115	21.055	7.988	10,044	0.000	1.252	8,024
Glatiramer acetate	101,412	21.055	8.079	9,747	0.000	1.161	8,398
Peginterferon	101,434	21.055	8.357	9,725	0.000	0.883	11,014
Interferon beta-1a 30 µg	101,930	21.055	8.096	9,229	0.000	1.144	8,070
Interferon beta-1a 44 µg	104,269	21.055	7.945	6,890	0.000	1.294	5,323
Interferon beta-1b 250 µg	111,660	21.055	8.626	-501	0.000	0.613	Cladribine tablets dominant
Ponesimod	127,000	21.055	8.130	-15,841	0.000	1.109	Cladribine tablets dominant
Teriflunomide	127,126	21.055	7.907	-15,967	0.000	1.333	Cladribine tablets dominant
Diroximel fumarate	154,185	21.055	8.214	-43,026	0.000	1.025	Cladribine tablets dominant
Dimethyl fumarate	157,908	21.055	8.235	-46,749	0.000	1.004	Cladribine tablets dominant
Ofatumumab	162,678	21.055	8.471	-51,519	0.000	0.769	Cladribine tablets dominant
Ocrelizumab	165,155	21.055	8.587	-53,996	0.000	0.653	Cladribine tablets dominant

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Additionally, we performed a scenario analysis, where the mean ARR of patients in BSC was doubled in the base case (e.g., ARR of 0.68 instead of the observed 0.34 in the CLARITY trial). In this scenario, there is a small (favourable for cladribine tablets) impact on the model results, with cladribine tablets being dominant vs. ponesimod, ocrelizumab, ofatumumab, dimethyl fumarate, diroximel fumarate, interferon beta-1b 250 µg and teriflunomide in the pairwise comparisons. Cladribine tablets also remained highly cost-effective (ICERs under £11.5k per QALY) versus other therapies compared (interferons and glatiramer acetate) as shown in Table 6.

Table 6: Scenario analysis doubling the annualized rate of relapse in BSC patients – Pairwise comparison (cladribine vs. comparator)

Technologies (from least to most expensive)	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER cladribine vs. comparator (£/QALY)
Cladribine Tablets	106,636	21.055	9.255	-	-	-	-
BSC	66,839	21.055	7.656	39,797	0.000	1.599	24,890
Peginterferon	96,798	21.055	8.372	9,837	0.000	0.883	11,146
Interferon beta-1a 22 µg	96,892	21.055	8.002	9,743	0.000	1.253	7,778
Glatiramer acetate	97,106	21.055	8.093	9,529	0.000	1.161	8,205
Interferon beta-1a 30 µg	97,615	21.055	8.110	9,021	0.000	1.144	7,883
Interferon beta-1a 44 µg	100,089	21.055	7.959	6,546	0.000	1.295	5,053
Interferon beta-1b 250 µg	106,752	21.055	8.643	-117	0.000	0.612	Cladribine tablets dominant
Ponesimod	122,609	21.055	8.145	-15,974	0.000	1.110	Cladribine tablets dominant
Teriflunomide	123,026	21.055	7.921	-16,391	0.000	1.334	Cladribine tablets dominant
Diroximel fumarate	149,730	21.055	8.229	-43,095	0.000	1.026	Cladribine tablets dominant
Dimethyl fumarate	153,439	21.055	8.250	-46,804	0.000	1.005	Cladribine tablets dominant
Ofatumumab	157,955	21.055	8.487	-51,320	0.000	0.768	Cladribine tablets dominant
Ocrelizumab	160,278	21.055	8.603	-53,642	0.000	0.651	Cladribine tablets dominant

BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life years; LYG: Life years gained; RRMS: Relapsing-remitting multiple sclerosis; QALYs: Quality-adjusted life years

Finally, as demonstrated in the real-world study utilising data from the international MSBase registry (GLIMPSE), and which assessed the comparative effectiveness of cladribine tablets vs. other oral DMTs, patients treated with cladribine tablets demonstrated a significantly lower ARR than the study comparators ($p<0.05$), with a median follow-up of 11.6 to 13.2 months; ARR for cladribine tablets compared with the matched fingolimod cohort (ARR=0.09, 95% CI: 0.07–0.13 vs. ARR=0.15, 95% CI: 0.12–0.18; p=0.016), the matched dimethyl fumarate cohort (ARR=0.10, 95% CI: 0.07–0.13 vs. ARR=0.15, 95% CI: 0.11–0.19; p=0.031), and the matched teriflunomide cohort (ARR=0.09, 95% CI: 0.06–0.12 vs. ARR=0.17, 95% CI: 0.14–0.21; $p<0.001$). Similarly, treatment with cladribine tablets was statistically significantly favoured

versus other oral DMTs when assessing time to first relapse ($p<0.05$) and as well as other outcomes, which are not directly related to efficacy; for more detail on GLIMPSE study results, please refer to Appendix E, Table 28) [35]. Overall, the GLIMPSE study demonstrated that cladribine tablets are an effective treatment for treatment of RRMS in the real-world setting, confirming the efficacy of cladribine tablets observed in the pivotal clinical trials, CLARITY and CLARITY-EXT [1, 9].

Additionally, please refer to response to question B1, which also addressed the concern on generalisability of the patient characteristics in the trial population and the population expected to be observed in the clinical practice.

Please note, the necessary changes were introduced in the CS documents. For a summary of all changes, please see Table 7 in Appendix.

B8. Please provide a detailed breakdown of the calculation that converts the change in the annualized relapse rate (ARR) over 5 years from 17% (based on the BCMS data) to the 22.9% value used in the company's economic model base case. The EAG is unable to follow the calculations from the description on page 107 of CS document B: "The ARR in the BCMS decreased by an average of 17% every 5 years, based on a median follow-up of 20.6 years, 51,120 person-years of exposure, and 11,722 post-onset relapses [177]. The age of onset of MS was strongly associated with the rate of decline of ARR, with estimates ranging from 30.5% for onset ages of 40+ years to 6.9% for onset ages of less than 20 years. The mean age and disease duration of the population in CLARITY were 38.7 years and 5.18 years, respectively, with a mean age of onset between 30 and 40 years. For the base case analysis, it was therefore assumed that the ARR would decline by 22.9% (95% CI: 19.4-26.2) for every 5 years of the simulated time horizon." Please clarify how the 22.9% decline in ARR over 5 years was calculated, given the initial 17% reduction based on the BCMS data.

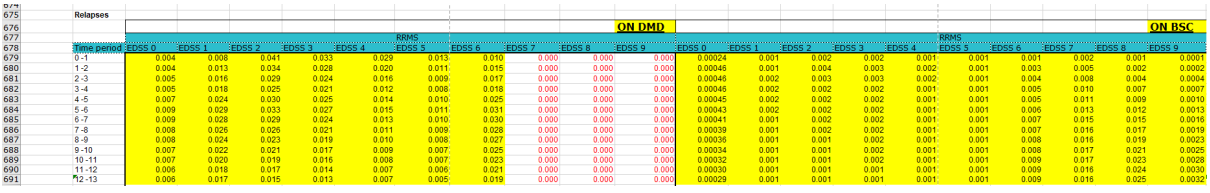
Both 17% and 22.9% decline in ARR values come from the same study (Tremlett et al. [36, 37]), which reported a retrospective statistical analysis of the relationship between ARR and characteristics of gender, age at onset, current age and disease duration using patient-level data from the BCMS registry.

The 17% reduction every 5 years was the average decline for the whole cohort in the study (i.e., regardless of the onset age) and it is not used in the model but only described in Section B.3.3.2 for completeness.

The value used in the model, i.e., 22.9%, was not calculated but directly extracted from Tremlett et al. As observed in the study, the decline in annualised relapse rate decreased with earlier onset of MS, with reported estimates of 30.5%, 22.9%, 16.9%, and 6.9% in people with onset ages of 40+ years, 30-40 years, 20-30 years and less than 20 years old respectively in the study. The mean age and disease duration of the population in CLARITY is 38.7 years and 5.18 years respectively, with a mean age of onset of between 30 and 40-years. For the base case analysis, it was therefore assumed that the ARR would decline by 22.9% (95% CI 19.4-26.2%) for every 5 years of the simulated time horizon. This has now been clarified in the CS (Section B.3.3.2)

B9. Please clarify whether or not patients in EDSS state >= 6 can relapse in the model?

All patients (i.e., all BSC patients and all patients on DMT following the discontinuation rule applied) can relapse in the model regardless of the EDSS state since the annualised relapse rates are modelled as a function of time and independent of EDSS state in the natural history reference model. The way in which the relapse rates are implemented and calculated can be verified in the model engine at rows 675 to 760 in every "*Transition sheets*" for each comparator. The following snapshot from the cladribine transition sheets (which applies for all DMTs sheets) shows the proportion of patients relapsing in all EDSS (yellow highlighted cells) except in the placeholders (in red) at EDSS state >= 7 for "ON DMD" due to the stopping rule being applied, i.e., there are no patients on DMT after progression to EDSS 7 or higher, but these patients can relapse after switching to BSC. Different discontinuation rules cutoff, enable or disable relapses in the "ON DMD" calculations depending on the EDSS level considered for discontinuation.



675	Relapses										ON DMD															ON BSC
676																										
677							RRMS													RRMS						
678	Time period	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9						
679	0 -1	0.004	0.008	0.041	0.033	0.029	0.013	0.010	0.000	0.000	0.000	0.00024	0.001	0.002	0.002	0.001	0.001	0.001	0.002	0.001	0.0001					
680	1 -2	0.004	0.013	0.034	0.028	0.020	0.011	0.015	0.000	0.000	0.000	0.00046	0.001	0.004	0.003	0.002	0.001	0.003	0.005	0.002	0.0002					
681	2 -3	0.005	0.016	0.029	0.024	0.016	0.009	0.017	0.000	0.000	0.000	0.00046	0.002	0.003	0.003	0.002	0.001	0.004	0.008	0.004	0.0004					
682	3 -4	0.005	0.018	0.025	0.021	0.012	0.008	0.018	0.000	0.000	0.000	0.00046	0.002	0.002	0.002	0.001	0.001	0.005	0.010	0.007	0.0007					
683	4 -5	0.007	0.024	0.030	0.025	0.014	0.010	0.025	0.000	0.000	0.000	0.00045	0.002	0.002	0.002	0.001	0.001	0.005	0.011	0.009	0.0010					
684	5 -6	0.009	0.029	0.033	0.027	0.015	0.011	0.031	0.000	0.000	0.000	0.00043	0.002	0.002	0.002	0.001	0.001	0.006	0.013	0.012	0.0013					
685	6 -7	0.009	0.028	0.029	0.024	0.013	0.010	0.030	0.000	0.000	0.000	0.00041	0.001	0.002	0.002	0.001	0.001	0.007	0.015	0.015	0.0016					
686	7 -8	0.008	0.026	0.026	0.021	0.011	0.009	0.028	0.000	0.000	0.000	0.00039	0.001	0.002	0.002	0.001	0.001	0.007	0.016	0.017	0.0019					
687	8 -9	0.008	0.024	0.023	0.019	0.010	0.008	0.027	0.000	0.000	0.000	0.00036	0.001	0.001	0.002	0.001	0.001	0.008	0.016	0.019	0.0023					
688	9 -10	0.007	0.022	0.021	0.017	0.009	0.007	0.025	0.000	0.000	0.000	0.00034	0.001	0.001	0.002	0.001	0.001	0.008	0.017	0.021	0.0025					
689	10 -11	0.007	0.020	0.019	0.016	0.008	0.007	0.023	0.000	0.000	0.000	0.00032	0.001	0.001	0.002	0.001	0.001	0.009	0.017	0.023	0.0028					
690	11 -12	0.006	0.018	0.017	0.014	0.007	0.006	0.021	0.000	0.000	0.000	0.00030	0.001	0.001	0.001	0.001	0.001	0.009	0.016	0.024	0.0030					
691	12 -13	0.006	0.017	0.015	0.013	0.007	0.005	0.019	0.000	0.000	0.000	0.00029	0.001	0.001	0.001	0.001	0.001	0.009	0.016	0.025	0.0032					

B10. PRIORITY: Glatiramer acetate 40 mg was excluded from the economic model due to "no data available for Glatiramer acetate 40 mg in the NMA" (page 104 of CS document B). However, the EAG has identified the GALA RCT, which compared Glatiramer acetate 40 mg to a placebo in people with RRMS. This study can be included in the NMA. For completeness, can the company update the NMA networks to include this treatment. The economic model will also need updating to include additional worksheets for Glatiramer acetate 40 mg, which

the EAG is unable to update. Here is the link to the GALA study:[https://pubmed.ncbi.nlm.nih.gov/23686821/](https://pubmed.ncbi.nlm.nih.gov/2368682

As discussed in the response to question A19, the NMA presented in the CS has included GALA study for assessment of ARR (B.2.9.3.1, Figures 10 and 11) and for the assessment of discontinuation (B.2.9.3.4, Figures 16 and 17). However, 3-month and 6-month CDP data were not available in the GALA study publication [17], as these outcomes were not measured in the study [16]. For this reason, the NMA presented in the CS excluded GALA study for assessment of CDP outcomes.

This question has been discussed with the EAG in the Clarification call on July 25th (12:00pm). The above rationale was accepted by the EAG and it was agreed that there is no need to re-run the present cost-effectiveness model.

B11. PRIORITY: Please provide the WinBUGS files used to perform the NMAs for ARR, 6-month CDP, and treatment discontinuation. The WinBUGS codes are given in appendix D of the company's submission but we require the actual files for timely re-analysis of the data and reproducibility. Ensure separate files for each of the three outcomes. The files should include the WinBUGS code and data files, or the R script and data files if the analysis was conducted by calling WinBUGS from R.

It is not possible to provide the files as a proprietary software is used to run NMA which uses the same WinBUGS code provided in the Appendix (D.1.1.4.4 Programming language for the NMA). The data input sheets used for the analyses in the present NMA are provided in the Excel file named: *"Merck_Input sheet with data from SLR",* and they can be used along with the code provided in Appendix D to replicate NMA results.

B12. The formula for applying the waning effect, as reported on page 116 of CS document B, appears to be incorrect. The correct formula should be HRw=(1−W)×HRNW. Please confirm that the correct formula has been applied in the company's economic model.

In the Clarification call on 25th July (12:00pm), the EAG confirmed that question B12 can be disregarded. However, the response to the question is provided below.

The formula **HRw=(1−(1−HRnw)×W)** described in the Section B of the submission is correct and properly implemented in the model, but we do recognize that the formula interpretation

can be misleading if W is not properly defined. In the cladribine cost-effectiveness model, W is the proportional treatment effect after applying the waning effect estimate (e.g., if a treatment waning of 25% is applied, then W is 75% of the treatment effect).

To clarify it, using as an example the CDP-6m treatment effect for cladribine (HRnw = 0.55, from NMA results) when 25% of the treatment effect waning is considered, the model considers a 75% (as W) of the treatment effect of the drug being applied in the calculations:

$$HRw=(1-(1-0.55)\times 0.75)$$
$$HRw=(1-(0.45)\times 0.75)$$
$$HRw=(1-(0.45)\times 0.75)$$
$$HRw=(1-(0.34))$$
$$HRw=0.66$$

Thus, 25% of CDP-6m waning effect for cladribine would translate into an adjusted hazard ratio (HRw) of 0.66 (as expected, higher than the initial CDP-6m HR since a higher HR means a decrease in the DMT effect/worse CDP-6m results compared to the placebo arm from NMA).

Since (1-W) is always a decimal value, the formula suggested (HRw=(1−W)×HRNW) would always generate lower HRw than the initial HR value, creating the opposite effect of a treatment waning (i.e., improving the treatment effect by decreasing the HR):

$HRw=(1-W)\times HRNW$	$HRw=(1-W)\times HRNW$
$HRw=(1-0.25)\times HRNW$	$HRw=(1-0.75)\times HRNW$
$HRw=0.75\times 0.55$	$HRw=0.25\times 0.55$
$HRw=0.42$	$HRw=0.14$

B13. PRIORITY: What assumptions are being made regarding treatment discontinuation for the Best Supportive Arm (BSU) in the economic model? Please clarify whether the discontinuation probabilities for each DMT applied in the economic model are the absolute probabilities presented in Table 37 of CS document B, or the difference in probabilities between the DMT and placebo (Table 37).

Patients who discontinue DMT are assumed to retain the cumulative benefits of treatment up to the point of discontinuation, and switch to a BSC regimen. When in the BSC regimen (i.e., supportive therapy), relapses and disability progression are modelled based on the natural history of MS (i.e., without active treatment) with no specific related cost being accrued to BSC patients other than the disease management costs already included in the model for all

patients (i.e., EDSS health state costs). Thus, discontinuation rates are not applied in the BSU but only for the DMT (active treatment).

Absolute probabilities for each DMT are applied in the base case analysis are presented in Document B, Section B.3.3.3, Table 37.

B14. For the discontinuation probabilities in Table 37 of CS document B, which estimate is being applied in the economic model as a central estimate (mean or median)?

The mean discontinuation probability estimates are being applied in the model.

B15. PRIORITY: Provide a definition of treatment discontinuation (how treatment discontinuation is assessed) in each of the studies included in the NMA for discontinuation. Table of the format below will be useful.

This question has been addressed in response to question A18.

Section C: Textual clarification and additional points

C1. Appendix D:

1. **For the systematic review of clinical evidence (Appendix D), a date of 4th January 2017 is given underneath Table 3 (Search strategy for MEDLINE® in-process via PubMed®). Please clarify if this search was updated. If not, please clarify if the version of MEDLINE available via Embase.com includes the database segments for in process and ahead of print records.**

   Searches of the electronic databases and relevant conference proceedings (Appendix Table 4 and Table 5) were made on 5 February 2016, with a further updated search conducted on 4 January 2017, 16 April 2023, and the final updated search on 6 February 2024 to ensure all contemporary evidence from database inception until 6 February 2024 was included. The search terms were designed to limit studies to ahead of print and in-process citations.

2. **For the systematic review of clinical evidence (Appendix D), only one publication per included study is cited. Please clarify if any other**

publications were used in data extraction and critical appraisal and provide references if any were.

We included 61 trials from a total of 802 publications. References for all 61 primary trials are provided. However, references for the secondary studies were not included, as they are already linked to their respective primary studies. The extraction process was conducted for all 802 publications, and the critical appraisal was performed only for the 61 primary trials, given that the methodology and linkage to primary studies made it redundant for the secondary publications to be critically appraised.

3. **The referencing in Appendix D Table 18 (NICE critical appraisal of clinical studies) is not linked to the reference list. Please confirm that the publications are the same for each study as those cited in Appendix D Table 7 or provide a revised version of table 18 with references cited for each study.**

The publications in Appendix D Table 18 are the same as the publications in Appendix D Table 7. Please see the revised version of Table 18 below with references cited for each study.

Appendix D Table 18: NICE critical appraisal of clinical studies

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
93 OPERA I trial [38]	5	A	Low risk; Patients were centrally randomized via an IVRS	Low risk; The allocation was done centrally, via an IVRS.	Low risk; Baseline demographics showed no significant differences between the 2 groups	Low risk; This was a double blind double dummy study	Low risk; There were no unexpected imbalance in the study. Reasons for withdrawals were well reported.	Not clear; This was a conference abstract and information on outcome section and reporting given in detail as provided in NCT01247324	Low risk; ITT population was used for efficacy while mITT approach was used for the safety outcomes.
131 OPERA II trial [38]	5	A	Low risk; Patients were centrally randomized via an IVRS	Low risk; The allocation was done centrally, via an IVRS.	Low risk; Baseline demographics showed no significant differences between the 2 groups	Low risk; This was a double blind double dummy study	Low risk; There were no unexpected imbalance in the study. Reasons for withdrawals were well reported.	Not clear; This was a conference abstract and information on outcome section and reporting given in detail as provided in NCT01412333	Low risk; ITT population was used for efficacy while mITT approach was used for the safety outcomes.
244 Decide Trial [39]	5	A	Low risk; Method of randomization was adequate. Randomization was done with the use of an interactive voice-response system	Low risk; Method of concealment of allocation was adequate.	Low risk; Baseline characteristics were well balanced between the treatment groups.	Low risk; This was a double blind, double dummy study. All the patients and study personnel, including the treating neurologists, were unaware of the treatment assignments.	Low risk; Drop-outs and withdrawals were well reported between all arms.	Low risk; Authors measured all the outcomes as reported in the protocol NCT01064401.	Low risk; An ITT analysis was used both for efficacy and safety outcomes.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
333 RESTORE [40]	3	A	Low risk; This was a randomize study. Randomization was performed by using a centralized IVRS at the baseline visit, and randomization was stratified by country and pretreatment disease activity (high vs low).	Low risk; Allocation concealment was adequate since randomization was performed using IVRS method	Low risk; except for baseline EDSS score, baseline demographics and disease characteristics were similar across the groups	High risk; the trial was a partially blinded trial. For a comparison of natalizumab with placebo, the trial was conducted in double blinded manner, while interferon b-1a, GA and methylprednisolone were administered to the patients in an open-label phase	Low risk, Withdrawals are reported in the study though reasons for withdrawals were not reported	High risk; Authors measured more outcomes as reported in the study protocol (NCT01071083).	Low risk; Efficacy analysis type was mITT and for safety type of analysis was ITT
386 ADVANCE trial [41]	5	A	Low risk; This was a randomized study and randomization was performed using IVRS and web based system	Low risk; Allocation concealment was adequate and treatment allocation was performed using matching placebo.	Low risk; Patients in all treatment groups had similar demographic and clinical characteristics at baseline.	Low risk; This was a double-blind study. Patients received either study drug or placebo QOW to maintain masking. All study management and site personnel, investigators, and patients were masked to treatment assignment.	Low risk; Withdrawals and reasons for withdrawals were reported adequately for all the treatment groups. The difference was not significant between the treatment groups.	Low risk; The clinical trial registry record NCT00906399 reported same number of outcomes.	Low risk; mITT analysis was used for efficacy and safety
486 BRAVO trial [42]	5	A	Low risk; A computer generated randomization schedule prepared by the Teva Global Biostatistics Unit employed a 1:1:1 treatment assignment ratio stratified by study center	Low risk; Allocation concealment was adequate since randomization sequence was computer generated	Low risk; At baseline, patients randomized to laquinimod or IFNb-1a had higher mean T2 lesion volume and were more likely to have Gd+ lesions than patients randomized to placebo. There were no other significant imbalances at baseline.	Low risk; This was an assessor blind study. Patients on laquinimod or oral placebo were evaluated in a double-blind manner, only the neurological rater was blinded to treatment with IFN beta-1a IM. In addition, matching placebo was used to preserve blinding.	Low risk; There were no unexpected imbalances in drop-outs between groups. The reasons for withdrawals were adequately reported.	Low risk; According to NCT00605215 the authors measured all the outcomes as reported in the protocol.	Low risk; An ITT analysis was used for efficacy and modified ITT for safety evaluations. Statistical methodology used was appropriate and included Cox Proportional Hazards model, Kaplan–Meier analysis, ANCOVA
1058 Kappos 2011 [43]	5	A	Low-risk; This was a randomized study. Randomization was performed with the use of an IVRS.	Low risk; Allocation concealment was adequate with the use of an IVRS.	Low risk; Patients in all treatment groups had similar demographic and clinical characteristics at baseline.	Low risk; This was a double-blind study. Both investigator and patients were blinded. All individuals directly involved in this study remain blinded to the dose of ocrelizumab. Project statisticians remained blinded until data lock and statistical analysis at week 24.	Low risk; The withdrawals, completers and the specific reasons for withdrawal were adequately reported.	Low risk; Author has measured the outcomes that have been reported in published protocol and clinical trial registry (NCT000676715).	Low risk; Efficacy and safety analysis was performed using mITT population

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
1873 REGARD trial [44]	3	A	Low risk; This was a randomized study. Treatments were assigned by a computer-generated randomization list	Low risk; Central randomization was used for allocation concealment.	Low risk; The author reported that there were no major differences in demographic and clinical characteristics between treatment groups at baseline.	Low risk; This was an open label trial. Neither the patients nor the treating physicians were blinded to treatment. However, the physicians who assessed patients at regular intervals were blinded to the treatment groups.	Low risk; Withdrawals and reasons for withdrawals were well reported.	Low risk; Author has measured the outcomes that have been reported in published protocol and clinical trial registry (NCT00078338).	Low risk; ITT method of analysis was used for efficacy outcome and for safety outcome mITT method of analysis was used. Author reported that the safety data were collected in an open-label manner, which introduces the potential for biased reporting.
3117 Gate trial [45]	5	A	Low risk; This was a randomized study. Method of randomization was adequate. Randomization was done with an interactive voice-response system and stratified by according to geographical region (EU, North America, or the rest of the world) and the number of Gd+ lesions at screening.	Low risk; Study group assignments were performed using an interactive web and voice response system.	Low risk; Baseline demographic and disease characteristics were balanced among the treatment groups	Low risk; This was a double-blind study. GA and placebo will be identical in appearance and was packaged identically and only be identified by means of a medication number. During the trial, participants, study personnel, MRI evaluators, steering committee members, and the study statistician were unaware of study group assignments.	Low risk; Withdrawals and reasons for withdrawals were well reported.	Low risk; Author has measured the outcomes that have been reported in published protocol and clinical trial registry (NCT01489254).	Low risk; Modified ITT analysis was carried out for carrying out safety and efficacy analysis. All efficacy and safety analyses were performed using the full analysis set and safety population, respectively (all randomized participants who received ≥1 study drug injection).
3897 Mokhbere 2014 [46]	4	B	Low risk; Method of randomization was adequate by using computer-generated list of random numbers	Low risk; Method of concealment of allocation was adequate.	Low risk; There was no significant difference in age, sex, or education level of participants among the three groups	Low risk; This was a double-blind trial. Method of blinding was not described. Patients and all those who are assessing the outcomes were unaware of treatment assignments throughout the study.	Low risk; Drop-outs and withdrawals were well reported between all arms.	Unclear; As no NCT ID was mentioned in paper so this parameter can't be assessed	Low risk; Efficacy analysis type was mITT and for safety type of analysis was unavailable
4111 TOWER trial [47]	5	A	Low risk; This was a randomized study. Randomization was done centrally, via an interactive voice recognition system	Low risk; The allocation was done centrally, via an interactive voice recognition system that generated an allocation sequence using a permuted-block randomization schedule with stratification according to study site and baseline EDSS score (=3.5 or >3.5).	Low risk; The treatment groups were generally balanced in terms of baseline characteristics.	Low risk; This was a double-blind study. Patients, individuals administering the interventions, and those assessing the outcomes were masked to treatment assignment (all identical in taste and appearance). Method of blinding was not reported.	Low risk; Withdrawals and reasons for withdrawals were reported.	Low risk; Authors measured all outcomes that they reported in the protocol (NCT00751881).	Low risk; Efficacy and safety analyses were performed on modified ITT population.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
4769 Gala trial [17]	4	B	Not clear; This was a randomized study but the method of randomization was unclear. During the randomization period, eligible patients were assigned to treatment groups in a 2:1 ratio (GA 40mg tiw or placebo) according to the randomization scheme produced by the study sponsor (Teva Pharmaceuticals). The randomization scheme used constrained blocks stratified by center.	Not clear; The concealment of treatment allocation was not reported.	Low risk; Baseline demographics showed no significant differences between the 2 groups	Low risk; This was a double-blind study. The investigators, the sponsor, and any personnel involved in patients' assessments, monitoring, analysis, and data management were blinded to treatment assignment. Study drugs were packaged and labelled in a way that maintained the masked nature of the study; the appearance, shape, colour, and smell were identical. Patients' general medical assessments were performed separately from the neurological assessments by 2 neurologists or physicians. The examining neurologist=physician was responsible for all neurological assessments.	Low risk; Withdrawals and reasons for withdrawals were well reported.	Not clear; It was unclear whether the author measured the same outcomes that were reported.	Low risk; Both efficacy and safety analyses were performed according to ITT principle.
4854 CombiRx trial [48]	5	A	Low risk; Randomization was adequate and was done centrally via a computerized data entry system that masked treatment arm allocation and drug dispensing to participants and all site personnel for the entire duration of the trial period	Low risk; Concealment of the allocation was adequate. It was done centrally	Low risk; Baseline characteristics were statistically balanced across treatment groups with the exception of age; results were assessed by group as well as with adjustments for age.	Low risk; This was a double blind trial and participants and all site personnel (treating clinician and an examining clinician) were blinded for the entire duration. In addition, blinding was preserved with the help of matching placebo.	Low risk; withdrawals were well balanced and reasons for withdrawals were adequately reported	Low risk; With reference to NCT00211887 authors measured all the outcomes that were pre-specified in the protocol.	Low risk; ITT analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
5531 TENERE Trial [49]	3	A	Low risk; Patients were centrally randomized via an IVRS in a 1:1:1 ratio.	Low risk; The allocation was done centrally, via an IVRS.	Low risk; Baseline demographics and characteristics were balanced. However, there was significantly lower DMT use in the past 2 years in the teriflunomide 14 mg group compared with the IFNß-1a group	Low risk; Patients were randomized 1:1:1 to teriflunomide 7 mg or 14 mg (double-blind) or IFNß-1a (open-label). Raters were blinded. The examining neurologist remained blinded to treatment and associated AEs. While the examining neurologist was blinded to treatment, patients were unblinded, which could have introduced a potential bias.	Low risk; Withdrawals were adequately reported	Low risk; Authors measured all outcomes that they reported in the protocol (NCT00883337).	Low risk; Efficacy analyses were conducted on the ITT population, which included all randomized patients. The safety analysis included m ITT population.
6025 REFORMS trial [50]	3	A	Low risk; This was a randomized study. Randomization was generated using a computer generated random code.	Low risk; Method of concealment of allocation was adequate.	Low risk; Baseline characteristics were similar between groups.	High risk; This was an open-label study except for blinded assessments of injection site reactions.	Low risk; There exists no imbalances in drop-outs between the treatment groups. Reasons for withdrawals were reported adequately.	Low risk; According to NCT00428584, the study reported all the outcomes as they reported in the protocol.	Low risk; An ITT analysis was used both for efficacy and safety outcomes.
6095 CARE-MS II trial [51]	4	A	Low risk; This was a randomized study. Method of randomization was adequate. Randomization was done with an interactive voice-response system and stratified by site	Low risk; Concealment of treatment allocation was achieved by an IVRS. Treatment group was not concealed from patients and clinicians as study drugs had distinctive adverse effects that precluded masking assignment. Clinical data integrity was however secured by stringent clinical and MRI rater masking	Low risk; Baseline characteristics were comparable between the two treatment groups.	Low risk; This was assessor blind study. Clinical data integrity was preserved by stringent clinical and MRI rater masking. In the absence of a masked rater, unmasked raters could submit EDSS assessments.	High risk; The reasons for withdrawals were well reported and there were some unexpected imbalances in drop-outs between the treatment groups.	Low risk; With reference to NCT00548405, authors measured all outcomes that were reported in protocol; Low risk: other source of bias were not identified	Low risk; A modified ITT approach was used for all evaluations. Statistical analysis used was appropriate and included HochbEAG analysis, proportional hazards model, Kaplan-Meier analysis, ANCOVA, logistic regression.
6096 CARE-MS I trial [52]	3	A	Low risk; Randomization was done by IVRS in a 2:1 ratio and it was stratified by site	Low risk; Concealment of treatment allocation was achieved by an IVRS. Treatment group was not concealed from patients and clinicians as study drugs had distinctive adverse effects that precluded masking assignment. Clinical data integrity was however secured by stringent clinical and MRI rater masking	Low risk; Baseline characteristics between both the treatment arms were comparable.	Low risk; This was single blind study (assessor blind). Patients and treating physicians were aware of the treatment allocation, but blinded reviewers assessed EDSS every three months and when a relapse was suspected	Low risk; Withdrawals and their reasons were reported.	Low risk; According to NCT00530348, the authors measured all the outcomes as they reported in the protocol.	Low risk; A modified ITT approach was used for efficacy and safety analyses. Statistical analysis used was appropriate and included HochbEAG analysis, proportional hazards model, Kaplan-Meier analysis, ANCOVA, logistic regression.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
6211 CONFIRM trial [53]	4	A	Low risk; Randomization was performed in a 1:1:1:1 ratio and stratified by site using a centralized IVRS.	Low risk; Central randomization was used for allocation concealment.	Low risk; There was no significant difference in the baseline characteristics reported between the treatment arms	Low risk; This was a double-blind study. All study management and site personnel, investigators, and patients were unaware of assignment to the BG-12 and placebo groups; examining neurologists, technicians at the MRI reading center, and members of the independent neurologic evaluation committee were unaware of all study-group assignments.	Low risk; The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00451451)	Low risk; The safety and efficacy analysis was done using mITT population
6212 DEFINE Trial [54]	5	A	Low risk Randomization was done centrally, using IVRS	Low risk: Method of concealment of allocation was adequate. To maintain concealment of the study-group assignments, each study center used separate examining and treating neurologists (all of whom remained unaware of the assignments throughout the trial).	Low risk: Author pointed that the baseline demographics and disease characteristics were similar across the study groups	Low risk: Double blind study. Placebo and DMF capsules were identical in size, shape, color, and taste. All study staff was blinded to the subjects' randomized treatment assignments for placebo and DMF	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all the outcomes that have been reported in published protocol and in clinical trial registry (NCT00420212)	Low risk; Both efficacy & safety were analyzed using mITT population.
6509 IMPROVE trial [55]	2	A	Not clear; This was a randomized study. Method of randomization was not reported	Low risk; Randomization was performed centrally.	Low risk; The author reported that patient demographics, baseline disease characteristics and baseline MRI variables were similar in both groups.	Not clear; This was a double-blind study. Method of blinding was not reported. Also it was unclear whether the participants, physician or assessor were blinded to the treatments.	Not clear; The reasons for withdrawals were not reported.	Low risk; The author measured the same outcomes as reported in protocol (NCT00441103).	Low risk; ITT method of analysis used for safety outcomes. The method of analysis for secondary efficacy outcomes of interest was unclear whereas, for the primary outcomes ITT method was used.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
6575 Calabrese 2012 [56]	2	A	Low risk; The random allocation sequence was computer generated	Low risk; Allocation concealment was adequate since randomization sequence was computer generated	Low risk; No differences were observed relative to disease duration or sex, although untreated patients were slightly older than DMT-treated patients.	Not clear; All imaging were assessed by the two experienced observers who were blinded to the patients identity and treatment. However, it was unclear whether the participants and physicians were blinded to treatment groups.	Not clear; Withdrawals and reason for withdrawals were not reported.	Not clear; It was unclear whether the author reported the same outcomes as in protocol.	High risk; The PP method of analysis was used for efficacy outcomes. Between-group differences were assessed using analysis of variance, followed by the Tukey test. Pearson chi-square was applied to test the effect of DMTs on the percentage of patients that developed new CLs compared with untreated patients.
6651 TEMSO trial [57]	5	A	Low risk; Patients were centrally randomized via an IVRS in a 1:1:1 ratio with blocks of six.	Low risk; Central randomization was used for allocation concealment.	Low risk; No significant differences were observed in baseline demographic and disease characteristics across the three groups	Low risk; This was a double blind study. The study medication teriflunomide (7 mg and 14 mg) and placebo were supplied as identical white to slightly yellow film-coated biconvex tablets sealed in child-resistant blister packs. Treating and examining neurologist were unaware of the treatment assignment.	Low risk; No unexpected imbalances in drop outs between the groups. Reasons for withdrawals were adequately reported in the study.	Low risk; Author has measured the outcomes that have been reported in published protocol and clinical trial registry (NCT00134563).	Low risk; Both efficacy and safety analyses were performed according to a modified ITT principle. The modified ITT population comprised patients who underwent randomization and were exposed to study medication for ≥1 day.
7367 TRANSFORMS trial [58]	5	A	Low-risk; This was a randomized study. Randomization was performed centrally in blocks of six within each site and was stratified according to site. Study-group assignments were performed with the use of an IVRS	Low risk; Method of concealment of allocation was adequate.	Low risk; Baseline characteristics were comparable between the study groups in terms of demographic features and disease characteristics.	Low risk; This was a double-blind study. Patients, study personnel, MRI evaluators, steering-committee members, and the study statistician were unaware of study-group assignments. Adequate blinding was achieved by double-dummy method.	Low risk; Withdrawals and reasons for withdrawals were reported.	Low risk; Authors measured all the outcomes as reported in the protocol (NCT00340834).	Low risk; Modified ITT analysis was carried out for carrying out safety and efficacy analysis. mITT population comprised of patients randomized and who received ≥one dose of study medication.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
7706 BECOME trial [59]	2	B	Not clear; This was a randomized study. Randomization was stratified by clinical site and the presence of enhancement on screening MRI	Not clear; Allocation concealment was unclear.	Low risk; The treatment groups were comparable in terms of demographic features and disease characteristics. However, greater proportion of Hispanic patients was present in the IFN beta-1b arm but no significant differences were observed in the subgroup analysis.	Low risk; This was an assessor blinded study.	Low risk; Withdrawals and reasons for withdrawals were reported. There were no unexpected imbalances in dropouts between the treatment groups.	Low risk; Authors have measured the outcomes that have been reported in published protocol and in clinical trial registry (NCT00176592).	Low risk; ITT analysis was used for efficacy. Various statistical methodologies were used viz. Fisher exact test, rank-sum tests, and Poisson regression models.
7909 CAMMS223 trial [60]	3	A	Low risk; This was a randomized study. Method of randomization was adequate. Randomization was done with an interactive voice-response system and stratified by site. Pocock and Simon minimization algorithm used to balance the study groups with regard to age, sex (<30 years or ≥30 years), sex, and baseline EDSS score (<2.0 or ≥ 2.0).	Low risk; Concealment of treatment allocation was achieved by an IVRS.	Low risk; Baseline demographic and clinical characteristics of the patients were comparable among the three treatment groups.	Low risk; This was a rater-blind, open-label study.	Low risk; Withdrawals and their reasons were reported.	Low risk; According to NCT00050778, the authors measured all the outcomes as they reported in the protocol.	Low risk; A modified ITT approach was used for efficacy and safety analyses.
8200 EVIDENCE trial [61]	3	A	Low risk; This was a randomized study. Randomization was adequate and done using a computer generated randomization list by block randomization method and was allocated equally through a centralized telephone randomization system to unblinded site personnel	Low risk; Allocation concealment was adequate, allocated equally through a centralized telephone randomization system to unblinded site personnel	Low risk; Baseline characteristics were comparable between the two treatment groups.	Low risk; This was an assessor blinded study. Both patients and investigators were unblinded to the treatment assigned. Patients were instructed to cover injection sites before scheduled and relapse-related neurologic examinations	Low risk; Drop-outs and withdrawals were well reported between all the treatment arms.	Not clear; It was unclear that author has measured same or more number of outcomes than reported.	Low risk; Efficacy analysis was performed using ITT analysis while safety using modified ITT analysis.
8574 Etemadifar 2006 [62]	3	B	Not clear; This was a randomized trial. Method of randomization was not reported	Not clear; Method of allocation concealment was not reported in the study.	Low risk; The author reported has that the three treatment groups were generally well matched at baseline with regard to age, gender, EDSS score, relapses 1 year prior to the onset of treatment, and duration of MS.	Low risk; The trial was single-blinded in that patients were aware but physicians who assessed the outcome were unaware of the treatment type that the patient had received.	Low risk; There were no withdrawal in the study. All patients completed the follow up.	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; An ITT analyses were performed for the efficacy outcomes.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
8615 O`Connor 2006 [63]	4	B	Not clear; This was a randomized study but method of randomization was not clear. Patients were randomized in 1:1:1 ratio to one of the three treatment arms. The patients were stratified by baseline EDSS score into two patient groups those with EDSS scores less than equal to 3.5 and those with scores greater than 3.5	Not clear; Allocation concealment was not reported.	Low risk; Baseline characteristics were well balanced between the treatment groups.	Low risk; This was a double-blind study. Patients were given matching placebo tablets to maintain blinding. Both relapse and disability assessments were made by the blinded neurologist.	Low risk; Withdrawals and their reasons were reported. For primary efficacy endpoint it was ITT, for other outcomes it was mITT and for T2 lesion volume data was given only for completer population	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; An ITT analysis was used for safety and for primary efficacy endpoint it was ITT, for other outcomes it was mITT and for T2 lesion volume data was given only for completer population.
8842 Wroe 2005 [64]	3	B	Not clear; This was a randomized study. Patients were randomized in blocks of six to either treatment group or placebo. Method of generation of randomization was not reported	Not clear; Allocation concealment was not reported.	Low risk; Baseline characteristics were well balanced between the treatment groups.	Not clear; Although this was a double-blind, however the details of blinding were not reported	Low risk; There were no unexpected imbalance in the study. Reasons for withdrawals were well reported.	Not clear; There was no evidence to conclude whether all outcomes assessed were reported or not.	Low risk; ITT population was used for efficacy and safety outcomes.
9463 INCOMIN trial [65]	3	A	Low risk; Randomization followed computer-generated random sequences of digits that were different for each centre and for each sex, to achieve centre and sex stratification	Low risk; Allocation concealment was adequate as randomization was done centrally by the coordinating centre.	Low risk; The baseline demographic and clinical characteristics were similar in the two treatment groups.	Not clear; The blinding was not reported. MRI outcomes assessor were blinded whereas clinical outcomes assessment was done in an open-label manner. Authors reported that their study was not double-blind but it was not clear whether the study was open-label or not.	Low risk; Withdrawals and reasons for withdrawals were adequately reported for both the treatment groups and included adverse events, progression, pregnancies and others.	Not clear; It was unclear whether authors measured more outcomes than they reported.	Low risk; Efficacy was analyzed using ITT while modified ITT analysis was employed for safety. Clinical outcomes were reported for the ITT population whereas MRI outcomes were reported only for the patients having available MRI data. Four centres did not participate in the MRI study as their MRI equipment was unable to meet study requirements. Also, four patients refused to have MRI scans. Chi-square test, Fisher's exact test for dichotomous outcomes, and parametric or non-parametric tests for continuous outcomes were used to test significance.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
9884 PRISM trial [66]	5	A	Low risk; This was a randomized study. Randomization list was computer-generated by Sereno Biometrics and stratified by centre with a block size of six.	Low risk; Allocation concealment was adequate. The study drug was packed accordingly and delivered to the centres so that treatment allocation remained concealed.	Low risk; Authors reported that baseline demographic characteristics of the patients were balanced across the treatment groups.	Low risk; This was a double-blind study. Doses were provided in identical vials. All personnel involved in the study were unaware of treatment allocation. Patients were assessed by two physicians. All injection sites were covered up at neurological examinations to ensure that masking was not compromised because of local reactions.	Low risk; Number of withdrawals and reasons for withdrawals were adequately reported.	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; Efficacy and safety analysis was performed using ITT population
10078 Copolymer 1 trial [67]	3	A	Not clear; This was a randomized study. Method of generation of randomization was not reported	Low risk; A centralized randomization scheme was use for concealment.	Low risk; The two groups were well matched for age, sex, race, duration of disease, mean relapse rate in the prior 2 years, EDSS, and ambulation index.	Low risk; This was a double blind trial. Matching placebo was used to maintain adequate blinding. A nurse coordinator at each centre distributed medication, noted concomitant treatments, and obtained blood and urine specimens for laboratory analysis. The coordinator nurse and both neurologists were blinded to study medication assignment. The safety committee was blinded throughout the course of the trial.	Low risk; There was no imbalance in drop outs from the trial. Reasons for withdrawals were not adequately reported.	Not clear; It was unclear from the published protocol (NCT00004814) whether authors measured more outcomes than they reported in the study.	Low risk; ITT analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
10121 Knobler 1993 [68]	4	B	Not clear; The study was reported to be randomized but the method of randomization was not reported	Not clear; The method of allocation concealment was not reported	Low risk; Authors reported that baseline characteristics like age, sex, mean EDSS, mean NRS, or number of exacerbations in the 2 years preceding entry into the study were comparable among the groups.	Not clear; Patients and investigators were blinded to treatment allocation. Blinding method was adequate as supplies of betaseron and placebo were identical in appearance. However it was unclear whether the assessors were blinded to the treatment groups.	Low risk; Withdrawals and their reasons were well reported.	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; Efficacy and safety analysis was based on an ITT basis and included data of patient who withdrew from the study because of becoming aware of the agent received; A discrepancy appeared in terms of number of patients randomized and number of patients enrolled. It was reported that 30 patients were randomized into five equal arms but baseline and relapse data was presented for 31 patients.
10129 IFNB MS trial [69]	3	A	Not clear; This was a randomized trial but the method of randomization was not reported	Low risk; Allocation concealment was adequate as central randomization was carried out.	Low risk; The baseline characteristics were similar across the treatment arms in terms of demographic features and disease characteristics.	Low risk; The study was reported to be double-blind. All personnel at each study site were blinded to treatment categories. MRI scans were interpreted by blinded assessors in a single centre. Also, identical vials containing lyophilized interferon beta and placebo were prepared.	Not clear; The reasons for withdrawals were not reported.	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; An ITT analysis was used for safety evaluation. Statistical methodology used was appropriate.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
10418 European and Canadian Glatiramer trial [70]	5	B	Low risk; Method of randomization was adequate by using computer-generated randomization list	Not clear; Method of allocation concealment was not reported.	Low risk; Baseline demographics and clinical characteristics did not differ significantly between the treatment arms in terms of baseline MRI characteristics, age, disease duration and EDSS score.	Low risk; This was a double-blind study. Method of blinding was not reported. All the personnel involved in the study were blinded.	Low risk; Reasons for withdrawals were well reported. More than 80% of patients were followed up in the final analysis. The study results were reported in multiple papers and there was ambiguity in the data reporting for withdrawals. The primary publication reported seven withdrawals from each arm at the end of nine months of double blind phase whereas in another paper authors reported six withdrawals each at the end of 9 months. Moreover, the patient withdrawal number in the GA arm did not add up to seven. It is nine instead of seven.	Not clear; It was unclear whether the author reported more outcomes as reported.	Low risk; Justification of the study sample size was reported. Sample size was projected based on literature data and on simulations modelled using Poisson cyclic variable. All patients were included in the final analysis. The method of last observation carried forward was employed for missing data. ANCOVA, two sided t test and Mann-Whitney test were used for statistical comparisons.
10630 MSCRG trial [71]	4	A	Low risk; This was a randomized study and Efron's biased coin method was used for randomization	Low risk; Allocation concealment was adequate. Opaque, double-sealed envelopes containing patient names and treatment assignments were used.	Low risk; Baseline characteristics were well balanced in terms of demographic, clinical disease, or MRI characteristics.	Low risk; This was a double blind study. All personnel (both neurologist and one technician) and patients were blinded to the treatment status. The vials containing study drug were identified only by ID and lot numbers	Not clear; Number of patients followed to each scheduled visit was reported, but the reasons for dropouts was not reported adequately.	Not clear; It was not clear whether authors measured more outcomes than they reported in the study: Low risk; No other sources of bias was reported.	Low risk; Data reported for both, all patients regardless of duration of follow-up and for patients in the study for ≥104 weeks. Methods used to account for missing data was not reported. An ITT population was used for safety analysis.
10831 BEYOND trial [72]	5	A	Low risk; This was a randomized study and randomization was performed using computerized (SAS based) block randomization with regional stratification	Low risk; Allocation concealment was adequate and treatment allocation was performed centrally.	Low risk; Patients in all treatment groups had similar demographic and clinical characteristics at baseline.	Low risk; Physicians and patients were double-blind to comparisons between the two doses. To ensure masking between the two doses of interferon beta-1b, medication was identical in appearance, packaging, and labelling.	Low risk; Withdrawals and reasons for withdrawals were reported adequately for all the treatment groups. The difference was not significant between the treatment groups.	Low risk; The clinical trial registry record (NCT00099502) reported same number of outcomes.	Low risk; mITT analysis was used for efficacy and safety

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
11123 CLARITY trial [1]	5	A	Low-risk; Patients were randomized by a central randomization system and allocated a computer-generated treatment randomization number.	Low risk; The allocation was done centrally.	Low risk; The treatment groups were generally balanced in terms of baseline characteristics.	Low risk; This was a double-blind study. Adequate blinding was achieved by matching placebo method.	Low risk; There were no unexpected imbalances in drop-outs between groups. The reasons for withdrawals were adequately reported.	Low risk; Authors measured all the outcomes as reported in the protocol (NCT00213135).	Low risk; ITT analysis was used for efficacy and modified ITT for safety evaluations.
10166 Bornstein 1987 [73]	2	B	Not clear; This was a randomized trial but method of randomization was not reported	Not clear; Method of concealment allocation was not reported.	Low risk; The two groups were similar in terms of distribution of baseline characteristics.	Low risk; This was a double blind trial. The neurologist performing neurological examination was unaware of the treatment while clinical assistant was responsible for reporting of patient`s self-evaluation was not blinded to the treatment.	Not clear; The reasons for withdrawals were not reported adequately.	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Low risk; mITT population was used for analysis. Statistical methods used were appropriate.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
1506_Gisleskog_2021 AC-058B201 trial [74]	4	A	Low risk; patients were randomised by assignment of a unique randomisation number using an interactive voice or web response system, supplied by an independent service provider (ICON Clinical, Research, USA). Patient randomisation was stratified by centre using a block size of four for the first two blocks and eight thereafter. The primary investigator/treating neurologist, independent evaluating neurologist, physician evaluating cardiac safety assessments, care providers, patients and sponsor were blinded to the treatment. The investigators and sponsor were blinded to the lymphocyte count results and first-dose effects of ponesimod, unless alerted for safety reasons. All ponesimod doses and matching placebo were indistinguishable and identically packaged.	Low risk; patients were randomised by assignment of a unique randomisation number using an interactive voice or web response system, supplied by an independent service provider (ICON Clinical, Research, USA). Patient randomisation was stratified by centre using a block size of four for the first two blocks and eight thereafter. The primary investigator/treating neurologist, independent evaluating neurologist, physician evaluating cardiac safety assessments, care providers, patients and sponsor were blinded to the treatment. The investigators and sponsor were blinded to the lymphocyte count results and first-dose effects of ponesimod, unless alerted for safety reasons. All ponesimod doses and matching placebo were indistinguishable and identically packaged.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; With reference to clinical trial authors (NCT01006265) measured all the outcomes that were pre-specified in the protocol.	High risk; the PP method was used. The per-protocol analysis set was defined as all randomised patients who received ≥80% of study drug from study drug initiation to the planned EOT and had ≥2 valid post-baseline MRIs at weeks 12–24. Appropriate statistical methods were reported.
4872_Saida_2019 APEX trial [75]	5	A	Low risk; randomization was performed using a centralized interactive voice/web response system (Endpoint Clinical Inc., San Francisco, CA) and was stratified by country (for more details, see Additional file 1 Additional methods).	Low risk; randomization was performed using a centralized interactive voice/web response system (Endpoint Clinical Inc., San Francisco, CA) and was stratified by country (for more details, see Additional file 1 Additional methods).	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov (NCT01838668)	Low risk; ITT analysis was used for efficacy. Appropriate statistical methods were followed. The primary and secondary endpoints were analyzed using negative binomial regression, adjusted for baseline values and region (East Asian vs. Other). Three sensitivity analyses were conducted for the primary endpoint.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
148_Kira_2022 APOLITOS trial [76]	4	B	Not clear; this was a randomized study. Randomization was stratified by geographical region (Japan or Russia) and the baseline number of gadolinium-enhancing (Gd+) T1 lesions (0 or⩾1).	Not clear; allocation concealment was unclear.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; ITT analysis was used for efficacy. Appropriate statistical methods were followed.
2962_Hauser_2020 ASCLEPIOS I trial [77]	5	A	Low risk; randomly assigned in a 1:1 ratio through interactive response technology to receive ofatumumab at a dose of 20 mg subcutaneously Q4W after 20-mg loading doses at days 1, 7, and 14 or oral teriflunomide at a dose of 14 mg once daily, for up to 30 months	Low risk; randomly assigned in a 1:1 ratio through interactive response technology to receive ofatumumab at a dose of 20 mg subcutaneously Q4W after 20-mg loading doses at days 1, 7, and 14 or oral teriflunomide at a dose of 14 mg once daily, for up to 30 months	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
2962_Hauser_2020 ASCLEPIOS II trial [77]	5	A	Low risk; randomly assigned in a 1:1 ratio through interactive response technology to receive ofatumumab at a dose of 20 mg subcutaneously Q4W after 20-mg loading doses at days 1, 7, and 14 or oral teriflunomide at a dose of 14 mg once daily, for up to 30 months	Low risk; randomly assigned in a 1:1 ratio through interactive response technology to receive ofatumumab at a dose of 20 mg subcutaneously Q4W after 20-mg loading doses at days 1, 7, and 14 or oral teriflunomide at a dose of 14 mg once daily, for up to 30 months	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
2281_Cree_2021 ASSESS trial [78]	5	A	Low risk; randomized (1:1:1) to receive fingolimod, 0.5 mg, or fingolimod, 0.25 mg, orally once per day or GA, 20mg, subcutaneously once per day using an interactive voice	Low risk; randomized (1:1:1) to receive fingolimod, 0.5 mg, or fingolimod, 0.25 mg, orally once per day or GA, 20mg, subcutaneously once per day using an interactive voice	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
3382_Naismith_2020 EVOLVE-MS 2 trial [79]	4	B	Not clear; this was a randomized study. Patients received orally administered DRF (231 mg twice daily in week 1, 462 mg twice daily in weeks 2–5) or DMF (120 mg twice daily in week 1, 240 mg twice daily in weeks 2–5) at their approved dosing regimens over the 5-week double-blind treatment period	Not clear; allocation concealment was unclear.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
6376_Comi_2017 GOLDEN trial [80]	4	B	Not clear; this was a randomized study. Eligible patients were randomised (2:1) to receive oral fingolimod (0.5 mg/day) or subcutaneous IFN β-1b	Not clear; allocation concealment was unclear.	Low risk; baseline characteristics comparable across the treatment groups	High-risk; open label trial	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
2263_Masjedi _2021 IR.MUI.REC.1396.3.786 trial [81]	2	A	Low risk; randomly divided into groups of treatment with Fingolimod and DMF using random allocation software.	Low risk; randomly divided into groups of treatment with Fingolimod and DMF using random allocation software.	Low risk; baseline characteristics comparable across the treatment groups	Not clear; The blinding was not reported.	Unclear: The withdrawals, completers, and the specific reasons for withdrawal were not reported	Unclear; authors did not mention the outcomes that were pre-specified in the protocol.	Unclear; not mentioned whether authors followed ITT analysis but mentioned patients were appropriatly randomized
4410_Montalban_2019 MS200527-0086 trial [82]	5	A	Low risk; Randomized by an interactive Web-response system	Low risk; Randomized by an interactive Web-response system	Low risk; baseline demographic and disease characteristics were balanced among the treatment groups	Low risk; This was a double-blind study.	Low risk; Withdrawals and reasons for withdrawals were well reported.	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; mITT analysis was carried out for carrying out safety and efficacy analysis.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
1851_Kappos_2021 OPTIMUM trial [43]	5	A	Low risk; The investigator, study staff and sponsor staff must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded randomization code for study treatment allocation through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended code break with Actelion.	Low risk; The investigator, study staff and sponsor staff must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded randomization code for study treatment allocation through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended code break with Actelion.	Low risk; baseline demographic and disease characteristics were balanced among the treatment groups	Low risk; This was a double-blind study.	Low risk; Withdrawals and reasons for withdrawals were well reported.	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; ITT approach was used for efficacy and safety analyses.
3796_Cohen_2019 RADIANCE trial [83]	5	A	Low risk; participants were randomised (1:1:1) via an IVRS to ozanimod 1·0 mg, ozanimod 0·5 mg, or interferon beta-1a. The randomisation sequence was generated by the contract research organisation and based on a blocked algorithm stratified by baseline EDSS score (≤3·5 vs >3·5) and country.	Low risk; participants were randomised (1:1:1) via an IVRS to ozanimod 1·0 mg, ozanimod 0·5 mg, or interferon beta-1a. The randomisation sequence was generated by the contract research organisation and based on a blocked algorithm stratified by baseline EDSS score (≤3·5 vs >3·5) and country.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; ITT approach was used for efficacy and safety analyses.

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
3797_Comi_2019 SUNBEAM trial [84]	5	A	Low risk; participants were randomly assigned 1:1:1 by a blocked algorithm stratified by country and baseline EDSS score to ≥12 months treatment of either once-daily oral ozanimod 1·0 mg or 0·5 mg or weekly intramuscular interferon beta-1a 30 µg.	Low risk; participants were randomly assigned 1:1:1 by a blocked algorithm stratified by country and baseline EDSS score to ≥ 12 months treatment of either once-daily oral ozanimod 1·0 mg or 0·5 mg or weekly intramuscular interferon beta-1a 30 µg.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured same number of outcomes as reported in clinical trial gov	Low risk; ITT approach was used for efficacy and safety analyses.
A_35_NCT EPOC [85]	2	B	Not clear; Participants were randomized in a 3:1 ratio to fingolimod or a standard DMT. but method of randomization was not given.	Not clear; Allocation concelament was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	High risk; open label	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; This study was taken from clinical trial.gov	Low risk; FAS analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
A_100_NCT NCT01006265 [86]	3	B	Not clear; Participants were randomized Ponesimod and placebo. but method of randomization was not given.	Not clear; Allocation concelament was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; This study was taken from clinical trial.gov	Low risk; mITT analysis was used both in efficacy and safety outcomes. Statistical details and power calculations were reported.
A_111_NCT NCT02727907 [87]	3	B	Not clear; Participants were randomized to receive Natalizumab and Fingolimod	Not clear; Allocation concelament was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; This study was taken from clinical trial.gov	Low risk; all randomized were analyzed (considered as ITT)
A_31_NCT COGNITION [88]	2	B	Not clear; Participants were randomized to receive Fingolimod or Interferon Beta 1b	Not clear; Allocation concelament was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	High risk; open label	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; This study is from clinicaltrial.gov	Low risk; FAS approach was used for efficacy analyses
A_108_NCT 2007-006338-32 [89]	4	B	Low risk; Eligible patients were randomized (1:1:1:1) to one of four treatment groups, A, B, C, or D. The treatment allocation was pre-assigned using an IVRS	Not clear; Allocation concealment was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; This study is from clinicaltrial.gov	Low risk; ITT approach was used for efficacy and safety population for safety analyses
A_105_NCT 2008-006786-92 [90]	3	B	Not clear, patients were randomized in a 1:1:1:1 ratio (10 mg ponesimod: 20 mg ponesimod: 40 mg ponesimod: placebo), with stratification by center	Not clear; Allocation concealment was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	Low risk; double blind	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all outcomes reported in methodology	High risk; Per protocol approach was used for efficacy and safety analyses

Citation ID Study name	Jadad score	Allocation concealment grade	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical methodology
Saida 2016 Saida 2016 [75]	2	B	Not clear; Participants were randomized to DMF or matching placebo	Not clear; Allocation concealment was not mentioned.	Not clear	Low risk; double blind	Unclear: The withdrawals, completers, and the specific reasons for withdrawal were not reported	Not clear; There was no evidence to suggest that the authors measured more outcomes than they reported.	Not clear
738_Nabavi_2022 NR [91]	3	B	Not clear, patients were randomized to Actoferon or Betaferon	Not clear; Allocation concealment was not mentioned.	Not clear	Low risk; double blind	Not clear: The withdrawals, completers, and the specific reasons for withdrawal were not reported	Low risk; Author has measured all outcomes reported in methodology	Not clear, approach was not specified
Svenningsson 2022 RIFUND-MS [92]	3	B	Not clear, patients were automatically randomly assigned (1:1) by the treating physician using a randomisation module in the Swedish multiple sclerosis registry, without stratification, to oral DMF 240 mg twice daily or to intravenous rituximab 1000 mg followed by 500 mg every 6 months	Not clear; Allocation concealment was not mentioned.	Low risk; baseline characteristics comparable across the treatment groups	High risk; rater blinded	Low risk: The withdrawals, completers, and the specific reasons for withdrawal were reported	Low risk; Author has measured all outcomes reported in methodology	Low risk; ITT approach was used for efficacy and safety population for safety analyses

4. **For the systematic review of clinical evidence (Appendix D), please provide a reference list of the 802 publications identified for the 61 included studies.**

For your reference, please see the supplementary Excel file named: *"Merck_MAVENCLAD_Clinical_List of included evidence (N=61 studies; 802 publications)"*

5. **For the systematic review of clinical evidence (Appendix D), please provide a list of the 1179 studies excluded at full text with reasons.**

For your reference, please see the supplementary Excel file named: "*Merck_MAVENCLAD_Clinical_List of excluded evidence (N=1179)"*

C2. Appendix G:

1. **For the systematic review of published cost-effectiveness literature (Appendix G), the introduction to section G.1.1 (Identification of studies) refers to searches of NHS EED, DARE (via CRD) and EconLit (via AEAweb.org), but search strings are not provided for these databases. Please confirm which databases (including interface and search date(s)) were searched and supply any missing search strings.**

The searches conducted in NHS EED, DARE, and EconLit were conducted before 2015. Due to archiving issues (decommissioning of one of the vendor's systems), we can no longer access files containing the specific search strings for these databases.

It is worth noting that this particular aspect of the submission has been evaluated in the previous NICE appraisal for cladribine tablets (TA493).

For additional context, in previous submission (TA493), the entire RRMS population was considered, and searches were not restricted to highly active RRMS; this broad scope for the searches was decided in order to ensure that no publications of interest were missed due to reporting of the highly active, RES or SOT RRMS data using different definitions of these sub-groups. The search strategy employed across various databases for this review included all key search terms without any limiting or restricting keywords that might have impacted the results. The approach used in the previous submission appraised by NICE (TA493) has been maintained in the current submission.

2. **For the systematic review of published cost-effectiveness literature (Appendix G), a list of included studies and the completed extraction grid is mentioned as being available separately as an Excel file. Please provide this file.**

   For your reference, please see the supplementary Excel file named: "*Merck_MAVENCLAD_Economic evaluation_List of included evidence (N=172)_V2"*

   For your reference, please see the supplementary Excel file named: "*Merck_MAVENCLAD_Economic evaluation_Extraction_Grid_(Data inception-2015),* "*Merck_MAVENCLAD_Economic evaluation_Extraction_Grid_(2015-2017), and* "*Merck_MAVENCLAD_Economic evaluation_Extraction_Grid_(2017-2023)"*

3. **For the systematic review of published cost-effectiveness literature (Appendix G), please provide a list of the 199 studies excluded at full text with reasons.**

For your reference, please see the supplementary Excel file named: "*Merck_MAVENCLAD_Economic_evaluation_List of excluded evidence (N=199)"*

C3. Appendix H:

1. **For the systematic review of published utility studies in RRMS (Appendix H), please provide a reference list of the 160 publications identified for the 143 included studies.**

   Regarding the systematic review of published utility studies in RRMS (Appendix H), the included evidence comprises 97 articles in total. The discrepancy in numbers is due to 61 articles that were excluded from the original pool of identified publications. This exclusion process was conducted prior to 2015. Due to archiving issues (decommissioning of one of the vendor's systems), we can no longer access files detailing the reasons for exclusion.

   The total of 97 included articles represents the final set of studies used in the utility review for RRMS. For your reference, please see the supplementary Excel file named: *Merck_MAVENCLAD_Utility_List of included evidence (N=97)_V2.* As outlined in question C2.1 above, this particular aspect of the submission has been evaluated in the previous NICE appraisal for cladribine tablets (TA493).

2. **For the systematic review of published utility studies in RRMS (Appendix H), please provide a list of the 239 articles excluded at full text with reasons**

As mentioned above, the exclusion process for the utility SLR was conducted prior to 2015. Due to archiving issues (decommissioning of one of the vendor's systems), we can no longer access files detailing the reasons for exclusion. However, the excluded evidence for studies published after 2015 can be provided. It should be noted that the evidence base for cladribine tablets prior to 2017 has been evaluated in the previous NICE appraisal for cladribine tablets (TA493).

For your reference, please see the supplementary Excel file named: *Merck_MAVENCLAD_Utility_List of excluded evidence (2015-2023).*

C4. Appendix I:

1. **For the systematic review of cost and healthcare resource use (Appendix I), the introduction to section I.1.3.1 (Identification of studies) refers to searches of EconLit and Cochrane, but search strings are not provided for these databases. Please confirm which databases (including interface and search date(s)) were searched and supply any missing search strings.**

The searches conducted in EconLit and Cochrane were conducted before 2015. The review of cost and healthcare resource use was conducted prior to 2015. Due to archiving issues (decommissioning of the vendors systems), we can no longer access files detailing the specific search strings for these databases are no longer accessible. The evidence base for cladribine tablets prior to 2017 has been evaluated in the previous NICE appraisal for cladribine tablets (TA493).

For additional context, in previous submission (TA493), the entire RRMS population was considered, and searches were not restricted to highly active RRMS; this broad scope for the searches was decided on in order to ensure that no publications of interest were missed due to reporting of the highly active, RES or SOT RRMS data using different definitions of these sub-groups. The search strategy employed across various databases for this review included all key search terms without any limiting or restricting keywords that might have impacted the results. The approach used in the previous submission appraised by NICE (TA493) has been maintained in the current submission.

2. **For the systematic review of cost and healthcare resource use (Appendix I), please provide a reference list of the 151 publications identified for the 135 included studies.**

As mentioned above, the cost and healthcare resource use SLR was conducted prior to 2015. Due to archiving issues (decommissioning of the vendors systems), we can no longer access files with screening of studies published before 2017 (n= 151 publication for 132 studies). However, the included evidence for studies published after 2017 (n=33 studies) can be provided. It should be noted that the evidence base for cladribine tablets prior to 2017 has been evaluated in the previous cladribine tablets submission (TA493) appraised by NICE.

For your reference, please see the supplementary Excel file named: *Merck_MAVENCLAD_Cost & Resource use_List of included evidence (2017-2023).*

3. **For the systematic review of cost and healthcare resource use (Appendix I), please provide a list of the 1162 articles excluded at full text with reasons.**

As mentioned above, the cost and healthcare resource use SLR was conducted prior to 2015. Due to archiving issues (decommissioning of the vendors systems), we can no longer access the files with the excluded evidence published before 2017. However, the excluded evidence for studies published after 2017 can be provided. It should be noted that the evidence base for cladribine tablets prior to 2017 has been evaluated in the previous cladribine tablets submission (TA493) appraised by NICE.

For your reference, please see the supplementary Excel file named: *Merck_MAVENCLAD_Cost & Resource use_List of excluded evidence (2017-2023).*

References

1. Giovannoni, G., et al., *A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis.* N Engl J Med, 2010. **362**(5): p. 416-26.
2. European Medicines Agency. *Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis*. 2015 26 March 2015; Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-multiple-sclerosis-revision-2_en.pdf.
3. European Medicines Agency, *Cladribine tablets SmPC*. 2024, EMA.
4. Merck Group., *CLARITY Clinical Trial Report. Data on file.* 2010.
5. National Institute for Health and Care Excellence, *Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA493)*. 2017.
6. National Institute for Health and Care Excellence. *Cladribine for treating relapsing-remitting multiple sclerosis (TA616)*. 2019; Available from: https://www.nice.org.uk/guidance/ta616/resources/cladribine-for-treating-relapsingremitting-multiple-sclerosis-pdf-82608960149701.
7. National Institute for Health and Care Excellence, *Ponesimod for treating relapsing–remitting multiple sclerosis (TA767).* 2022.
8. Sofia Dias, N.J.W., Alex J Sutton, AE Ades, *NICE DSU TECHNICAL SUPPORT DOCUMENT 2: A GENERALISED LINEAR MODELLING FRAMEWORK FOR PAIRWISE AND NETWORK META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS*. 2011, DECISION SUPPORT UNIT.
9. Giovannoni, G., et al., *Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study.* Mult Scler, 2018. **24**(12): p. 1594-1604.
10. Giovannoni, G., et al., *Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Supplmentary materials (msj727603).* Mult Scler, 2018. **24**(12): p. 1594-1604.
11. Kalincik, T., et al., *Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study.* The Lancet Neurology, 2017. **16**(4): p. 271-281.
12. Kalincik, T., et al., *Towards personalized therapy for multiple sclerosis: prediction of individual treatment response.* Brain, 2017. **140**(9): p. 2426-2443.
13. National Institute for Health and Care Excellence, *Ponesimod for treating relapsing multiple sclerosis (ID1393) - Committee Papers*. 2021.
14. National Institute for Health and Care Excellence, *Ofatumumab for treating relapsing multiple sclerosis (ID1677) - committee papers*. 2021.
15. National Institute for Health and Care Excellence, *Cladribine tablets for treating relapsing-remitting multiple sclerosis - Committee Papers*. 2017.
16. ClinicalTrials.gov. *A Study in Subjects With Relapsing-Remitting Multiple Sclerosis (RRMS) to Assess the Efficacy, Safety and Tolerability of Glatiramer Acetate (GA) Injection 40 mg Administered Three Times a Week Compared to Placebo (GALA NCT01067521)*. Available from: https://clinicaltrials.gov/study/NCT01067521#study-plan.
17. Khan, O., et al., *Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis.* 2013. **73**(6): p. 705-713.

18. Palace, J., et al., *UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model.* BMJ Open, 2014. **4**(1): p. e004073.
19. National Institute for Health and Care Excellence, *Ofatumumab for treating relapsing multiple sclerosis (TA699).* 2021.
20. National Institute for Health and Care Excellence, *Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533).* 2018.
21. NHS England, *Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies. NHS England Reference: 170079ALG. Gateway reference: 07603. 20 June 2023.* 2023.
22. National Institute for Health and Care Excellence, *Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (TA254).* 2012.
23. National Institute for Health and Care Excellence, *Alemtuzumab for treating highly active relapsing–remitting multiple sclerosis (TA312)*. 2014.
24. National Institute for Health and Care Excellence, *Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320)*. 2014.
25. National Institute for Health and Care Excellence, *Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303)*. 2014.
26. National Institute for Health and Care Excellence, *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624).* 2020.
27. Papathanasiou, A., et al., *Real-world annualized relapse rates from contemporary multiple sclerosis clinics in the UK: a retrospective multicentre cohort study.* Neurological Sciences, 2023. **44**(10): p. 3629-3635.
28. Duddy, M., et al., *The UK patient experience of relapse in Multiple Sclerosis treated with first disease modifying therapies.* Multiple Sclerosis and Related Disorders, 2014. **3**(4): p. 450-456.
29. Nicholas, R., et al., *Time-patterns of annualized relapse rates in randomized placebo-controlled clinical trials in relapsing multiple sclerosis: A systematic review and meta-analysis.* Multiple Sclerosis Journal, 2012. **18**(9): p. 1290-1296.
30. Lavery, A.M., L.H. Verhey, and A.T. Waldman, *Outcome Measures in Relapsing-Remitting Multiple Sclerosis: Capturing Disability and Disease Progression in Clinical Trials.* Multiple Sclerosis International, 2014. **2014**(1): p. 262350.
31. Inusah, S., et al., *Assessing changes in relapse rates in multiple sclerosis.* Multiple Sclerosis Journal, 2010. **16**(12): p. 1414-1421.
32. Nicholas, R., et al., *Trends in annualized relapse rates in relapsing–remitting multiple sclerosis and consequences for clinical trial design.* Multiple Sclerosis Journal, 2011. **17**(10): p. 1211-1217.
33. Steinvorth, S.M., et al., *Explaining temporal trends in annualised relapse rates in placebo groups of randomised controlled trials in relapsing multiple sclerosis: systematic review and meta-regression.* Multiple Sclerosis Journal, 2013. **19**(12): p. 1580-1586.
34. Stellmann, J.-P., et al., *Placebo Cohorts in Phase-3 MS Treatment Trials – Predictors for On-Trial Disease Activity 1990-2010 Based on a Meta-Analysis and Individual Case Data.* PLOS ONE, 2012. **7**(11): p. e50347.
35. Spelman, T., et al., *Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry.* Mult Scler, 2023. **29**(2): p. 221-235.

36. Tremlett, H., et al., *Relapses in multiple sclerosis are age- and time-dependent.* Journal of Neurology, Neurosurgery & Psychiatry, 2008. **79**(12): p. 1368-1374.
37. Tremlett, H., et al., *New perspectives in the natural history of multiple sclerosis.* Neurology, 2010. **74**(24): p. 2004-2015.
38. Hauser, S.L., et al., *Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis.* N Engl J Med, 2017. **376**(3): p. 221-234.
39. Kappos, L., Wiendl, H., Selmaj, K., Arnold, D.L., Havrdova, E., Boyko, A., Kaufman, M., Rose, J., GreenbEAG, S., Sweetser, M., Riester, K., O`Neill, G., Elkins, J., *Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis.* New England Journal of Medicine, 2015. **373**(15): p. 1418-1428.
40. Fox, R.J., Cree, B.A.C., De Séze, J., Gold, R., Hartung, H.-P., Jeffery, D., Kappos, L., Kaufman, M., Montalbán, X., Weinstock-Guttman, B., Anderson, B., Natarajan, A., Ticho, B., Duda, P., *MS disease activity in RESTORE: A randomized 24-week natalizumab treatment interruption study*
Neurology, 2014. **82**(17): p. 1491-1498.
41. Calabresi, P.A., et al., *Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study.* 2014. **13**(7): p. 657-665.
42. Vollmer, T., et al., *A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis.* 2014. **261**: p. 773-783.
43. Kappos, L., et al., *Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial.* Lancet, 2011. **378**(9805): p. 1779-87.
44. Mikol, D.D., et al., *Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial.* 2008. **7**(10): p. 903-914.
45. Cohen, J., et al., *Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial.* 2015. **72**(12): p. 1433-1441.
46. Mokhber, N., Azarpazhooh, A., Orouji, E., Rao, S.M., Khorram, B., Sahraian, M.A., Foroghipoor, M., Gharavi, M.M., Kakhi, S., Nikkhah, K., Azarpazhooh, M.R., *Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial.* Journal of the Neurological Sciences, 2014. **342**(42371): p. 16-20.
47. Confavreux, C., et al., *Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial.* 2014. **13**(3): p. 247-256.
48. Lublin, F.D., et al., *Randomized study combining interferon and glatiramer acetate in multiple sclerosis.* 2013. **73**(3): p. 327-340.
49. Vermersch, P., et al., *Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial.* 2014. **20**(6): p. 705-716.
50. Singer, B., et al., *Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonβ-1a versus subcutaneous interferonβ-1b: results of the randomized, multicenter, Phase IIIb REFORMS study.* 2012. **12**: p. 1-11.
51. Coles, A.J., et al., *Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial.* 2012. **380**(9856): p. 1829-1839.

52. Cohen, J.A., et al., *Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial.* 2012. **380**(9856): p. 1819-1828.
53. Fox, R.J., et al., *Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis.* 2012. **367**(12): p. 1087-1097.
54. Gold, R., et al., *Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis.* 2012. **367**(12): p. 1098-1107.
55. Stefano, N., et al., *Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study.* Journal of the neurological sciences 2012. **312**(24): p. 97-101.
56. Calabrese, M., et al., *Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis.* Mult Scler, 2012. **18**(4): p. 418-24.
57. O'Connor, P., et al., *Randomized trial of oral teriflunomide for relapsing multiple sclerosis.* 2011. **365**(14): p. 1293-1303.
58. Cohen, J.A., et al., *Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis.* 2010. **362**(5): p. 402-415.
59. Cadavid, D., et al., *Efficacy of treatment of MS with IFNβ-1b or glatiramer acetate by monthly brain MRI in the BECOME study.* 2009. **72**(23): p. 1976-1983.
60. Coles, A.J., et al., *Alemtuzumab vs. interferon beta-1a in early multiple sclerosis.* N Engl J Med, 2008. **359**(17): p. 1786-801.
61. Schwid, S.R., Panitch, H.S., *Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: A multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon ÃŸ-1a for relapsi.* Clinical Therapeutics, 2007. **29**(9): p. 2031-2048.
62. Etemadifar, M., Janghorbani, M., Shaygannejad, V., *Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis.* Acta Neurologica Scandinavica, 2006. **113**: p. 283-287.
63. O`Connor, P.W., Li, D., Freedman, M.S., Bar-Or, A., Rice, G.P.A., Confavreux, C., Paty, D.W., Stewart, J.A., Scheyer, R., *A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses.* Neurology, 2006. **66**(6): p. 894-900.
64. Wroe, S.J., *Effects of dose titration on tolerability and efficacy of interferon beta-1b in people with multiple sclerosis.* Journal of International Medical Research, 2005. **33**(3): p. 309-318.
65. Durelli, L., Verdun, E., Barbero, P., BEAGui, M., Versino, E., Ghezzi, A., Montanari, E., Zaffaroni, M., *Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: Results of a 2-year prospective randomised multicentre study (INCOMIN).* Lancet, 2002. **359**(9316): p. 1453-1460.
66. Ebers, G.C., *Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.* The Lancet, 1998. **352**(9139): p. 1498-1504.
67. Johnson, K., et al., *Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial.* 1995. **45**(7): p. 1268-1276.
68. Knobler, R.L., Greenstein, J.I., Johnson, K.P., Lublin, F.D., Panitch, H.S., Conway, K., Grant-Gorsen, S.V., Muldoon, J., Marcus, S.G., WallenbEAG,

J.C., Williams, G.J., Yoshizawa, C.N., *Systemic recombinant human interferon-ÃŸ treatment of relapsing-remitting multiple sclerosis: Pilot study analysis and six-year follow-up.* Journal of Interferon Research, 1993. **13**(5): p. 333-340.
69. Duquette, P., Girard, M., Despault, L., DuBois, R., Knobler, R.L., Lublin, F.D., Kelley, L., Francis, G.S., Lapierre, Y., Antel, J., Freedman, M., Hum, S., Greenstein, J.I., Mishra, B., Muldoon, J., Whitaker, J.N., Evans, B.K., Layton, B., Sibley, W.A., *Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial.* Neurology, 1993. **42**(4): p. 655-661.
70. Comi, G., M. Filippi, and J.S. Wolinsky, *European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group.* Annals of neurology, 2001. **49**(3): p. 290-297.
71. Jacobs LD, C.D., *Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG).* Annals of neurology, 1996. **39**(3): p. 285-294.
72. O`Connor, *250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study.* The Lancet Neurology, 2009. **8**(10): p. 889-897.
73. Bornstein, M.B., Miller, A., Slagle, S., *A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis.* New England Journal of Medicine, 1987. **317**(7): p. 408-414.
74. Gisleskog, P.O., et al., *An Exposure-Response Analysis of the Clinical Efficacy of Ponesimod in a Randomized Phase II Study in Patients with Multiple Sclerosis.* Clin Pharmacokinet, 2021. **60**(9): p. 1227-1237.
75. Saida, T., et al. *Placebo-controlled phase 3 study of delayed-release dimethyl fumarate in patients with relapsing multiple sclerosis from Asia-Pacific and other countries*. in *MULTIPLE SCLEROSIS JOURNAL*. 2016. SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.
76. Kira, J.I., et al., *Effect of ofatumumab versus placebo in relapsing multiple sclerosis patients from Japan and Russia: Phase 2 APOLITOS study.* Mult Scler, 2022. **28**(8): p. 1229-1238.
77. Hauser, S.L., et al., *Ofatumumab versus Teriflunomide in Multiple Sclerosis.* N Engl J Med, 2020. **383**(6): p. 546-557.
78. Cree, B.A., et al., *Efficacy and safety of 2 fingolimod doses vs glatiramer acetate for the treatment of patients with relapsing-remitting multiple sclerosis: a randomized clinical trial.* JAMA neurology, 2021. **78**(1): p. 48-60.
79. Naismith, R.T., et al., *Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study.* CNS Drugs, 2020. **34**(2): p. 185-196.
80. Comi, G., et al., *Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-*

month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). J Neurol, 2017. **264**(12): p. 2436-2449.
81. Masjedi S.-S., E.M., Zadeh N.M., Afzali M., *Assessment of fingolimod versus dimethyl fumarate for the treatment of multiple sclerosis; a 24-month follow-up study.* Am J Clin Exp Immunol., 2021. **10**(3): p. 86-92.
82. Montalban, X., et al., *Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis.* N Engl J Med, 2019. **380**(25): p. 2406-2417.
83. Cohen, J.A., et al., *Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (RADIANCE): a multicentre, randomised, 24-month, phase 3 trial.* Lancet Neurol, 2019. **18**(11): p. 1021-1033.
84. Comi, G., et al., *Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial.* Lancet Neurol, 2019. **18**(11): p. 1009-1020.
85. ClinicalTrials.gov. *Evaluation of Patient Reported Outcomes in RRMS Patients Candidates for MS Therapy Change and Transitioned to Fingolimod 0.5 mg (EPOC) (A_35_NCT01534182)*. Available from: https://clinicaltrials.gov/study/NCT01534182.
86. ClinicalTrials.gov, *Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of ACT-128800 in Patients With Relapsing-remitting Multiple Sclerosis (A_100_NCT01006265).*
87. ClinicalTrials.gov. *Study of Efficacy and Safety of Drugs BCD-033 and Rebif for Treatment of*
Patients With Multiple Sclerosis (A_111_NCT02727907). ClinicalTrials.gov; Available from: https://classic.clinicaltrials.gov/ct2/show/NCT02727907.
88. ClinicalTrials.gov. *Fingolimod Versus Interferon Beta 1b in Cognitive Symptoms (Cognition) (A_31_NCT01333501)*. Available from: https://clinicaltrials.gov/study/NCT01333501.
89. EU Clinical Trials Register. *Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex controlled dose finding study to evaluate the efficacy, as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with relapsing-remitting multiple sclerosis. (A_108_EudraCT: 2007-006338-32)*. 2016; Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2007-006338-32.
90. A_105, *A multicenter, randomized, double-blind, placebocontrolled, parallel-group, dose-finding study to evaluate the efficacy, safety, and tolerability of three doses of ponesimod (ACT-128800), an oral S1P1 receptor agonist, administered for twenty-four weeks in patients with relapsing-remitting multiple sclerosis.* Clinical study report **ACT-128800**.
91. Nabavi, S., et al. *A randomized, double-blind controlled clinical study to determine the effectiveness, safety and tolerability of actoferon (R) compared to betaferon (R) in subjects with relapsing remitting multiple sclerosis (RRMS)*. in *MULTIPLE SCLEROSIS JOURNAL*. 2022. SAGE PUBLICATIONS LTD 1 OLIVERS YARD, 55 CITY ROAD, LONDON EC1Y 1SP, ENGLAND.
92. Svenningsson, A., et al., *Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial.* 2022. **21**(8): p. 693-703.

Appendix

The CS documents were updated following the clarification procedure and discussions with the EAG. All changes were marked in the CS documents in green highlighting for visibility.

The summary of changes is provided in Table 7 below.

Table 7: Summary of changes in the CS documents

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
A4. Appendix D; Could you please look into the PRISMA study flow diagram, 61 trials were published in 802 publications (Appendix D, Figure 1 and table 7). Could you please clarify the PRISMA for both the SLR and NMA separately?	An extra box under the included studies and records for the SLR, which specifies number of studies from the SLR which were used in the NMA (Figure 1, PRIMSA diagram) The following footnote was added under Figure 1: Note: *Of the 61 trials identified in the SLR, following the feasibility analysis, 38 studies were selected for inclusion in the NMA Please note, Mokhber 2014 study was mistakenly included in the list of studies included in the NMA. This has been now corrected, therefore, the number of studies in the NMA is 38 (not 39 as initially stated). The following changes were introduced in the CS documents: Document B: • Table 21 – Mokhber study removed • Section B.2.9.4.1 (Risk of bias) was updated Appendix D: • Table 7 (D.1.1.2)- Mokhber study marked as "No", i.e., not included in the NMA • Table 8, Table 9 and Table 10 (D.1.1.3) – Mokhber study removed • Section D.1.1.5 (Risk of bias of studies included in NMA) was updated • Figure 2 was updated	**Document B (redacted and unredacted version)** **Appendix D (redacted and unredacted version)**
A9. The outcome specified for NMA 'Treatment discontinuation' (Document B, Figure 16) corresponds to which of the following outcome specified in Appendix D (Table 6): 'All-cause study withdrawals', 'Study withdrawals due to AEs', 'All-cause treatment withdrawals' or 'Treatment withdrawals due to AEs'?	The following sentence was re-written for clarity in Section B.2.9.2 (page 60): "In line with recent NICE appraisals in MS (TA493/ TA616, TA533, TA624, TA699, TA767), the outcomes listed in the Decision Problem, and the outcomes considered in the cost-effectiveness model for cladribine tablets (described in Section B.3), NMAs were conducted for ARR, 3-month CDP, 6-month CDP and treatment discontinuations (all-cause treatment withdrawals). The 3-month and 6-month CDP were measured at 24-months of follow-up."	**Document B (redacted and unredacted version)**

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
	The following sentence was re-written for clarity in Section A.8.2, page 21: "Based on the model fit statistics and the studies included in the NMA, a random effects model was determined to be the best fit to analyse ARR, 3-month CDP, 6-month CDP and treatment discontinuations (all-cause treatment withdrawals)."	**Document A (redacted and unredacted version)**
A10. When was the NMA outcomes 3-month and 6-month CDP (Document B, Figures 13 and 15) measured? at 12 or 24 months of follow-up?	The following sentence was re-written for clarity in Section B.2.9.2, page 60: "In line with recent NICE appraisals in MS (TA493/ TA616, TA533, TA624, TA699, TA767), the outcomes listed in the Decision Problem, and the outcomes considered in the cost-effectiveness model for cladribine tablets (described in Section B.3), NMAs were conducted for ARR, 3-month CDP, 6-month CDP and treatment discontinuations (all-cause treatment withdrawals). The 3-month and 6-month CDP were measured at 24-months of follow-up."	**Document B (redacted and unredacted version)**
A22. The league tables for ARR, 3-month CDP, 6-month CDP, and treatment discontinuation cannot be found.	The following note was added in Section B.2.9.3, page 64: "The league tables and the SUCRA plots for the four outcomes of interest are provided in Appendix D." (page 64)	**Document B (redacted and unredacted version)**
	The league tables were added to Appendix D.1.1.6 (NMA results)	**Appendix D (redacted and unredacted version)**
A23. Can you provide surface under the cumulative ranking curve (SUCRA) curves for cladribine, comparator DMTs, and placebo?	The following note was added in Section B.2.9.3, page 64: "The league tables and the SUCRA plots for the four outcomes of interest are provided in Appendix D."	**Document B (redacted and unredacted version)**
	The SUCRA plots were added to Appendix D.1.1.6 (NMA results)	**Appendix D (redacted and unredacted version)**
B6. PRIORITY: Please clarify whether the discontinuation rates reported in the RCTs included in the NMA for discontinuation also encompass people who discontinue due to disease progression to SPMS. If so, this may result in double counting, as discontinuation due to progression is already included in the model. This is noted in the statement on page 105 of CS document B: "The modelling of	Scenario without stopping rule was added as Scenario S11a in Document B, Table 60, Section B.3.8.3. (page 153) A summary of key results from Scenario S11a of cladribine tablets vs. ponesimod, ocrelizumab, ofatumumab was added in Document B, Table 61, Section B.3.8.3. (pages 156-157)	**Document B (redacted and unredacted version)**

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
discontinuation due to the onset of SPMS causing an inability to walk was captured through the transition of patients between EDSS states, and the application of a 'discontinuation rule' for patients who transition beyond a set EDSS level in the model. It was assumed that any patient transitioning to EDSS state 7.0 or greater would be considered SPMS and hence discontinued from therapy in line with previous appraisals [93-95, 98]. The modelling of discontinuations due to reasons unrelated to clinical diagnosis (e.g., tolerability) was captured through a separate annual discontinuation probability, based on the NMA, applied in each cycle; see Section B.3.3.3.5 for more detail." Please clarify that there is no double counting with respect to treatment discontinuation in the economic model.	Scenario without stopping rule was added as Scenario in Document A, Section A.14.3, Table 7, page 36	**Document A (redacted and unredacted version)**
	Scenario S11a is presented in Appendix J.1.3.1, Table 59	**Appendix J (redacted and unredacted version)**

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
B7. On page 106 of CS document B, the following sentence suggests a trend towards lower relapse rates in RRMS in recent years compared to the past: "By relating relapse rate to EDSS state, previous models incorporated an additional indirect effect of DMT on relapse rate through its effect on progression rate, which leads to double counting of the benefits of DMT when applying independent effects to both EDSS progression and relapse rate. This approach also relies upon historical data from previous UK MS surveys dating back at least 10 years that may not accurately reflect relapse rates in contemporary practice given the trend towards lower annualised rates in the placebo arms of contemporary clinical trials [102, 128, 176]." Can the company provide a rationale or explanation for the observed trend of lower relapse rates in recent years, particularly in the placebo arms of RCTs? The EAG is concerned that this may be due to the selection of well-fit patients for RCTs and the enhanced care they receive as part of the RCT, which may result in	Scenario with relapse rate modelled as a function of time (doubled rate) was added as Scenario S2b in Document B, Table 60, Section B.3.8.3., page 153 A summary of key results from Scenario S2b of cladribine tablets vs. ponesimod, ocrelizumab, ofatumumab was added in Document B, Table 61, Section B.3.8.3., pages 156-157	**Document B (redacted and unredacted version)**
	Scenario with relapse rate modelled as a function of time (doubled rate) was added as Scenario in Document A, Section A.14.3, Table 7, page 35	**Document A (redacted and unredacted version)**

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
lower relapse rates compared to those seen in clinical practice.	Scenario S2b is presented in Appendix J.1.3.2 (Table 60)	**Appendix J (redacted and unredacted version)**

EAG Question	Summary of changes to the CS document(s)	Document where the updates were made
B8. Please provide a detailed breakdown of the calculation that converts the change in the annualized relapse rate (ARR) over 5 years from 17% (based on the BCMS data) to the 22.9% value used in the company's economic model base case. The EAG is unable to follow the calculations from the description on page 107 of CS document B: "The ARR in the BCMS decreased by an average of 17% every 5 years, based on a median follow-up of 20.6 years, 51,120 person-years of exposure, and 11,722 post-onset relapses [177]. The age of onset of MS was strongly associated with the rate of decline of ARR, with estimates ranging from 30.5% for onset ages of 40+ years to 6.9% for onset ages of less than 20 years. The mean age and disease duration of the population in CLARITY were 38.7 years and 5.18 years, respectively, with a mean age of onset between 30 and 40 years. For the base case analysis, it was therefore assumed that the ARR would decline by 22.9% (95% CI: 19.4-26.2) for every 5 years of the simulated time horizon." Please clarify how the 22.9% decline in ARR over 5 years was calculated, given the initial 17% reduction based on the BCMS data.	The text was updated with following sentences for clarity, Section B.3.3.2.1.,pages 107-108: "The 17% reduction is the average decline for the whole cohort in the study (i.e., regardless of the onset age) and it is not used in the model. (page 107-108) The age of onset of MS was strongly associated with the rate of decline of ARR, with estimates of 30.5%, 22.9%, 16.9%, and 6.9% in people with onset ages of 40+ years, 30-40 years, 20-30 years and less than 20 years old respectively in the study [175, 176]. The mean age and disease duration of the population in CLARITY was 38.7 years and 5.18 years respectively, with a mean age of onset of between 30 years and 40 years. Based on the data from Tremlett et al. [175, 176], it was therefore assumed that for the base case analysis the ARR would decline by 22.9% (95% CI: 19.4-26.2) for every 5 years of the simulated time horizon." (page 107-108)	**Document B (redacted and unredacted version)**
B14. For the discontinuation probabilities in Table 37 of CS document B, which estimate is being applied in the economic model as a central estimate (mean or median)? The mean discontinuation probability estimates are being applied in the model.	The following footnote was added under Table 37, Section B.3.3.3.5., pages 120-121: "[a]Mean discontinuation probability estimates are applied in the model base-case"	**Document B, (redacted and unredacted version)**

NICE National Institute for Health and Care Excellence

Single Technology Appraisal
Cladribine for treating relapsing multiple sclerosis [ID6263]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	Head of Information and Engagement
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. The MS Trust is in contact with over 40,000 people affected by MS - that's people with MS, their families, friends and the health care professionals who help manage MS. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. We are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	Funding received from August 2023 to March 2024. Biogen £18640 conference sponsor Merck £32300 conference platinum sponsor Merck £1163.45 funding for honorarium Novartis £32548.33 conference platinum sponsor

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	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
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. We speak daily to people who are dealing with issues relating to MS: coping with the impact of diagnosis, coping with physical, emotional and financial consequences of MS, and making decisions about their treatment and care. Working with people with relapsing remitting MS (RRMS) and MS specialist health professionals, we have published a book, comparison chart and associated web decision tool which covers the disease modifying drug options available to people with RRMS These can be viewed on our website: **MS Decisions | MS Trust** **Disease modifying drugs | MS Trust**

	Disease modifying drugs: comparison chart | MS Trust

Living with the condition6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations. MS is sometimes mild, frequently relapsing remitting, but generally progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will be diagnosed with relapsing remitting MS (RRMS). MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms. Many of these invisible symptoms are sensitive areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect financial burden, both for the individual, their family and the state. They can have a profound

	effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends. In a cash-strapped NHS, the reality is that services to support people coping with the effects of a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. This has deteriorated further since the pandemic, and access can be delayed by six months or more. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS. Research evidence supports the treatment of people with relapsing remitting MS with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS. Cladribine has been used effectively in the NHS since 2017 but can currently only be prescribed under constrained conditions when it could be an appropriate choice for many more people living with RRMS.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	It is important to have options to suit MS patient's health and personal needs. As MS is lifelong from diagnosis it is likely that people will need to change from one DMD to another at times. There is no one drug that suits everyone, and so neurologists and patients need to have a range available in order to select the best fit for each person.
8. Is there an unmet need for patients with this condition?	The way that disease modifying drugs have come to licencing and use on the NHS has been piecemeal and inconsistent. Neurologists are unable to offer cladribine to everyone that they think could benefit from it.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	People currently prescribed cladribine tell us several reasons that they like taking it: - Minimal impact on daily life, making it possible to 'forget' they have MS, unlike drugs that are taken daily. Spontaneous travel and activity possible without having to remember to stock up on treatments, time trips around infusions, remember to take pills or self-inject, or keep medication refrigerated. - Minimal travel needed for e.g. monthly infusions or blood tests in clinics or hospitals. The drug is taken at home. - Minimal exposure to needles for those who are phobic – only four blood tests in the four years of treatment. - Knowing that they are taking an immune reconstitution therapy, meaning that there is a chance of longer-term remission from MS.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	There is currently some uncertainty about what happens to cladribine patients after the four years, but research is underway to understand what, if any, treatment may be required as a follow on.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Multiple sclerosis is typically diagnosed between the ages of 20 and 50 years. Because most patients with MS are women (approximately 70%), diagnosis often coincides with patients' reproductive years. Pregnant women are excluded from clinical trials and therefore also from the licenced use of many DMDs. Although cladribine should not be taken by men or women who are planning a pregnancy, the long period of time after the second course of tablets (up to three years) offers an opportunity for pregnancy and birth with no exposure to disease modifying drugs. This is an attractive feature especially for women of childbearing age. These women might otherwise opt to avoid disease modifying drugs until they had completed their families or choose less effective DMDs. Either way, they risk both relapses and disability progression unnecessarily. In practice, neurologists and their female patients pick a delicate line between the safety risks for mothers and babies based on the little research data in existence, much interpreted from registries and experiences with similar drugs. Women with RRMS may suffer anxiety due to having pregnancies exposed to DMDs in order to manage their MS.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Cladribine is taken as two short courses of tablets at home, within a four-year period. For most of this period it is also anticipated that monitoring requirements (for example blood tests) for cladribine will be moderate with low impact on patients and NHS services. For years three and four of treatment, no monitoring is required. As a result, cladribine may be an appropriate treatment for people with no fixed address, such as homeless people, the Roma or Traveller communities, and people who need to travel often and for long periods of time e.g. for military or offshore work.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• • • • •

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] on behalf of the ABN AG for MS and neuroinflammation
2. Name of organisation	Association of British Neurologists
3. Job title or position	Consultant neurologist with special interest in MS and neuroinflammation
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' is a professional membership organisation and its mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. The ABN receives funding mainly from its member subscriptions and annual conference income. Additional funding from external charity organisations is received to solely fund fellowships. The ABN also receives sponsorship from pharmaceutical companies. Sponsoring companies have no input, control nor opportunity to influence the ABN.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB

5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is reduction in relapse rate in patients with relapsing remitting MS
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Absence of disease activity – i.e. reduction of inflammatory activity to no evidence of disease activity on clinical and/or radiological grounds, In other words suppression of relapses and MRI activity.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is a critical area for improving treatment options. Currently, there's a lack of readily available induction therapies as first-line treatment for patients with relapsing-remitting MS (RRMS). Alemtuzumab, the only other option, has significant limitations on its use. Expanding access to effective treatments for all MS patients is crucial. Early access to induction therapies, particularly for women with MS, offers a significant advantage: the opportunity for a drug-free pregnancy while maintaining disease control. Currently, women with active RRMS who don't meet highly active/RES criteria and want to get pregnant face a difficult choice: stop disease-modifying therapy (DMT) or use an off-label DMT during pregnancy. Wider availability of mavenclad for this population would eliminate this dilemma. The benefits of early access to induction therapies extend beyond women with MS. It would offer a broader range of treatment options for all patients, allowing them to maintain their usual activities without the concerns associated with long-term immunosuppression.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	There are NICE approved disease modifying treatments for relapsing remitting MS
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes there is the NHS England treatment algorithm which details commissioning guidance, and the ABN guidelines which detail clinical approaches.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There NHSE DMT commissioning treatment algorithm and NICE guidelines for MS care aim to remove variability of care and prescribing. These mandate that all patients receiving highly effective MS DMT are discussed at a dedicated MS multidisciplinary meeting in order to further reduce variability across professionals.
9c. What impact would the technology have on the current pathway of care?	It would enable access to an induction treatment for people with active relapsing remitting MS irrespective of line of treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used as per the current care in NHS clinical practice patients with relapsing remitting MS
10a. How does healthcare resource use differ between the technology and current care?	The current treatment is based on NICE TA616 which allows use of cladribine tablets for treating either rapidly evolving severe relapsing–remitting disease or disease that has responded inadequately to treatment with disease-modifying therapy. The current single technology appraisal will consider the use of Cladribine for active RRMS irrespective of line of use
10b. In what clinical setting should the technology be	Specialist clinics as currently prescribed for all other disease modifying treatments with MDT approval

used? (For example, primary or secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment is required as cladribine tablets are already used in current routine clinical practice.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	This approach would significantly expand the use of induction therapy to a group of patients at high risk of developing significant disability. Early treatment would prevent clinical teams from needing to wait for high disease activity, a requirement often encountered when considering treatment access (e.g., while patients contemplate pregnancy). Furthermore, it would broaden access to effective early therapies for a wider group of patients. This would empower them to make informed decisions about life events, such as family planning, aging, lifestyle adjustments, and work, with greater confidence in their disease management.
11a. Do you expect the technology to increase length of life more than current care?	Current evidence suggests that when treated early with DMT, MS does not shorten life expectancy at population level. This additional access to treatment would not be expected to change this.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes for the reasons already listed above.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None currently identified within the population (RRMS) that is currently being appraised.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	It will broaden use and allow easier access to clinical teams who can use Cladribine tablets in patients depending on the clinical need irrespective or line of treatment. It will allow oral use of treatment and thereby reduce administrative burden and result in cost savings to the NHS. The administrative and monitoring burden is very low with cladribine as opposed to their DMTs. Given that it is an induction/infrequent treatment given orally, it will allow help patients who for financial and other reasons do not engage well with MS teams (time off work, cost of travel to the specialist centre to access treatments regularly, or blood test appointments), to get better MS treatments.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment will be used for RRMS and the current start and stop criteria will be as per NHSE treatment algorithm that is used by clinicians in England as the principal guide to prescription.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The main consideration is use in populations considering family planning, work planning and generally looking to enhance quality of life without commitment to a continuous disease modifying treatment.
16. Do you consider the technology to be	Yes

innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	No.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, it will allow access to populations who typically face challenges in accessing specialist healthcare. The combination of an induction therapy and oral mode of delivery for cladribine allows groups of people who have poor social determinants of health or live far from specialist centres access to effective treatment that does not require frequent travel, with associated time/financial costs. This has the potential to improve equality of treatment access across England (and potentially across the UK if changes are mirrored in the devolved nations). Further, as detailed above in answer to question 8, this change would be beneficial from a wider equalities perspective. It would enable access to women and of child bearing age to an induction treatment that can allow them plan drug free pregnancy without the risk of relapse inherent in treatment pausing/withdrawal. 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 after that. Both women and men can safely consider trying for a family after the six-month washout period following treatment.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects related to treatment are unchanged in this population when compared to the previous TA (616)

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Relapses, relapse-associated disability, sustained accrual of disability. These were all measured in the trials
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None so far in real world studies of large cohorts
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There are a number of real world studies across the globe that support use of Cladribine tablets in the RRMS population. This is evidence that is not currently available in clinical trials. Brownlee W, Amin A, Ashton L, Herbert A. Real-world use of cladribine tablets (completion rates and treatment persistence) in patients with multiple sclerosis in England: The CLARENCE study. Mult Scler Relat Disord. 2023 Nov;79:104951. doi: 10.1016/j.msard.2023.104951. Lizak N, Hodgkinson S, Butler E, Lechner-Scott J, Slee M, McCombe PA, Shaw C, Skibina O, Vucic S, Shuey N, Barnett MH, Parratt J, Butzkueven H, Jack D, Fabris J, Kalincik T. Real-world effectiveness of cladribine for

	Australian patients with multiple sclerosis: An MSBase registry substudy. Mult Scler. 2021 Mar;27(3):465-474. doi: 10.1177/1352458520921087. Epub 2020 Jun 12. L, Evans H, De Cock E. Quantifying the administration and monitoring time burden of several disease-modifying therapies for relapsing multiple sclerosis in the United Kingdom: A time and motion study. Mult Scler Relat Disord. 2024 Feb;82:105380
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA794, TA767, TA699, TA624, TA616, TA533, TA527, TA303, TA320, TA312, TA254, TA127, TA527, TA656?	None to date that we are aware of
21. How do data on real-world experience compare with the trial data?	Real world evidence data supports the current trial evidence but provides further insights such as wider access to populations that were not specially referred to in the trial outputs.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	RRMS affects females significantly more than males - a lack of access of treatments that enable effective pregnancy planning with no loss of disease control is likely to affect females disproportionately compared to males. Lack of access to highly effective treatments that do not require frequent visits to hospital for administration and/or monitoring will be of benefit to people with MS living in rural or remote areas, those without easy access to a tertiary neuroscience centre, and/or those with adverse social determinants of health.
22b. Consider whether these issues are different from issues with current care and why.	Yes as current use does not allow use of high efficacy oral induction treatment in RRMS unless the patient meets the TA616, this disproportionately disadvantages the groups described above.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Access to oral cladribine in RRMS irrespective of line of use will allow reduction of relapse associated disability accrual that can be tackled earlier than what the current access allows. • It will allow access to those populations (childbearing age groups, travelling communities, lower socioeconomic groups, patients dependent on others to take them to appointments) • Will allow cost savings to the NHS due to reduced appointment burden and monitoring costs • Will broaden access thereby reduce the impact on those that are likely to be disproportionately affected due to lack of treatment options such as women •

Thank you for your time.

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Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Clinical expert statement

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **10 October 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating active relapsing multiple sclerosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Ruth Dobson
2. Name of organisation	Queen Mary University London/Barts Health NHS Trust
3. Job title or position	Professor of Clinical Neurology/Consultant Neurologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with active relapsing multiple sclerosis? ☒ A specialist in the clinical evidence base for active relapsing multiple sclerosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for active relapsing multiple sclerosis?	The primary aim of treatment for active relapsing remitting multiple sclerosis (RRMS) is to prevent further clinical relapses and inflammatory activity (on MRI),

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	as measured in clinical practice by a reduction in relapse rate/reduced number of relapses and/or reduced new or active disease on MRI. Failure to supress relapses and inflammatory disease activity early in the MS disease course has been associated with the risk of longer-term progression and disability in multiple large real-world cohorts; thus reducing these short term metrics links in to an aim to reduce the risk of (and potentially prevent) longer term progression and disability.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response would be reduction and/or suppression of clinical relapses and inflammatory MRI activity. Whilst the goal of treatment is to reduce this inflammatory disease activity as much as possible, a clinically significant response would be reduction of relapse rates to less than pre-treatment baseline (either compared to prior to any treatment or compared to first line treatment where breakthrough disease activity has occurred).
10. In your view, is there an unmet need for patients and healthcare professionals in active relapsing multiple sclerosis?	Despite the number of available therapies for active RMS, there remains a need to improve treatment options. An important unmet need is equitable access to treatment for women planning pregnancy – women are commonly de-escalated or denied access to highly effective treatments because of their pregnancy plans, potentially leading to longer term avoidable disability. The use of cladribine for this population carries the potential for access to active therapy with drug free pregnancy following a full course. Early data suggests durable disease control both during pregnancy and in the postpartum period following cladribine treatment in this population, who currently have limited access to effective treatments with induction effects whilst trying to conceive and during pregnancy. There is currently a lack of readily available non-immunosuppressive therapies as first-line treatment for patients with relapsing-remitting MS (RRMS). The mainstay of non-immunosuppressive therapies are induction treatments. Alemtuzumab, the only other option, is associated with significant adverse events, and has limitations on its use. The benefits of wider early access to

	induction therapies would offer a broader range of treatment options for all patients, allowing them to maintain their usual activities without the concerns associated with long-term immunosuppression. It would also enable patients to receive effective treatment without needing to repeatedly be in contact with healthcare providers for serological monitoring, drug prescription and delivery, and other intensive monitoring, meeting important unmet needs around equitable treatment access regardless of location, as well as reducing healthcare utilisation and improving patient quality of life.
11. How is active relapsing multiple sclerosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NHSE commissioning criteria guide clinical practice; these are based on NICE TAs. These are contained within the following hyperlink: https://www.england.nhs.uk/wp-content/uploads/2024/03/treatment-algorithm-for-multiple-sclerosis-disease-modifying-therapies-july-23.pdf These clearly detail which therapies can be used first and second line, and when. Whilst the pathway is well defined, and MDT meetings ensure that differences in individual clinical practice are evened out to some degree there remain challenges. A major challenge for all MS clinicians prescribing DMTs is around the variable eligibility requirements. Due to differences in clinical trial eligibility and the ways in which these have been applied within TAs, the resulting NHSE DMT prescribing algorithm is overly complex, and does not reflect the practical uses of these treatments internationally. There is an urgent need to rationalise this in order to ensure that patients are able to access the most suitable DMT for them in a timely manner. This has been highlighted in the recent ABN DMT guidelines (currently in press). This TA would be an important step forward to rationalise the current pathway of care, improving efficiency within the MDT. It would also offer more equitable access to highly effective treatments for those who are planning pregnancy, which has not been properly considered in previous iterations of this pathway.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes, although this MTA would expand potential access to a wider group of patients. The current treatment is based on NICE TA616 which allows use of cladribine tablets for treating either rapidly evolving severe relapsing–remitting disease or disease that has responded inadequately to treatment with disease-modifying therapy. The current single technology appraisal will consider the use of Cladribine for active RRMS irrespective of line of use. Importantly, this approach was used in part during the initial stages of the COVID pandemic due to concerns regarding immunosuppressive DMTs (antiCD20s). This did not lead to destabilisation of services, and the slight extension in access was clinically welcomed and used appropriately. Importantly, it offered patients improved chose with access to highly effective non-immunosuppressive medication.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	This approach would significantly expand the use of induction therapy to a group of patients at high risk of developing significant disability. Access to early treatment would free patients and clinical teams from needing to wait for high disease activity, a requirement often encountered when considering treatment access (e.g., while patients contemplate pregnancy). This option would be of particular relevance to those patients for whom other treatments are not suitable, particularly those who are planning pregnancy in the medium-term future. There is currently inequity, in that many of the treatments suitable for patients with highly active MS whilst on therapy are incompatible with pregnancy (demonstrated to be teratogenic, or presumed so due to class effect), or have restricted use within TAs. Extending the availability of cladribine, an induction therapy with durable efficacy through pregnancy, would have meaningful clinical benefit compared to forcing patients to de-escalate or accept lower efficacy therapy purely on the basis of protected characteristics. Furthermore, this change would broaden access to effective early therapies for a wider group of patients. This would empower a range of people with MS to make informed decisions about life events, such as family planning, aging, lifestyle adjustments, and work, with greater confidence in their disease management.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None currently identified within the population (RRMS) that is currently being appraised.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	If approved, this TA would simplify things for healthcare professionals within the MDT along with the patients they care for. At present, in the cohort of patients who have active MS, the criteria for different therapies is different. Aligning the criteria across DMTs will rationalise and simplify MDT team working. It will also make things easier for patients when weighing up different treatments to have all highly active therapies on an equal footing. The current restriction additionally raises questions regarding stratification by level of efficacy, which are not fully justified based on existing evidence. Additionally, it will allow the use of an oral, induction treatment and thereby reduce administrative burden and result in cost savings to the NHS. The administrative and monitoring burden is very low with cladribine as opposed to their DMTs. Given that it is an induction/infrequent treatment given orally, it will allow help patients who for financial and other reasons do not engage well with MS teams (time off work, cost of travel to the specialist centre to access treatments regularly, or blood test appointments), to access better MS treatments.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment will be used for RRMS and the current start and stop criteria will be as per the current NHSE treatment algorithm, as is currently used by clinicians in England as the principal guide to prescription.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	The equalities impact is substantial and supports this TA, as discussed in some of the responses above (Q10,11,13,15). The main consideration is use in populations considering family planning, work planning, those living in rural, remote or deprived areas who may struggle to access ongoing regular specialist

are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	neurological care. It will enable access for these populations to potentially improve MS disease control and enhance quality of life without requiring a continuous disease modifying treatment and monitoring (which incurs individual expense)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – this would enable a step change in the access to induction therapy for those with active disease. This was previously possible with the use of alemtuzumab, prior to the emergence of significant safety concerns. These concerns have not been noted with the use of cladribine, which has the potential to substantially improve care for those with active disease who do not want to be immunosuppressed and/or take regular treatments. This has important equalities implications as discussed above.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Real world data has not demonstrated any significant concerns in terms of treatment emergent adverse effects with substantial impact on QoL.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. The trials measured outcomes in terms of relapses, relapse-associated disability, and sustained accrual of disability in a population reflected within this TA. Initially, a more restrictive licence was based on theoretical concerns regarding adverse event profile, however this has not been shown to be justified in large real world evidence studies with longitudinal follow up. Further, no additional concerns regarding adverse event profiles have been raised following initial licensing.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance (TA320), (TA794), (TA527), (TA303), (TA533), (TA312), (TA624), (TA699), (TA767), (TA656), (TA527)?	TA794 is for diroximel fumarate and dates to 2022. A number of NICE TAs have been updated since this time in light of new evidence.
23. How do data on real-world experience compare with the trial data?	TA794 is for diroximel fumarate and dates to 2022. A number of NICE TAs have been updated since this time in light of new evidence.
24. Is training on how to self-inject disease-modifying therapies provided by the NHS or company-sponsored nurses? **How long would it take a nurse to train a patient how to self-inject?**	This is provided by company sponsored nurses. It takes a number of visits at the patients home to establish safe storage, injection practices, and safe disposal of medication along with injection technique. There is also the need for follow up with injection nurses to evaluate how this is working and provide ongoing support, which may be provided either in person or via telephone as appropriate to the patient. Needs may vary between patients.
25. Is ongoing monitoring for patients on cladribine required beyond the first year and if so what resources would be needed?	Ongoing monitoring is required in terms of annual MS review and monitoring MRI as appropriate and recommended by NICE and ABN clinical guidelines.
26. In the NHS are follow-up neurology appointments routine practice in the first year for patients on glatiramer acetate and beta interferons?	All patients with MS should be followed up at least annually according to NICE guidance. Often patients will have more frequent follow up in the first 1-2 years of treatment to ensure that they are tolerating this well and learning how to live with MS and their DMT.
27. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.	Yes, and these are discussed in many of the responses above. In brief, RRMS affects females significantly more than males - a lack of access of treatments that enable effective pregnancy planning with no loss of disease control is likely to affect females disproportionately compared to males. Lack of access to highly effective treatments that do not require frequent visits to hospital for administration and/or monitoring will be of benefit to people with MS living in rural or remote areas, those without easy access to a tertiary neuroscience centre, and/or those with adverse social determinants of health. As current

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	commissioning does not allow use of high efficacy oral induction treatment in RRMS unless the patient meets the TA616, this disproportionately disadvantages the groups described above.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Cladribine is an effective induction treatment for MS, which does not incur ongoing safety monitoring or treatment costs.
Current restrictions to those with RES/highly active disease are not in line with evidence from clinical trials, where efficacy has been shown in those with active disease, many of whom may benefit from this treatment
Increasing access to cladribine treatment has the potential to increase access to DMT for populations who may currently be unable to access effective treatments, such as those from travelling communities, those who live further from neuroscience centres, and those who are unable to afford time off work for regular monitoring appointments.
Cladribine offers the potential of both effective DMT and drug-free pregnancies with durable effect, with emerging data supporting the use of this medication as part of proactive pregnancy planning – many women are currently denied this option.
Wider use of cladribine has the potential to save the NHS money in terms of effective treatment, reduced monitoring costs (appointments and tests), and reduced complications of long term immunosuppression, alongside reduced longer term disability.

Thank you for your time.

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Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

Clinical expert statement

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Part 1: Treating active relapsing multiple sclerosis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Wallace Brownlee
2. Name of organisation	University College London Hospitals NHS Foundation Trust
3. Job title or position	Consultant Neurologist and Honorary Associate Professor of Neurology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with active relapsing multiple sclerosis? ☐ A specialist in the clinical evidence base for active relapsing multiple sclerosis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for active relapsing multiple sclerosis?	To reduce the incidence of active relapses and decrease MRI activity, with the intention to reduce disease progression and disability accumulation in MS patients.

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Significant reduction in the annualised relapse rate, significant decrease in the number of new/active MRI lesions, significant reductions in disability progression compared with placebo
10. In your view, is there an unmet need for patients and healthcare professionals in active relapsing multiple sclerosis?	Yes – there are a number of approved therapies for active relapsing MS but all of them required continuous immunosuppression, provide low efficacy, or both.
11. How is active relapsing multiple sclerosis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NHS England Treatment algorithm for multiple sclerosis disease-modifying therapies is used as a clinical guidance for treatments that can be used at different stages of MS patient care. The prevailing approach to treating MS is to use more effective medications early in the disease, to maximise long term health outcomes. This is reflected in the recently revised ABN guidelines for multiple sclerosis. However, there is a great deal of variation in prescribing of high efficacy medicines across the NHS in England, that cannot be accounted for by patient-related factors alone. For patients with active relapsing MS, highly-effective treatment options recommended by NICE include ponesimod, ocrelizumab and ofatumumab. The choice of medicine depends on multiple factors including patient age, comorbidities, family planning decisions, and importantly capacity at the treating hospital within the MS team. The addition of cladribine tablets as a treatment option for active relapsing MS would be expected to increase the number of patients able to access highly effective therapy given the unique dosing schedule, low burden of administration and monitoring for patients and NHS staff, and the ability to treat special patient populations, for example, older patients, women planning a pregnancy, and patients at risk of infection (including

	patients needing to stop immunosuppressive medicine because of an unacceptable burden of infections and/or serious infections).
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Currently, cladribine tablets are only an option for patients with highly active MS. This places significant restriction on where they can be used within the current treatment paradigm, with 80% of more of patients who are newly diagnosed not able to access this treatment. This change will allow cladribine tablets to be used in a similar way to other medicines recommended for treatment of active relapsing MS. This technology is prescribed and managed by specialist MS centres within secondary and tertiary care, by clinicians experienced in the use of disease modifying therapies (DMTs). No additional investment would be required to introduce this technology, as there is already experience and processes in place. The manufacturer currently also provides a patient support programme that facilitates safe monitoring reducing the burden of pharmacovigilance on MS teams that are working well beyond capacity.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Treatment for MS has been shown to improve survival. The majority of deaths in people with MS are due to the effects of advanced disability, more widespread use of highly effective medicines like cladribine tablets that have a greater impact on disability accumulation and control of relapses would be expected to improve this situation. Having the option of a short, course oral therapy that does not require continuous immunosuppression would be expected to enhance quality of life among people with MS by reducing the burden of treatment and monitoring, and reducing the risk of infectious complications, which are an issue with

	maintenance immunosuppressive drugs, particularly the antiCD20 monoclonal antibodies.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology would be particularly effective for patients with active MS, who do not want continuous treatment, want to avoid frequent hospital visits, live in less privileged and lower socio-economic status groups and those patients who are planning for a family. The dosing schedule and absence of continuous immunosuppression also make cladribine tablets an attractive option in older patients who are at higher risk of MS progression, but also adverse events in the context of continuous immunosuppression with other therapies recommended for active relapsing MS. Earlier use of cladribine tablets is likely to lead to more favourable outcomes, as evidenced by data from the ORACLE study in people with a first demyelinating event, and in real-world evidence including the CAMELOT-MS study in the UK. The current NICE recommendation to only offer the treatment to patients with high disease activity means patients who may benefit the most, for example treatment naïve patients or those with a single attack of demyelination, are not able to be treated.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Cladribine tablets have the lowest burden of treatment administration and monitoring than any available high-efficacy MS therapy. This was demonstrated by a multicentre 'Time-in-Motion study' carried out in the UK. The medicine can be given at home, and the monitoring burden is minimal. Multiple reports including the 'Transforming MS for All' report have highlighted the dire state of MS services in the UK with many centre well beyond capacity. Treatments with a lower burden of administration of monitoring like cladribine tablets will help build capacity within MS services.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As this is a short-course treatment, with up to 20 days of treatment over 2 years followed by monitoring to assess treatment response. Unlike maintenance immunosuppressive therapies there is no dilemma on when to stop treatment,

	which is a major area of uncertainty in the field in the context of an ageing MS population.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The most substantial health-related benefit is the treatment regimen, as a short-course oral treatment, this fills an unmet need for patients with active relapsing MS and provides considerable ease of administration compared to the current standard of care in this setting.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The treatment regimen is innovative, as we have no other short-course oral treatment options for patients with relapsing MS patients. This meets an unmet need for patients who do not want to be restricted by their treatment, either by frequent repeated administration, or regular hospital visits. It also expands access to highly effective therapies in special patient populations (e.g women planning pregnancy, older patients), and makes highly effective treatment more accessible for people at risk of health inequalities for example people with MS living in rural areas, and those in difficult social circumstances. At my hospital in Central London cladribine tablets have been very valuable in treating homeless people with MS who are unable to refrigerate medicine.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	All MS clinics in the UK are currently prescribing cladribine tablets in people with highly active disease. Clinical experience and real-world evidence studies have confirmed the excellent tolerability of the medicine. The most commonly encountered issues are lymphopenia (which we monitor for routinely with blood tests), and shingles. Steps are taken to reduce the risk of shingles in at risk patients e.g. Zoster vaccination in people >50 years, prophylactic antiviral medicines in people with severe lymphopenia.

20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes – the two phase III trials were conducted in an active MS population i.e. patients with signs of recent disease activity. Long term follow-up if the trial population has demonstrated sustained efficacy in the longer term with many patients not requiring any further disease-modifying therapy (representing a potential saving to the NHS), and very low rates of severe disability including loss of ambulation/need for a wheelchair. Cladribine tablets have been associated with reductions in relapse rates, MRI evidence of disease activity, and disability progression over time. These measures are all highly relevant to the evolution of disability and development of secondary progressive MS. The only new safety signal to emerge in the post-marketing setting has been deranged liver function tests. We already monitoring liver tests routinely withs safety bloods, and we screen patients for pre-existing liver disease as part of treatment work-up.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Real-world experience from both UK (including the CAMELOT-MS and CLARENCE studies) and the Time-in-Motion study.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance (TA320), (TA794), (TA527), (TA303), (TA533), (TA312), (TA624), (TA699), (TA767), (TA656), (TA527)?	No
23. How do data on real-world experience compare with the trial data?	There are a number of real-world cohorts published from the UK, Germany, Italy and elsewhere that demonstrate efficacy in line with what is reported in the clinical trials.
24. Is training on how to self-inject disease-modifying therapies provided by the NHS or company-sponsored nurses?	This is an oral treatment and does not require self-injection.

How long would it take a nurse to train a patient how to self-inject?	N/A
25. Is ongoing monitoring for patients on cladribine required beyond the first year and if so what resources would be needed?	Blood tests and MRI are required before treatment in year 1 and year 2, during the active dosing period, no additional blood tests are required in years 3 and 4 (and beyond) but MRI scanning is recommended to identify patients with breakthrough radiological activity that might require further disease-modifying therapy.
26. In the NHS are follow-up neurology appointments routine practice in the first year for patients on glatiramer acetate and beta interferons?	Patients with MS are generally reviewed annually
27. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	As noted if cladribine tablets were to be recommended then it would expected to reduce health inequalities, including in women who are family planning (data suggests this group are less likely to be treated, and less likely to prescribed highly effective MS therapies), older patients (also less likely to be prescribed high efficacy therapies), and people living in rural areas who may live further from MS centres and opt for less effective treatment for conveience.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Cladribine tablets are a highly effective, innovative, short-course treatment option for patients with MS.
Cladribine tablets do not require continuous immunosuppression providing a valuable treatment option for certain groups of patients.
Real-world experience has been positive and in line with the clinical trial experience, with high levels of treatment persistence (reflecting excellent overall tolerability and efficacy) and no concerning safety signals with over 7 years of clinical experience.
Due to the dosing schedule, cladribine tablets have the lowest burden of administration and monitoring of any highly effective MS therapy.
The company's patient support programme has helped to reduce the burden on the NHS, for supply and monitoring of treatment, including periodic the blood tests required in the first 2 years of treatment.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Patient expert statement r

Cladribine for treating relapsing Multiple Sclerosis [ID6263]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Carla King**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	The MS Trust
4. Did your nominating organisation submit a submission?	☐ yes, they did ☒ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with Multiple Sclerosis (MS) is like living with a permanent lodger that has outstayed their welcome. I have lived with MS officially for nineteen years, many more unofficially. MS can affect almost every part of our bodies and our lives, and is unpredictable in its timing, format and severity. Some will live symptom-free for many years, others will have visible effects at the point of diagnosis. A common saying in the MS community is "No two people are alike" referring to the fact that not everyone will experience every symptom, and symptoms do not affect everyone in the same way. Whatever our situation, living with MS is accepting that there will be an ebb and flow. MS is not just a physical condition; it is cognitive and can also affect our mental wellbeing (the MS Society quotes the figure of those with MS living with depression as up to fifty per cent). In MS, the grief cycle is not just associated with diagnosis – you can revisit this cycle many times, be it triggered by a new

	symptom, an unforeseen adjustment in lifestyle or a change in healthcare professional or treatment. However, when we digest our new normal, we are adaptive and resilient. With MS, you have extra things to consider compared to someone without MS. After diagnosis, our team of specialists grows depending on the symptom need. For example, over time, I have experienced care from Neuro-gastroenterology, Neuro-physiotherapy, Urology, Neuro-psychology, as well as my core MS team. It is unlikely that all specialist teams are in one clinic, department or hospital, which often means travel is required, which can mean multiple appointments, extra cost and planning. Many of us have to be strategic with our energy and time. Around 90% of people with MS experience fatigue, one of the more intrusive symptoms in MS, due to the impact it has. Being unable to take medication for fatigue, I must plan my day around its peaks and troughs, rationing energy and prioritising tasks. On weekends, I batch cook for myself and for my family which prepares me for the week ahead, but also ensures that we eat healthy, home-cooked meals. At work, as an individualised work adjustment, I work on a Monday, Wednesday and Friday between 7am and 3pm. I work from home, and meetings or any tasks requiring in-depth work (what I call 'thinking time') are positioned in the morning. Consequently, I am able to work in the earlier part of my day when I am at my most productive and work independently, and I am more able to control my fatigue on non-working days. Some of my MS peers, however, have not been as fortunate and have felt little choice but to stop working or to take ill health retirement. Not only does this mean huge financial consequences and having to apply for state benefits, but this can also have a huge impact on socialisation and overall wellbeing. Having supportive employers is very inconsistent despite most work adjustments being inexpensive. As life progresses, and more 'adulting' is required, we build similar strategies into the decisions we make and future-proof, where we can. For example, being a very pragmatic person, I bought my home with potential future adaptations in mind. Whilst these may never be necessary, this means I do not have to worry about such issues right now. Regular considerations feature around medication and equipment: every month, we have to remember to request prescriptions and then ensure that we make time to receive the order at home via a courier. Practically, this means placing regular reminders to ensure we don't forget, and putting time aside

	(sometimes the whole day) to receive courier deliveries. For those not able to work from home, this can be challenging as medical deliveries are generally only available during weekdays.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The range of treatments available on the NHS has increased dramatically since my first relapse in 2005. Those with Relapsing-Remitting MS currently have access to around twenty MS treatments consisting of injectables, infusions and oral treatments. There seems to be a general understanding that these medications will slow down disease progression, but not heal what has come before. Today, with information more freely available, people with MS have a deeper knowledge of their condition and an appreciation for how important it is to start treatments earlier and the knowledge that should a treatment fail us, we will generally have further options. Through charities, the UK MS Register and social media, there is increased awareness of available clinical trials (e.g. ChariotMS, the 'mega-trial' Octopus for progressive MS), phase III trials (e.g. Tolebrutinib) and emerging new treatments. Within the advanced MS community, e.g. for those with Primary Progressive MS, there is a great concern over the lack of prescribing and administering of Ocrelizumab, the single treatment available for this form of MS, due to ineligibility and cost. Siponimod is available for those with Secondary Progressive MS but only if the MS is still active, unlikely to be received if you are a permanent wheelchair user. HSCT is available for both forms of advanced MS, but many still consider this risky (it is offered in very few NHS centres), is limited in the number of spaces available, and is very costly to undertake abroad. It may be useful for the Committee to understand how a patient might come to decide on a treatment, the decision process and what might impact this. When I was finally eligible for treatment in 2016, due to changes in my balance, Cladribine would not yet be on the market for another year. When I came off my treatment almost two years later, I was offered Cladribine, but was concerned by its unclear association with Cancer, and I chose a less efficacious drug. Fortunately, guidance is now much more tempered in tone and attitudes toward this have changed.

	In late 2021, when I was presented with treatments after a series of relapses, I put together an A3 spreadsheet of treatment options and, using the MS Trust's MS Decisions tool, I systematically wrote up each drug looking at efficacy, life style implications and clinical data. I then scoured online forums, joined treatment-specific online groups and asked my peers with lived experience of those medications questions which I felt were pertinent to me. Only then did I feel I was making the most informed decision I could in choosing Cladribine. What treatment is chosen can depend on the person's attitude to risk, how they will fit the medication into their lives and their overall support system. With all treatments available on the NHS there are side effects and risks. Relapses and disease activity are not the only reasons for coming off a treatment - it is possible that patients come off their medications having had side effects that they feel are too difficult to manage. Not all people with MS making new treatment choices will do the level of research I did. They are more likely to listen to MS peers or to their MS Specialist Nurses (if one is allocated).
10. Is there an unmet need for patients with this condition?	Please note that the following is not an exhaustive list, and other people with MS may have different priorities. **A lack of MS Specialist Nurses** There is very much a postcode lottery when it comes to being appointed the support of an MS Specialist Nurse, an essential 'Jack of all trades' nurse who, despite their 'specialist' title, provide a range of care from guidance on treatments and symptom management to looking holistically at a patient's life and how a range of symptoms may be impacting their MS, including support with work and social care. There are many areas in England where MS patients are not allocated a nurse. In 2021, an MS Trust report noted that the caseload of each MS Specialist Nurse now sits at almost 50% above the recommended level, which surely has an impact on services for those 80% of patients from areas where this is happening. In 2021, almost 150 additional nurses were required for caseloads to be considered sustainable.

	In context, earlier this year, the MS Society estimated that the figure of those living with MS in the UK had risen from 130,000 people to 150,000 (of which 123,442 are in England, a 15% increase from the previous figure). This is worrying as this increase will undoubtedly have an impact on access to care available on the NHS, but is also likely to have wider implications in terms of support in benefits and social care. **'Old School' Attitudes** For a few years, it has been established that treating MS early and aggressively can lead to better patient outcomes delaying disease progression and disability. Yet there are still people with MS who are unable to receive treatment due to the 'wait and see' strategy employed by some Neurologists, becoming an issue when the patient falls out of the eligibility criteria as their MS is considered to be stable. A related issue is around mental health. This is very rarely discussed in appointments either by the patient or by the HCP. Even if the patient does raise this as an issue, there are discrepancies patients face around referral and receiving customised, useful support. One of the necessary skills we learn early on from diagnosis is self-advocacy, and this is commonly used in conversations about treatments, new medications, referrals and support. However, it is difficult to advocate for yourself when you are suffering from pain, overwhelm or fatigue, or if the HCP does not see you as a partner in your care, does not listen, or worse still, gaslights you. Presently, where information is shared openly online, it can be very hard for patients in this position to read and hear their peers receiving different care, as this highlights a disparity in approach. **Delays in receiving treatment** When a new treatment pathway is discussed at a Neurology appointment, the case is then referred to MDT. If approved, there can be tests involved, which can take weeks to book. Once results are in, the distributor has to be informed and medication ordered. Depending on the medication, there needs to be a further discussion with the patient to train them on how to use the drug, the method of delivery, timings, etc. From start to finish, the process may take months. In the meantime, and particularly if there needs to

	be a lead time from the end of one drug to the initiation of another, there is the potential for rebound where the patient is at risk of relapse. **Lack of joined up care** Given that, for many of us, our MS 'team' builds over time, there often feels as if there is a lack of joined up care across the different specialties that become involved in our care and our treatment. The patient is the conduit, which is difficult when they may be suffering from cognitive issues, pain or fatigue on the day of the appointment. There is no one person who has oversight, pulling all the threads together. Consequently, being a patient sometimes feels like being in a full-time job. **Disability progression** Despite the great strides that have been made in disease modifying therapies, particularly over the last decade, people with MS are still accruing disability, and therefore disability progression is still, by far, the greatest unmet need in MS. The other 'holy grail' would be neuroprotection, i.e., repair is surely creating treatments with neuroprotective qualities. Symptoms we currently face can be medicated but they cannot be eradicated.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Previously, I managed the MS using injectables and other oral treatments. I am almost eighteen months post-treatment and Cladribine has been, by far, the most potent and easy-to-use. For the first time since 2021, my last two scans (one during my second year) have showed NEDA. The following are further reasons why I think Cladribine is advantageous to people with MS: 1. Care is carefully managed before treatment begins: • Thorough medical history taken, a blood test and an x-ray are taken before beginning. • Before receiving the tablets, we are fully versed in how to take it. For example, a Neuro-pharmacist met with me and we discussed the medication in great detail, including timings and providing a written plan with dates based on the amount I should take.

	2. Very convenient and easy-to-take – the packaging is a little tricky for those with dexterity issues, however the tablets can be taken at home, there are no special arrangements, and you can carry on with your day. 3. Contraindications anticipated – where other medications may conflict, guidance is given to ensure that you are taking Cladribine at the right three hour 'window' before or after taking the Cladribine, vaccines are recommended 4-6 weeks prior to starting Cladribine. 4. Side effects are temporary. 5. Side effects can be anticipated and planned for, e.g. I stayed away from crowds during the brief window where my lymphocytes were at their lowest, a neurogenic bowel meant I worked with my Neuro-gastroenterologist to pre-empt issues so that I always had a plan of action. 6. You receive support from the MS Specialist Nurse and Adveva teams. 7. There are established patient-led online forums where patients share experiences. This can lead to better management during the courses, e.g. ensuring good levels of hydration to avoid headaches and muscle aches. 8. Based on discussion on these forums, most people seem to have mild side effects and are able to continue working. 9. Patients take two courses of tablets over two separate weeks, for two years, and in between do not have to worry about taking anything else (if/until there is further MS activity). 10. Four relapses in 2021 led me to taking Cladribine in early 2022. Clinical data suggesting a 58% drop in relapses for two years following treatment and 33% slowing of disability (MS Society) gave me more hope than I had had in many years and, to me, it was an obvious choice.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	1. Planning for approximately 1-3 months of feeling energy depletion and increased infection. This can mean your roles and responsibilities at home are delegated and taking sick days from work. 2. In uncommon cases, there can be much longer lymphopenia which means that, for those affected, it can be a waiting game. 3. Those with severe bowel dysfunction prior to the treatment should be aware of the risks, and put in place provision for these.

	4. Side effects, such as hair thinning, though most patients accept this temporary side effect versus disease progression. 5. There are some people for whom Cladribine is not appropriate, e.g. those with issues with the liver, Cancer patients, those planning to conceive in the short-term, etc, however this treatment (like some other MS treatments) should not be offered to these patients.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Cladribine currently sits in the 'More effective' category of disease modifying treatment options, and is currently limited to those with highly active MS or to those for whom MS becomes active whilst taking another treatment. For some time, Neurologists have been discussing 'smouldering' MS, the idea that MS continues to progress without a patient having to have had relapses or that relapses are happening under the radar. I appreciate that this may be a new way of thinking about MS, but it is absolutely key to our decision-making as people with the condition, particularly as we are all doing our best to delay disability for as long as possible. Whilst there have been many more treatment options released in the last decade, the criteria for these tends to narrow down options unless there is proven activity. I believe the current eligibility criteria for Cladribine does not work for people with MS who wish to tackle their condition in a more aggressive way either from the outset or during the course of their disease. It would be more beneficial for Cladribine to reach a larger group of people with MS so that they could have a better chance at delaying any decline. I am not aware of any studies looking at how many times, after being diagnosed, we switch treatments but I would suggest that a person is unlikely to stay on *one* treatment for the duration of their lifetime. Before I switched to Cladribine, I had tried two other treatments and was awaiting receipt of my third when I had the rebound activity of 2021, after which it was decided that we approach this more aggressively with

	Cladribine. If research is correct, there would be far less necessity to switch, potentially for a few years, if Cladribine was offered as a first line treatment.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	I understand that there are inequities but I appreciate that, as a white woman, I am in a more privileged position than others and therefore it would be worth speaking to others more informed on the subject. However, I will relay my concern that those in areas with low social mobility may be without access to MS Specialist Nurse services and thus less informed or able to self-advocate for treatments such as Cladribine.
Other issues	
15. Are there any other issues that you would like the committee to consider?	I appreciate that when considering extending this treatment to a wider MS audience the Committee will be thinking about cost versus gain. To me, this is apparent as per the following: 1. Clinical trials show patients taking Cladribine saw a reduction of 58% in relapse rates in the two years following treatment and 33% slowing of worsening disability (MS Society) 2. For those for whom Cladribine works, there is less reason to switch to other disease modifying therapies. The benefits of receiving Cladribine can continue for many years – • "In terms of time-to-event analysis, patients exposed to cladribine tablets had an estimated median time of 12.0 years until the first subsequent DMT; the corresponding timeframe for patients never exposed to cladribine tablets was 2.8 years " (Classic-MS study) 3. The cost of the treatment in the short-term is likely to make a serious dent in the long-term NHS costs associated with increased disability (reminder: the *current* number of those diagnosed with MS in England is approximately 123,442)

	I understand that Cladribine is costly, however I would ask the Committee to balance this against the long-term costs impacting the NHS and beyond if we do not attempt to give as many patients as possible access to better long-term outcomes.
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether this is appropriate. Ask specific, targeted questions such as "Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?"]	

if not delete highlighted rows and renumber below	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Cladribine is a convenient MS treatment for MS patients which has a good record for reducing relapses and progression and, for those for whom it is most effective, offers long-term benefits, sometimes many years.
- The cost of Cladribine in the short-term, however, is likely to make a serious dent in the long-term NHS (and government) costs associated with increased disability (current estimated figures for MS in England is 123,442).
- The current eligibility criteria for Cladribine does not work for people with MS who wish to tackle their condition in a more aggressive way either from the outset or during the course of their disease.
- It would be more beneficial to offer Cladribine to a larger group of people with MS so that they could have a better chance at delaying disease progression, particularly activity which cannot be seen by MRI scans.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

External Assessment Group's report

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

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None.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Sources are listed under all table and figures in the report where applicable.

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Contributions of authors
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.

Please note that: Sections highlighted in blue and underlined are 'confidential' (CON). Figures that are CON have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink."

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List of Abbreviations

Abbreviation	Definition
ABN	Association of British Neurologists
AE	Adverse event
ARR	Annualised relapse rate
BCMS	British Columbia Multiple Sclerosis
BSC	Best supportive care
CDP	Confirmed disability progression
CI	Confidence interval
CNS	Central nervous system
CRPD	Clinical Practice Research Datalink
CSR	Clinical study report
DMF	Dimethyl fumarate
DMT	Disease-modifying therapy
DP	Disease progression
DRF	Diroximel fumarate
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ERG	Evidence Review Group
FDA	Food and Drug Administration
HL	Cladribine tablets 3.5 mg/kg in Year 1 followed by cladribine tablets 1.75 mg/kg in Year 2 (cumulative dose of 5.25 mg/kg)
HLLL	Cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, Year 3 and Year 4
HLPP	Cladribine tablets 3.5 mg/kg in Year 1, cladribine tablets 1.75 mg/kg in Year 2, followed by placebo in Year 3 and Year 4
HPV	Human papilloma virus
HR	Haraz ratio
HSE	Health Survey for England
HSU	Health state utility
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IRT	Immune reconstitution therapy
ITC	Indirect treatment comparison
ITT	Intention-to-treat
KFS	Kurtzke Functional Systems
LL	Cladribine tablets 1.75 mg/kg in Year 1 and Year 2 (cumulative dose of 3.5 mg/kg)
LLLL	Cladribine tablets 1.75 mg/kg in Year 1, Year 2, Year 3 and Year 4
LLPP	Cladribine tablets 1.75 mg/kg in Year 1 and Year 2, followed by placebo in Year 3 and Year 4
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MS	Multiple sclerosis

NEDA	No evidence of disease activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PICOS	Population, interventions, comparators, outcomes, study design
PP	Placebo in Year 1 and Year 2
PPLL	Placebo in Year 1 and Year 2, followed by cladribine tablets 1.75 mg/kg in Year 3 and Year 4
PPMS	Primary progressive multiple sclerosis
PSS	Personal Social Services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RMS	Relapsing multiple sclerosis
RRMS	Relapsing-remitting multiple sclerosis
SD	Standard deviation
SLR	Systematic literature review
SMPC	Summary of product characteristics
SPMS	Secondary progressive multiple sclerosis
TA	Technology appraisal
UK	United Kingdom
VAS	Visual Analogue Scale

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID 16263	Summary of issue	Report sections
Issue 1	The population include RRMS	2.3
Issue 2	The NMA results should be interpreted with caution	3.4.3
Issue 3	Estimating treatment discontinuation based solely on RCT data may not reflect real-world conditions.	3.5.1.2, 4.2.5.3, 4.2.5.4, 4.2.5.5, 4.2.5.6 & 4.2.5.7
Issue 4	A fixed standardised mortality assumption does not align with the natural history of RRMS.	4.2.5.9.1 & 4.2.5.10
	Potential error in the company's method for deriving treatment discontinuation probabilities from the NMA of RCT data, particularly when real-world evidence on DMT persistence is available.	3.5.1.1
Issue 5	Miscalculation in the acquisition costs of cladribine tablets.	4.2.7.1 & 4.2.7.2
Issue 6	Nurse time to train patients in self-administration of injectable DMTs	4.2.7.2
Issue 7	Incomplete consideration of monitoring costs for cladribine beyond the first year of treatment.	4.2.7.3 & 4.2.7.4
Issue 8	First-year monitoring costs (neurology appointments) for patients on glatiramer acetate and the beta interferons	4.2.7.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are source of data to treatment persistence for cladribine and other DMTs, allowing mortality in RRMS to change based on disability level and type

of MS, and how the resources needed for monitoring cladribine and competitor DMTs are estimated.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Reducing the annualised relapse rate
- Slowing the progression of disease-related disability over time.
- Lessening the care burden associated with more severe disability states.
- Improving treatment persistence, which in turn reduces relapses and slows the progression from healthier to more severe disability health states.

Overall, the technology is modelled to affect costs by:

- One-off drug acquisition and monitoring costs
- Hospitalisation costs associated with occurrence of relapses requiring hospitalisation
- Management and treatment of ill-health associated with worsening disease progression and disability
- Adverse events costs

The modelling assumptions that have the greatest effect on the ICER are:

- Probability of treatment discontinuation
- Assumptions about waning of treatment effect
- Acquisition and monitoring costs of cladribine

1.3 *The decision problem: summary of the EAG's key issues*

Issue 1: The population include RRMS

Report section	2.3
Description of issue and why the EAG has identified it as important	The population of interest include RRMS only in contrast to NICE scope for RMS population. In addition to it, TA493/TA616 explicitly focused on two subgroups of highly active RRMS excluding the population with SPMS. It is worth to note that the over 20 years 50% of RRMS can progress to SPMS**.**
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	None

1.4 *The clinical effectiveness evidence: summary of the EAG's key issues*

Issue 2: The NMA results should be interpreted with caution

Report section	3.4.3
Description of issue and why the EAG has identified it as important	The EAG notes that the NMA results should be interpreted with caution owing to statistically and/or clinically determined uncertainties. Statistical uncertainty could be a result of a smaller number of RCTs that contributed data to the CDP and treatment discontinuations compared to ARR outcomes. Additional uncertainties might have arisen due to differences in the outcome definitions (ARR, CDP, and treatment discontinuation), their time of measurement, and the duration of trials included in the NMA. There is a great uncertainty in the definition and consistency of the NMA outcomes across the trials, especially for CDP and treatment discontinuations.
What alternative approach has the EAG suggested?	The EAG notes that this may have led to inconsistencies between the direct and indirect treatment comparisons in the closed NMA loops thereby suggesting that the transitivity assumption may have been violated.
What is the expected effect on the cost-effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	None

1.5 *The cost-effectiveness evidence: summary of the EAG's key issues*

Issue 3: Treatment discontinuation

Report sections	3.5.1.2, 4.2.5.3, 4.2.5.4, 4.2.5.5, 4.2.5.6 & 4.2.5.7
Description of issue and why the ERG has identified it as important	The probability of treatment discontinuation for cladribine and competitor Disease Modifying Therapies (DMTs) was derived from RCT data. For cladribine, the all-cause treatment discontinuation probability was taken from the CLARITY trial. For competitor DMTs, absolute discontinuation probabilities were generated for each treatment directly from a company-sponsored NMA, which was based on heterogeneously reported treatment discontinuation outcomes in RCTs.
What alternative approach has the ERG suggested?	The EAG thinks the NMA estimates of discontinuation probabilities are not appropriate for the model, primarily because they are derived from RCT data. EAG re-analyses of the company data could not reproduce the company's estimates of treatment discontinuation probabilities generated from the NMA. The EAG considers real-world evidence to be more reflective of the experiences of RRMS patients regarding the discontinuation of DMTs.
What is the expected effect on the cost-effectiveness estimates?	Probability of treatment discontinuation generated from EAG parametric survival modelling of treatment persistence based on observational real-world evidence on UK RRMS patients. For cladribine, this worsens the ICER compared with BSC from the company base case worsens from [redacted] per QALY to [redacted] per QALY (Exponential model prediction of cladribine persistence), [redacted] per QALY gained (Log-normal prediction of cladribine persistence) and [redacted] (Weibull model prediction of cladribine persistence). The ICERs compared with competitor Disease Monitoring Therapies (DMTs) worsened as well.
What additional evidence or analyses might help to resolve this key issue?	The EAG conducted survival modelling of treatment persistence for individuals on DMTs. The probabilities of treatment discontinuation generated from this work could only be used in the deterministic analysis. Incorporating them into the probabilistic modelling requires substantial modification to the company's economic model, which the EAG lacks the resources and time to implement. Observational data on the persistence of some newer drugs (ofatumumab and ponesimod) was lacking.

Issue 4: Constant mortality in RRMS

Report sections	4.2.5.9.1 & 4.2.5.10
Description of issue and why the ERG has identified it as important	The company used a fixed standardised mortality rate (SMR) in its base-case model, which implies that mortality rates for patients with RRMS do not vary with changes in disability progression as indicated by EDSS scores or the form of MS.
What alternative approach has the ERG suggested?	The EAG considers that a variable SMR is more realistic and aligns better with the natural history of RRMS, where mortality increasing with disease progression. The model submitted by the Company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b).
What is the expected effect on the cost-effectiveness estimates?	Changing from fixed to variable SMR worsens the company's base-case deterministic ICER slightly from [redacted] per QALY gained to [redacted] per QALY gained compared with BSC.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is needed as the model accommodates implementation of a variable mortality assumption.

Issue 5: Cost of cladribine tablets

Report sections	4.2.7.2
Description of issue and why the ERG has identified it as important	The dosage of cladribine is weight-dependent, which affects the acquisition cost of the tablets. In the model, acquisition costs are calculated based on the weight distribution observed in the 3.5 mg cladribine and placebo arms of the CLARITY trial. Truncating the weight distribution at the extreme ends (either very high or very low weights) has led to minor errors in calculating the cost of cladribine.
What alternative approach has the ERG suggested?	The EAG corrected this error in the company's model, resulting in an increase in the total acquisition cost per patient from [redacted] (as reported in the company's base case) to [redacted] (as estimated by the EAG). Consequently, the base-case deterministic Incremental Cost-Effectiveness Ratio (ICER) increased marginally from [redacted] to [redacted] per QALY gained compared with BSC. Despite this adjustment, cladribine remained dominant in comparisons with teriflunomide, ocrelizumab, ofatumumab, ponesimod, and diroximel fumarate.
What is the expected effect on the cost-effectiveness estimates?	The base-case deterministic ICER increased marginally from [redacted] to [redacted] per QALY gained compared with BSC. Cladribine remained dominant in comparisons with teriflunomide, ocrelizumab, ofatumumab, ponesimod, and diroximel fumarate.
What additional evidence or analyses might help to resolve this key issue?	None.

Issue 6: Nurse time to train patients in self-administration of injectable DMTs

Report sections	4.2.7.2
Description of issue and why the ERG has identified it as important	The company estimated that 3 hours of nurse time is required for a one-time training of patients on how to self-inject. This was applied to DMTs that require injection, including glatiramer acetate, interferon betas, teriflunomide, and ofatumumab.
What alternative approach has the ERG suggested?	EAG's clinical advice indicates that training patients to self-inject DMTs is conducted by company-sponsored nurses, meaning it does not represent an opportunity cost for the NHS. Therefore, EAG adjusted the model to set the nurse training visits in the first year after treatment initiation to zero for patients on injectable DMTs requiring self-administration.
What is the expected effect on the cost-effectiveness estimates?	The base-case deterministic ICER increased slightly for the injectable DMTs, but not enough to affect the overall conclusions regarding cost-effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence, whether published or from clinical practice, regarding whether training is provided by the healthcare service or the industry, as well as the duration of nurse time required for the training, would help clarify uncertainties related to this parameter in the cost-effectiveness analysis.

Issue 7: Treatment monitoring (neurology consultations and MRI scans) beyond the first-year of treatment initiation.

Report sections	4.2.7.3 & 4.2.7.4
Description of issue and why the ERG has identified it as important	The company assumed that patients treated with cladribine would attend two neurology appointments and have one MRI scan in the first year of treatment initiation. Following this, only annual neurology assessments would be required, with no need for additional MRI scans.
What alternative approach has the ERG suggested?	The EAG's clinical advice suggests that cladribine, as an immune reconstitution therapy (IRT) similar to alemtuzumab (another IRT used for highly-active RRMS), necessitates regular monitoring with clinical and MRI assessments to detect MRI activity or relapse. The EAG interpreted "regular monitoring" to mean two neurology visits and one MRI scan annually, continuing into the second year and beyond for as long as patients remain on cladribine in the model, similar to the company's assumption for the first year.
What is the expected effect on the cost-effectiveness estimates?	This interpretation increases the total discounted monitoring costs of cladribine under the company's base-case assumptions from [redacted] to [redacted] over the modelled 50-year time horizon. The corresponding impact on the ICER for cladribine versus best supportive care (BSC) is an increase from [redacted] per QALY gained to [redacted] per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence, whether published or from clinical practice, is needed to clarify whether ongoing treatment monitoring is required for patients on cladribine beyond the first year and to understand the resource implications for the NHS.

Issue 8: First-year monitoring costs (neurology appointments) for patients on glatiramer acetate and the beta interferons.

Report sections	4.2.7.2
Description of issue and why the ERG has identified it as important	The company's base-case assumed that neurology appointments are required for patients on glatiramer acetate and beta interferons.
What alternative approach has the ERG suggested?	The EAG's clinical advice indicates that neurology appointments in the first year are not routine practice in the NHS for patients on these treatments. Consequently, the number of neurology appointments in the first year was reduced from 2 to zero for patients on glatiramer acetate and beta interferons.
What is the expected effect on the cost-effectiveness estimates?	This adjustment does not affect the ICER for cladribine compared with BSC. Although the ICER for cladribine compared with glatiramer acetate and the beta interferons increased slightly, the change is not significant enough to alter the overall company's base-case cost-effectiveness conclusions.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence, whether published or from clinical practice, regarding routine follow-up neurology appointments for patients on these treatments would help resolve uncertainties related to this parameter in the cost-effectiveness analysis.

1.6 *Summary of EAG's preferred assumptions and resulting ICER*

The summary of the EAG's preferred assumptions on the ICER are presented for the comparison of cladribine with Best Supportive Care (BSC). Comparisons with other ICERs are presented in the EAG report.

Table 2: Summary of EAG's preferred assumptions and ICER

Preferred assumption	Incremental costs	Incremental QALYs	ICER	Change in ICER versus CS base-case
Company base case versus BSC	[redacted]	[redacted]	[redacted]	[redacted]
EAG01: treatment discontinuation sourced from real-world evidence (exponential distribution)	[redacted]	[redacted]	[redacted]	[redacted]
EAG02: Variable SMR	[redacted]	[redacted]	[redacted]	[redacted]
EAG03: Corrected error in acquisition cost of cladribine	[redacted]	[redacted]	[redacted]	[redacted]
EAG04: Monitor of patients on cladribine beyond first-year updated to include 1	[redacted]	[redacted]	[redacted]	[redacted]

MRI and 2 neurology appointments each year				
EAG05: Nurse time to train self-administration reduced from 3 to 0 hours	[redacted]	[redacted]	ICER vs. BSC not affected. ICER compared with affected DMTs increased very slightly	[redacted]
EAG06: Number of neurology appointments in the first-year changed from not routine practice in the NHS for patients on glatiramer acetate and beta interferons.	[redacted]	[redacted]	ICER vs. BSC not affected. ICER compared with affected DMTs increased very slightly	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 *Introduction and Background*

The disease and the treatment overview in the CS section B 1.3 provide a clear and concise description of the classification of multiple sclerosis (MS) into four distinct disease types such as clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). It also appropriately introduces the concept of relapsing MS (RMS) as encompassing both RRMS and SPMS. Epidemiological evidence, indicating that (85%) of MS patients have RRMS [1] and that over 50% progress to SPMS within 20 years [2] provides a strong foundation for understanding the disease's natural history. The progressive nature of MS is primarily linked to a gradual decline in neurological function, leading to increasing disability over time. This progression significantly impacts a patient's quality of life, hindering their ability to carry out everyday activities.

In the UK, over 130,000 people live with MS, affecting about 1 in 500 individuals with nearly 7,000 new cases diagnosed annually. MS is twice as common in women as in men, with an average onset age of 32 years. Among young adults, it is the most common disabling neurological condition and the leading cause of non-traumatic disability in several countries, including the UK.[1]

A UK-based observational study, using data from the Clinical Practice Research Datalink (CPRD), examined comorbidities in 1,713 MS patients from 1993 to 2006, where 77% had RRMS. The study identified chronic lung disease, depression, and cardiovascular conditions.[3] as common comorbidities among MS patients, which are linked to increased relapse rates and negatively affect treatment persistence and disease progression.[4-6]

The CS highlights the impact of MS on quality of life (QoL) by referencing a study across several European countries using the PRIMUS questionnaire, which found that daily living activities become more impaired as disease severity increases.[7] However, the diagram in the CS (Document B 1.3.2 Figure 3) shows progressive impairment for the overall population but does not specifically depict impairment for the UK population.

Economically, the CS estimated the total average annual cost for MS patients in the UK to range from £11,400 to £36,500, based on a study sample of 779 participants, 36.7% of whom had RRMS. The study reported that the total cost of MS is dominated by the cost of disease-modifying therapies (DMTs), particularly for patients with Expanded Disability Status Scale (EDSS) scores of 0-6.5.[8]

While many DMTs for RRMS are effective, they often require continuous immunosuppression and frequent monitoring, which can interfere with daily life. Patients often prefer oral DMTs over injectable or infusion therapies due to convenience,[9] yet non-compliance is common, with over 25% discontinuing treatment within a year due to demanding schedules and treatment fatigue.[10] Moreover, the burden extends to healthcare services, with MS specialist nurses facing unsustainable caseloads. The MS Trust highlights the need for treatments with reduced administration and monitoring burdens to improve patient adherence and alleviate healthcare pressure.

The burden extends to healthcare services, with MS specialist nurses facing unsustainable caseloads and a shortage of multidisciplinary MS services. The CS has reported that the MS Trust specifically highlighted the need for treatments with reduced administration and monitoring burdens to alleviate pressure on healthcare resources and improve patient adherence and quality of life.[11-13]

Regarding equality considerations, the company reported that while MS is more common in the white population, its occurrence in ethnic minorities is increasing. Systemic healthcare disparities and socioeconomic challenges often results poorer outcomes for these groups. High-efficacy DMTs recommended by NICE can be burdensome, making them less accessible to those facing these challenges. The CS states that Cladribine tablets, with a short-course treatment schedule offer efficacy without continuous immunosuppression.

Given this context, the CS argues that cladribine is a more effective treatment option for the RRMS population based on their submitted evidence. Additionally, the submission seeks to broaden the RRMS population eligible for Cladribine, as described and approved in previous NICE recommendations (TA493/TA616).[14, 15]

2.2 *Critique of CS background information on current treatment*

MS affects both the peripheral and central nervous systems, with central nervous system (CNS) issues like local inflammation or degradation becoming more prominent as the disease progresses Therefore, targeting the CNS can be of beneficial for treatment.[16]

Cladribine is a nucleoside analogue of deoxyadenosine that when activated in lymphocytes, selectively reduces T and B lymphocytes, with minimal impact on other immune cells. This leads to pro-inflammatory activity and enhanced anti-inflammatory responses.[17-20] Cladribine also crosses the blood-brain barrier, potentially reducing the CNS inflammation. The company claims that, despite its short half-life, its unique dosing regimen provides effective treatment for at least four years, offering a low treatment burden for patients with active RRMS.
According to the CS section B1.2.2 (and figure 1) the dosing regimen of Cladribine for RRMS as follows:

- Cladribine tablets are taken orally with a recommended cumulative dose of 3.5 mg/kg over two years.
- This is administered as one treatment course of 1.75 mg/kg per year.[17]
- Each course includes two treatment weeks in the first two months of each year, where patients take 10 mg or 20 mg daily, depending on body weight.
- After completing the two courses, no further treatment is needed in Years 3 and 4.[17]

This regimen offers a minimal treatment burden for patients and helps reduce hospital capacity demands by avoiding frequent infusions.

While no curative treatments for MS exist, various oral, injectable, and infusion therapies are available for active RRMS in the UK. Traditionally, treatment follows an escalation strategy, starting with moderately effective, low-toxicity therapies and advancing to more potent options if the disease progresses. However, growing evidence supports early intensive treatment with high-efficacy DMTs, which may provide better long-term outcomes by reducing the risk of irreversible disability, early disease progression, and conversion to secondary progressive MS.

The company cites a retrospective study from the MSBase and Swedish MS registries, which found that starting high-efficacy DMTs within two years of MS onset led to less disability after 6 to 10 years compared to starting treatment later (4 to 6 years after onset).[21] Similar findings from other studies, including a UK cohort, indicate that early intervention with high-efficacy therapies results in more favourable long-term outcomes than beginning with platform therapies.[22-25]
The company argues that the traditional escalation strategy, which starts with less effective therapies, is designed to address safety concerns associated with high-efficacy DMTs.[22, 26, 27] However, long-term safety data for many of these high-efficacy DMTs is favourable. Therefore, relying solely on the escalation approach may be inadequate, as evidence suggests that high-efficacy DMTs are most effective when used early in the disease course.[25, 27, 28]
Among current NICE-recommended options, ponesimod is the only oral DMT for RRMS but requires daily administration whereas Cladribine's unique regimen involves only two weeks of oral treatment per year in Years 1 and 2, providing sustained efficacy for over four years with no need for re-treatment in Years 3 and 4, thereby reducing treatment burden and optimizing healthcare resources.
The company argues that, based on clinical trial evidence and the extended MHRA indication, cladribine should be a high-efficacy option for all active RRMS patients, including those new to treatment or switching therapies. Supported by extensive post-marketing data, this proposal suggests expanding NICE recommendations to match the MHRA indication.

2.3 *Critique of company's definition of decision problem*

Table 3: Summary of decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adult patients with relapsing forms of multiple sclerosis (RMS). The population for whom cladribine tablets has already been evaluated in TA493/TA616 (adults with highly active relapsing multiple sclerosis) will not be considered.	Adults with active relapsing-remitting multiple sclerosis (RRMS)	The decision problem is focused on adults with active RRMS rather than adults with active RMS, as RRMS excludes patients with secondary progressive multiple sclerosis (SPMS). This reflects the target population for reimbursement and is aligned with the submitted evidence. The evidence presented in the submission is based on a phase III RCTs (CLARITY and CLARITY-EXT) that evaluated cladribine tablets compared to placebo in people with RRMS. The submitted evidence does not include data on people with SPMS.	The population of interest include RRMS only in contrast to NICE scope for RMS population. In addition to it, TA493/TA616 explicitly focused on two subgroups of highly active RRMS excluding the population with SPMS. It is worth to note that the over 20yrs 50% of RRMS can progress to SPMS.[2]
Intervention	Cladribine tablets	As per scope	n/a	As per NICE scope
Comparator(s)	For people with active RMS:	For people with active RRMS:	As the company submission does not include evidence on the	As per NICE scope except for SPMS population.

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• optimised standard care with no DMT • beta interferon • peginterferon beta-1a • dimethyl fumarate • diroximel fumarate • glatiramer acetate • teriflunomide • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab • ponesimod For people with SPMS with evidence of active disease: • siponimod • beta-interferon For people that progress on previous lines of treatment and after	• optimised standard care with no DMT • beta interferon • peginterferon beta-1a • dimethyl fumarate • diroximel fumarate • glatiramer acetate • teriflunomide • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ofatumumab • ponesimod	SPMS population and focuses on patients with RRMS (see above), the comparators for the SPMS subgroup are not considered in this submission. Autologous haematopoietic stem cell is not included as a comparator in this submission as it does not address the decision problem: • It is not licenced by the MHRA, the European Medicines Agency (EMA) or the Food and Drug Administration (FDA) for the treatment of RRMS • It is not used routinely in clinical practice in the UK • While it is funded by the NHS, there is currently no NICE	

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	discussion with specialist multidisciplinary team: • autologous haematopoietic stem cell transplantation		recommendation for its use in RRMS • Autologous haematopoietic stem cell is typically reserved for a more severe or progressive population, based on clinical expert opinion.	
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example EDSS) • disease progression • symptoms of multiple sclerosis (such as fatigue,	As per scope	n/a	As per NICE scope

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	cognition and visual disturbance) • freedom from disease activity • mortality • adverse effects of treatment • HRQoL			
Subgroups to be considered	If the evidence allows, the following subgroup of people will be considered: • people who could not tolerate previous treatment	No additional subgroups are suggested.	Merck is not aware of any available data that indicates the relative effectiveness of DMTs will vary between patients who tolerate treatment and those who switch due to intolerance and therefore will not be presenting evidence for this subgroup in this submission. Additionally, the efficacy data in this subgroup is not publicly available for competitor DMTs to be able to assess comparative effectiveness. TA533, TA699, TA767 also did not consider this	

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			subgroup due to lack of evidence.	

3 CLINICAL EFFECTIVENESS

3.1 *Critique of the methods of review(s)*

The company conducted a systematic literature review (SLR) to identify relevant clinical trials supporting the assessment of efficacy, health-related quality of life (HRQoL), safety, and tolerability outcomes in the treatment of relapsed-remitting multiple sclerosis (RRMS). Methods and findings from the SLR are summarized in Appendix D of the Clinical Summary in the CS. However, a predefined protocol for the SLR was not supplied.

Broad searches in a relevant set of bibliographic databases were undertaken in various timepoints and last updated on 6 February 2024 (clarification response C1). Suitable terms, including those for the interventions and comparators listed in the CS decision problem, were included. The searches also included terms for seven other comparators, making it broader. MEDLINE and Embase were searched simultaneously via the Embase.com interface and, appropriately, thesaurus terms for both databases were included in the search. To look for recent records in the first update search, the PubMed interface was searched separately for 'In process' and 'ahead of print' MEDLINE records. Searches were limited to RCTS in MEDLINE and Embase using search filter adapted from a recognised, though unvalidated, source; the Scottish Intercollegiate Guidelines Network (SIGN) search filters.[29] No date limits were used for the database searches, but some publication types (editorials, letters and notes) and animal studies were removed, which is reasonable. The CS states that some supplementary searches were undertaken; it is reported in appendix section D.1.1.1. that the proceedings of 9 relevant conferences between 2013 and 2023 were searched and in the introduction to the flow diagram, numbers of records included from trial registers, bibliographic searching and regulatory agencies are given, but no details of the searches or selection process are provided and therefore the EAG are unable to critique the methods used.

Appendix D, section 1.1.1.2, and Table 7 (pages 27-30, Document B) in the CS reported the full list of included and excluded studies. The EAG team counted 22 excluded (Red) and 39 included (Green) studies, which do not correspond to the numbers reported in the PRISMA diagram (Figure 1, page 25, Document B).

Appendix D, section 1.1.2 in Document B of CS, reported that the company undertook data extraction according to systematic review methodology. However, the items of the data extraction template (such as population characteristics, intervention details, and outcome details) were not clearly reported. Additionally, the method used to agree the data extraction template (e.g., piloting forms) was not clearly defined. The EAG has asked for clarification on SLR methodology, however the clarification responses did not clearly address this.

The company mentioned that the included studies were critically appraised using the NICE manufacturer template (Appendix D, section 1.1.2). However, a complete analysis of quality assessment (QA) and its implications on the final synthesis was not reported. When the EAG sought clarification, the company replied that the Excel file : *Merck_Clinical_NICE quality assessment* evaluated 61 trials from 802 publications. However, QA details were not provided for the 801 publications included in the SLR.

The quality of the steps for searching, assessing eligibility, extracting data, assessing the risk of bias, and synthesising evidence in the SLR was reviewed by EAG team

using a modified version of the ROBIS tool.[30] According to the EAG assessment, the overall risk of bias was classified as 'Unclear concern' because several domains were not reported in detail, Table 4 .

The EAG noted that the study protocol and the restrictions applied to study eligibility in the SLR were not adequately justified, leading to an assessment of "Unclear Concern." Although the company employed a relevant method for study selection, the EAG identified moderate concern regarding data collection and study appraisal. This was due to the company not providing data for all 802 publications, which includes the 61 trials. The EAG consider that limited reporting the 802 publications eligible for SLR as a deviation from the SLR methodology. Additionally, the synthesis of findings from the SLR was also assessed as "Unclear Concern," primarily because the outcomes measured across the trials eligible for the NMA varied.

Table 4. SLR risk of bias

ROBIS domain, and signalling questions	EAG's rating	Reasoning
1: Study eligibility criteria : **Unclear Concern**		
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably No**	There is no mention of protocol reporting, redefined objectives, and eligibility criteria
1.2 Were the eligibility criteria appropriate for the review question?	**Probably No**	The SLR focused on RRMS population and have excluded SPMS [Appendix D 1.1.2, table 6, page 22-24]
1.3 Were eligibility criteria unambiguous?	**Probably Yes**	Eligibility criteria were sufficiently detailed in Appendix 1.1.2, table 6 (page22-24). However, it differed from the NICE scope where the population of interest reported RMS.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Unclear concern**	Restrictions were applied to include only RCTs which the EAG considers appropriate. The justification to focus on RRMS population [B 1.1, table 1, page 13-14] was not satisfactory.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Unclear concern**	Restrictions (such as excluding reviews, editorial, and animal studies) were applied which is reasonable but it was not described/ justified sufficiently in methods [D 1.1.1, table 1- table 5, page 11-20]
Concerns regarding specification of study eligibility criteria	**Unclear concern**	There might be a chance to exclude relevant studies as a result of deviation from NICE's

		scope [B 1.1, table 1, page 13-14]
2: Identification and selection of studies: **Unclear concern**		
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**	Searches were conducted in MEDLINE, Embase, MEDLINE In-process, Cochrane and relevant conference proceedings. Numbers of records from clinical trial registers and regulatory agencies are given in the results, although no details of the searches or selection processes for these sources are provided.
2.2 Were methods additional to database searching used to identify relevant reports?	**Unclear concerns**	Relevant conference proceedings were searched from 2013 to 2023 [D 1.1.1, table 5, page 20], however the restriction on year was not justified. In addition, the method for conducting this search was not reported in detail (e.g. no search terms and initial number of hits).
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably Yes**	The EAG identified a discrepancy in search terms used in Embase and MEDLINE: For line #34 (concept: dimethyl fumarate), the search does not contain the 'freetext' term 'dimethyl fumarate' or the recent EMTREE term 'dimethyl fumerate', which was added into EMTREE in 2021. The previous EMTREE term 'fumaric acid dimethyl ester', various drug ID synonyms and the trade name are used. The EAG tested searching with and without the newer terms and found they did not have a large effect on the overall total and note that in the Cochrane search the MeSH descriptor: [Fumarates] explode all trees, is used, which will help to mitigate this omission.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Probably yes**	There were no restrictions based on date in the database searches. Publication type restrictions such as excluding editorials, letters or

		animal studies, although applied, were not reported in details.
2.5 Were efforts made to minimise errors in selection of studies?	**Probably Yes**	For the primary selection of studies titles and abstracts and full text articles were screened independently by two reviewers with discrepancies resolved by a third reviewer. However, it is not clear whether the method was used in subsequent search updates.
Concerns regarding methods used to identify and/or select studies	**Yes**	Details were provided for study assessment such as a full list of studies with reason for exclusion at the clarification stage.
3: Data collection and study appraisal: **Moderate Concern**		
3.1 Were efforts made to minimise error in data collection?	**Yes**	Data extraction was performed by two independent reviewer and discrepancies were resolved by a third reviewer,
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Probably No**	A list of data extraction file was provided in clarification submission [Merck_Clinical_Data Extraction Grid_inception-2024]. However the document not clearly supporting data extraction for 802 publications.
3.3 Were all relevant study results collected for use in the synthesis?	**Unclear Concern**	Data extraction file was submitted in to answer clarification questions provide outcome data [Merck_Clinical_Data Extraction Grid_inception-2024]. However, the document not clearly reporting outcomes for 802 publications.
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	**Yes**	The company states that risk of bias was assessed using the 'NICE manufacturer's template' assessment tool and assessment was done by two reviewer, with a third independent reviewer to resolve disagreement.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Yes**	The assessment of risk of bias was undertaken by two reviewers and any discrepancies resolved by a third reviewer.
Concerns regarding methods used to	**Unclear Concern**	The clarification document provided QA assessment

collect data and appraise studies		document to support this[*"Merck_Clinical_NICE quality assessment".].* However, the file reported QA for 61 items and not clarify the QA for 802 publications.
4: Synthesis and findings: **Unclear Concern**		
4.1 Did the synthesis include all studies that it should?	**Yes**	The CS identified 61 trials from 802 publications [D1.1.1.1, Figure 1, page 25] and the company clarified in the clarification document [A.4, figure1, page 6] that 61 tries were included in the SLR.
4.2 Were all predefined analyses followed or departures explained?	**Unclear Concern**	No protocol was provided, nor data analysis plan was clearly reported
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Probably Yes**	As per the NICE scope and SLR inclusion criteria, the selected trials for the NMA were composed of adult patients with a confirmed diagnosis of active RRMS. Although some studies also included patients with progressive disease, those trials that included >20% of progressive patients, were not included in the NMA. The posology and mode of administration of any given DMT regimen did not differ across the trials and corresponded to those recommended by NICE scope. Overall, general characteristics of the studies included in NMA were comparable with respect to design features with some variation in trial duration and diagnostic criteria for RRMS.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Probably Yes**	No meta-analysis was conducted. [B2.8page 58]
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	**Yes**	Funnel plots were presented, and sensitivity analysis was conducted.

4.6 Were biases in primary studies minimal or addressed in the synthesis?	**Probably Yes**	The majority of trials included in NMA were generally of good quality (low risk of bias). For about 35%-40% of trials, there was uncertainty with respect to allocation concealment, outcome reporting or randomisation.
Concerns regarding the synthesis and findings	**Unclear Concern**	The NMA outcomes for 3-month CDP, 6-month CDP, and all-cause treatment discontinuations were highly uncertain due to wide and non-significant credible intervals around the estimates of NMA, due to the small number of RCTs that contributed the outcome data. Some trials were not designed to have had a power sufficient for detecting the outcomes of disability progression. It is unclear if the CDP and treatment discontinuation outcome definitions were similar across the trials. Most primary trial publications did not report on ethnicity and prior treatment history. It is not clear what are the treatment modifiers of the cladribine effect.
Summary of concerns identified (Overall risk of bias) in the review		
Risk of bias	**Unclear Concern**	A number of domains were assessed as unclear concern because of limited reporting

The EAG rate the SLR reviewing methods at unclear concern because the majority of the domains were not clearly reported.

3.2 *Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)*

The efficacy, safety, and tolerability of Cladribine were supported by data from the CLARITY and CLARITY-EXT trials.[31, 32] These trials evaluated Cladribine tablets as a monotherapy for treating patients with active RRMS. Both trials were included in the marketing authorisation application to the MHRA and previous NICE submissions (TA493/TA616).[14, 15] The CLARITY trial [31] serves as the foundation for the evidence supporting Cladribine tablets, being included in both the indirect treatment comparison and the economic model. While the CLARITY-EXT trial was not used to inform the economic model, it is detailed in sections B.2.2 to B.2.6 of the CS.

The CLARITY trial was a Phase III, double-blind, parallel-group, placebo-controlled, multicentre study lasting 96 weeks. It compared low-dose Cladribine tablets (3.5

mg/kg cumulative over 96 weeks), high-dose Cladribine tablets (5.25 mg/kg cumulative over 96 weeks), and a placebo. For the current submission, only the outcome data from the low-dose and placebo groups were considered.

After completing CLARITY trial, patients could enter the CLARITY-EXT trial,[32] a Phase IIIb, double-blind, parallel-group, placebo-controlled, multicentre randomised (1:1:1) study also lasting 96 weeks. This trial aimed to evaluate the sustained efficacy, safety, and tolerability of Cladribine. In CLARITY-EXT, patients were re-randomised (2:1) to receive either 3.5 mg/kg of Cladribine tablets or a placebo.

Additionally, the company identified the ORACLE MS [33] and PREMIERE [34] studies, which were included in the safety analysis alongside CLARITY [31] and CLARITY-EXT [32] (Section B.2.10.3 of the CS). The clarification document noted that both studies were conducted by Merck and contribute to the evidence base for oral Cladribine tablets, providing supplementary safety data. However, the full methodology, including the dosage regimen, was not clearly presented.

A summarised overview of the methodologies for the CLARITY and CLARITY-EXT trials is presented in the table Table 5 and Table 6, with cross-references to the specific sections in CS for more additional information. Any areas identified by the EAG for further consideration are discussed in the following sections.

Table 5. Summary overview of the trial methodology (CLARITY)

Method step	**Summary of approach used**	**Section(s) of CS of relevance or other source**
Method of randomisation	Randomization was carried out using a central system and a computer-generated code, with dynamic site allocation in permuted blocks of six.	Giovannoni et al 2010 [31]
Eligibility criteria	• Diagnosis of MS according to the McDonald criteria • RRMS with ≥1 relapses within 12 months before study • Clinically stable and not had a relapse within 28 days prior to day 1 of study • MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria • EDSS score between 0 to 5.5, inclusive	CS Section B2.3 Table 5

Trial drugs by period of study	Patients (N=1,326) were randomised to receive: • LL- Cladribine tablets 3.5 mg/kg cumulative over 96 weeks (n=433) • HL - Cladribine tablets 5.25 mg/kg cumulative over 96 weeks (n=456) *[this group is not considered for the scope of this appraisal]* PP- Placebo (n=437)	CS Section B2.3 Table 5, Section B2.3.1
Primary endpoints of relevance to the decision problem	The primary end point was the rate of relapse at 96 weeks. Annualised relapse rate xwas defined as an increase of 2 points in at least one functional system of the Kurtzke Functional Systems (KFS), also known as Expanded Disability Status Scale (EDSS), or an increase of 1 point in at least two functional systems (excluding changes in bowel or bladder function or cognition) in the absence of fever, lasting for at least 24 hours and to have been preceded by at least 30 days of clinical stability or improvement.	Giovannoni et al 2010 [31]
Statistical analysis	The primary analysis was performed on the intention-to-treat (ITT) population. • The ARR endpoint was analysed using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable • An approximate Chi-square test based on Wald statistics was	CS Section B 2.4 Table 10

	used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error • The assumption for proportional hazards held for the ITT population and therefore the Cox regression methodology was appropriate; this was acknowledged by the ERG in TA493/TA616	

Table 6. Summary overview of the trial methodology (CLARITY-EXT)

Method step	**Summary of approach used**	**Section(s) of CS of relevance or other source**
Method of randomisation	Followed the same procedure of CLARITY. Patients were assigned using a central system and a computer-generated randomization code. Each patient received a unique 12-digit ID number, where the first five digits represented the trial number, the next three indicated the site number, and the last four were the sequential subject number. Patients retained the same last seven digits from the previous CLARITY trial, with only the five-digit trial number prefix updated.	Giovannoni et al 2018 [32] Clarification response A7
Eligibility criteria	Patients who were enrolled in CLARITY and either completed treatment and/or completed scheduled visits for the full 96 weeks	CS Section B2.3 Table 5

Trial drugs by period of study	Patients from CLARITY (N=806) were randomised (2:1) to receive either further doses of Cladribine tablets (LL) or placebo (PP): • LLPP - cumulative 3.5 mg/kg (n=98), licenced does • HLPP - cumulative 5.25 mg/kg (n=92) • LLLL - cumulative 7.0 mg/kg (n=186) • HLLL - cumulative 8.75 mg/kg (n=186) PPLL - cumulative 3.5 mg/kg (n=244)	CS Section B2.3 Table 5,
Primary endpoints of relevance to the decision problem	At 120 weeks, the safety endpoints included: • Incidence of all treatment-emergent adverse events (AEs) and serious adverse events (SAEs). • Proportion of patients developing Grade 3 or 4 lymphocyte toxicity (lymphopenia) based on CTCAE criteria. • Counts of white blood cells, neutrophils, platelets, CD4+ cells, haemoglobin, alanine aminotransferase, aspartate aminotransferase, and bilirubin levels. Clinical endpoints included the annualized relapse rate (ARR), the percentage of patients without qualifying relapses, the duration until the first qualifying	Giovannoni et al 2018 [32]

	relapse, and the time to confirmed progression on the Expanded Disability Status Scale (EDSS).	
Statistical analysis	• The primary safety analysis included all patients who received at least one dose of Cladribine tablets and underwent at least one safety assessment during the trial. Efficacy analyses were conducted using the ITT patient population. • The ARR endpoint was analysed using a Poisson regression model with fixed effects for treatment group and region with log of time on trial as an offset variable • An approximate Chi-square test based on Wald statistics was used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error • The assumption for proportional hazards held for the ITT population and therefore the Cox regression methodology was appropriate; this was acknowledged by the EAG in TA493/TA616	CS Section B 2.4, Table 10

3.2.1 Trial drugs and posology

CS Section B2.3.3 outlines the SmPC for Cladribine, recommending a cumulative dose of 3.5 mg/kg over 2 years, with 1.75 mg/kg per year. Each year includes two treatment weeks, one at the start of the first month and one at the start of the second month. If necessary, the second year's treatment can be delayed up to 6 months for

lymphocyte recovery. Each treatment week involves 4-5 days of 10 mg or 20 mg doses, depending on body weight. No further treatment is needed in years 3 and 4.

Patients completing CLARITY were eligible to join CLARITY-EXT based on lymphocyte count. There was a treatment gap period with varying start times for CLARITY-EXT (the median gap duration for the overall population was 40.3 weeks).[32] The company clarified that in the CLARITY trial, four patients required a delay in their treatment course: two in the placebo arm and two in the high-dose Cladribine arm. No delays were reported for patients receiving the low dose Cladribine tablets (response to clarification question A2).

3.2.2 Trial population

The phase III CLARITY trial randomized patients diagnosed with relapsing–remitting multiple sclerosis (RRMS) based on the McDonald criteria. Eligible patients had MRI lesions consistent with multiple sclerosis (per Fazekas criteria), experienced at least one relapse within the past 12 months, had an EDSS score of 5.5 or lower, and were clinically stable with no relapses in the 28 days prior to the study. The CLARITY trial was conducted across 32 countries,[31] including the UK, while CLARITY-EXT took place in 30 countries, with six sites in the UK.[32]

Baseline characteristics for the CLARITY trial population are detailed in CS Section B.2.3.5 Table 9. Overall, the baseline characteristics were similar between the low-dose and placebo groups. However, a higher percentage of patients in the placebo group had previously been treated with DMT compared to the Cladribine 3.5 mg/kg group ([redacted], respectively, as reported in Merck Group., CLARITY GEVD Re-Analysis. Data on file. 2017. provided with the CS). Additionally, about two-thirds of the participants in both treatment groups were female. The mean EDSS score was comparable for both groups [2.9 (1.3) Vs 2.8 (1.2)]

In the CLARITY-EXT trial, the LLPP treatment group exhibited patient characteristics similar to those in the CLARITY trial. However, only [redacted] [CS Section B.2.3.5 Table 9. and Merck Group., CLARITY GEVD Re-Analysis. Data on file. 2017, provided with the CS] of these patients had received treatment within three months prior to the study, and the average disease duration was shorter. Similar to CLARITY, the CLARITY-EXT has [redacted] of female patients

3.2.3 Risk of bias assessment

The company assessed the risk of bias for the trials based on criteria such as randomisation method, allocation concealment, blinding of treatment assessors, baseline characteristics of prognostic factors, and outcome assessment. These assessments were reported in CS Section B.2.5 Table 11 and Appendix D.1.3 Table 18. Although the tool used for the risk of bias assessment was not mentioned in CS Section B.2.5, the company clarified this in the EAG's clarification document A8.

The EAG conducted an independent risk of bias assessment using the Cochrane RoB tool [35] and compared their findings with those in CS Section B.2.5 Table 11. For the CLARITY trial, the EAG's judgments differed regarding prognostic factors, dropout rates, and outcome measures between groups, Table 7. Overall, both trials were well conducted.

Table 7. Critique of Risk of bias assessment

Trial	CLARITY	EAG Judgement	CLARITY-EXT	EAG Judgement
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	No (More DMT treatment among Placebo group)	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Yes (13% withdrawal in placebo group with 3.4% due to 'other' reasons. Whereas 8.1% withdrawal among Cladribine 3.5mg/kg group with 2.6% due to 'other' reasons) [31]	No	Yes (CLARITY EXT was completed by 89, 90.8% patients with four patients discontinued due to 'other' reasons)[32]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Unclear (There was revised approach and re analysis)[36]	No	Unclear (No protocol was supplied)

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Appropriate methods were used to account for missing data*	Yes	Yes. Appropriate methods were used to account for missing data*	Yes

3.2.4 Description and critique of the results of CLARITY and CLARITY-EXT

The clinical outcome of CLARITY was reported in CS Section B.2.6. The analysis was done among the ITT population. The values presented in this submission were from 2017 re analysis where the company amended the statistical regarding the missing data and reanalysed.[36]

3.2.4.1 CLARITY- endpoint associated with relapse

CS Section B.2.6.1.1, Table 12 reported the qualifying ARR at 96 weeks in the CLARITY trial. The data indicated that the 3.5 mg/kg Cladribine group had a statistically significant [redacted] relative reduction in qualifying ARR compared to the placebo group: [redacted] Vs [redacted]. Additionally, there was a significant delay in the time to first qualifying relapse for the Cladribine group compared to placebo ([redacted]. The proportion of patients who remained relapse-free at both 48 and 96 weeks was higher in the Cladribine group compared to the placebo group: at 48 weeks [redacted] and at 96 weeks [redacted] [CS Section B.2.6.1.1 table 13].

3.2.4.2 CLARITY- endpoint associated with disability (CDP)

In Section B.2.6.1.2 of the CS, the 3-month and 6-month CDP outcomes were presented for patients treated with 3.5 mg/kg Cladribine compared to those received placebo. According to Table 14 in the CS, the Kaplan-Meier estimates indicated that a greater proportion of patients in the Cladribine group[redacted] remained progression-free at 3 months compared to the placebo group [redacted], with statistically significant hazard ratio (HR [redacted], p [redacted]) estimates supporting this finding. Moreover, at the 96-week mark, a higher percentage of patients in the Cladribine group remained free from 3-month CDP [redacted] and a greater number also experienced 3-month CDP [redacted], compared to the placebo group.

In Table 15 of Section B.2.6.1.2 of the CS, the post hoc analysis for the 6-month CDP was presented. It is worth noting that this post-hoc was conducted because NICE prefers CDP6 compared to CDP3. This analysis, much like the 3-month CDP, showed a significant [p [redacted]] reduction in the risk of disease progression for patients in the Cladribine group [redacted] compared to those receiving a placebo [redacted], as indicated by the reported hazard ratio [redacted]. Additionally, a higher percentage of patients in the Cladribine group remained progression-free ([redacted], and fewer patients

experienced progression ([redacted]) compared to the placebo group suggestive of better improvement with Cladribine 3.5mg/kg dosage.

3.2.5 Additional outcomes

3.2.5.1 CLARITY- end point associated with MRI lesions

Appendix D 1.4.1 reported additional endpoint outcomes associated with MRI lesion and table below describes the relative reduction of MRI lesion at 96 weeks. Overall, treatment with 3.5 mg/kg Cladribine tablets significantly reduced T1 Gd+, active T2, CU, and T1 hypointense lesions compared to placebo ($p<0.001$). Additionally, more patients on Cladribine were free of MRI lesion activity. These results confirm the efficacy of Cladribine in reducing relapses and disability progression.

3.2.5.2 CLARITY NEDA 3 post-hoc analysis

The post-hoc analysis included the measurement of NEDA-3, a cumulative measure encompassing no relapses, no new MRI lesions, and no 3-month confirmed disability progression (CDP) over 0-96 weeks. The CLARITY trial reported a significant improvement in NEDA-3 status for the Cladribine group (compared to placebo, with a reported hazard ratio (HR) estimate [redacted] [CS section B 2.6.1.3 Table 18].

The company performed additional outcome analyses for the CLARITY trial, which were deemed satisfactory in the previous submission (TA493/TA616). However, post-hoc analyses can introduce bias, and the lack of pre-specified validation may undermine the robustness of the findings. Notably, the results from these post-hoc analyses were not included in the indirect comparison of Cladribine 3.5 mg/kg efficacy.

3.2.5.3 CLARITY Rescue medicine

Fewer patients in the Cladribine group required rescue medication ([redacted]% Vs [redacted] %), and the mean duration ([redacted]) of rescue medication was shorter compared to the placebo group.

3.2.5.4 CLARITY HRQoL

In the CLARITY trial, patient-reported outcomes were assessed using several HRQoL measures, including the MSQoL-54, EQ-5D, and SF-36. The CS reported that the measure for SF-36 was not evaluated at the baseline and justified that the measure will not impact the treatment effect analysis. In the previous review (TA493/TA616), the EAG expressed general satisfaction with the HRQoL analysis methodology but highlighted some concerns about data handling. Similarly, the EAG team for this submission also raised concerns regarding these issues.

The primary outcome measure was the MSQoL-54 physical function domain, which showed no statistically significant difference between the 3.5 mg/kg cladribine tablets and placebo groups [redacted] for non-imputed and imputed results, respectively). Secondary MSQoL-54 outcomes showed no significant differences, possibly due to high baseline HRQoL and ceiling effects.

In contrast, the EQ-5D VAS and index scores indicated a slight but statistically significant improvement in HRQoL with 3.5 mg/kg cladribine tablets ([redacted], respectively).

3.2.5.5 CLARITY EXT- endpoint associated with relapse

CS Section B.2.6.2.1, Table 18 reported the qualifying ARR at 96 weeks in the CLARITY-EXT trial. It was found that in the LLPP group, patients who received a cumulative dose of 3.5 mg/kg cladribine tablets over 4 years, including data from the CLARITY trial, had an ARR of [redacted]. During the CLARITY-EXT trial, the ARR was numerically higher in the LLPP treatment group compared to the CLARITY group, although this difference was not statistically significant (p=[redacted]). It is worth to note that an exception was made for defining qualifying relapses during the gaps between the CLARITY and CLARITY-EXT trials, as well as between the end of CLARITY-EXT and the start of the follow-up phase. Relapses during this were self-reported and included regardless of qualifying status. Analyses cover the entire period from CLARITY to CLARITY-EXT, including these gaps.

3.2.5.6 CLARITY-EXT endpoint associated with disability (CDP)

In Section B.2.6.2.2 of the CS, CDP outcomes at 3 months and 6 months for CLARITY EXT were reported. Table 19 showed that the progression-free 3-month CDP rate for the LLPP group was [redacted] at 48 weeks, dropping to [redacted] at 96 weeks, and ending at [redacted] by the study's conclusion. In contrast, Table 20 reported that the progression-free 6-month CDP rate was [redacted] at 48 weeks, decreased to [redacted] at 96 weeks, and reached [redacted] by the end of the study, indicating a better efficacy of Cladribine.

3.2.5.7 CLARITY-EXT end point associated with MRI lesions

Appendix D1.4.2 reported MRI lesion outcomes evaluated as part of additional outcome measure. The EAG raised concern on the interpretation of MRI results due to variability in scan timing and clinical events during treatment gaps between CLARITY and CLARITY-EXT. Overall, the proportion of patients without new T1 Gd+ lesions was [redacted] at 48 weeks, [redacted] at 96 weeks, and [redacted] at the study's end. Conversely, the proportion of patients with new T1 Gd+ lesions was [redacted] at 48 weeks, [redacted] at 96 weeks, and [redacted] at the end of the study [table 22 of appendix]

For active T2 lesions-free patients, there was a gradual decrease over time: [redacted] were free of active T2 lesions at 48 weeks, [redacted] at 96 weeks, and [redacted] by the end of the study. However, Table 23 of the appendix (reported below) reported an increase in the proportion of patients with active T2 lesions, with [redacted] at 48 weeks, [redacted] at 96 weeks, and [redacted] at the study's conclusion.

Table 8. Active T2 lesions in CLARITY-EXT

Outcome	LLPP (N=98)
Number of active T2 lesions	
Adjusted mean (95% CI)	[redacted]
Cumulative number of active T2 lesions	
Mean (SD)	[redacted]
Median (min, max)	[redacted]
Proportion of patients with no active T2 lesions at week 48, n (%)	
Active T2 lesion	[redacted]
Active T2 lesion lesion-free	[redacted]

Outcome	LLPP (N=98)
Unknown*	[redacted]
Proportion of patients with no active T2 lesions at week 96, n (%)	
Active T2 lesion	[redacted]
Active T2 lesion lesion-free	[redacted]
Unknown*	[redacted]
Proportion of patients with no active T2 lesions at end of the study, n (%)	
Active T2 lesion	[redacted]
Active T2 lesion lesion-free	[redacted]
Unknown*	[redacted]

The adjusted mean number of CU lesions in the LLPP treatment group was [redacted] as shown in Table 24of appendix. The mean cumulative number of CU lesions for the licensed LLPP treatment group was [redacted]. By week 48, [redacted] of patients had no CU lesions, but this proportion decreased to [redacted]% by week 96. At the end of the study, [redacted] of patients were reported to have no new CU lesions.

As detailed in Table 25 of CS appendix. the LLPP treatment group had an adjusted mean of [redacted] new T1 hypointense lesions per patient per scan ([redacted]). The cumulative mean number of new T1 hypointense lesions for LLPP patients was [redacted]). At week [redacted], [redacted] of patients in the LLPP group had no new T1 hypointense lesions. This proportion decreased to [redacted] at week 96 and further dropped to [redacted] by the end of the study,

The volume of T1 hypointense lesions showed a general reduction over time. Initially, there was a decrease of [redacted]mm³ at week 48, with a confidence interval indicating variability. This reduction continued at week 96, with a further decrease of [redacted] mm³. For active T2 lesions, a substantial reduction was observed: a decrease of [redacted] mm³ at week 48 and an additional reduction of [redacted] mm³ at week 96. The data suggest a significant decrease in both types of lesions over the study period.[Table 26 of appendix].

3.2.5.8 CLARITY-EXT NEDA 3

CS reported that, in the CLARITY EXT trial, [redacted] of patients in the LLPP group achieved NEDA-3 at Year 1, while [redacted] reached this milestone by Year 2.

3.2.5.9 CLARITY-EXT Rescue treatment

Only [redacted] of LLPP patient required rescue treatment.

3.2.5.10 CLARITY-EXT HRQoL

Patients in the LLPP treatment group experienced overall improvements in HRQoL, as evidenced by enhanced EQ-5D VAS and index scores, as well as better mental and physical health composite scores on the MSQoL-54.

No subgroup analysis or meta-analysis was performed.

3.2.6 CLASSIC MS

CS Section B2.6.3.1 reported addition evidence of CLASSIC MS which reported long term mobility and disability of Cladribine.[37] This is a follow up study of CLARITY and CLARITY EXT. CLASSIC MS is a multicentre, ambispective Phase IV trial conducted across 98 centres in 29 countries. However, the methodology did not explicitly detail the inclusion of UK centres.

The analysis included patients from the CLARITY trial, regardless of whether they later enrolled in the CLARITY-EXT trial, for which the median time to follow-up in CLASSIC-MS since the last parent study dose was 10.9 years (range: 9.3-14.9). The participants to be eligible required ≥1dosage of Cladribine or placebo. The primary objective of the CLASSIC-MS study was to assess long-term mobility, defined as no wheelchair use in the 3 months before the first visit and no bedridden status since the last dose of the parent study (EDSS score <7). The secondary objective aimed to evaluate long-term disability status, specifically ensuring no use of an ambulatory device (EDSS <6) since the last parent study dose. The tertiary objectives focused on analysing real-world treatment patterns, including the number, type, and timing of subsequent DMTs.

The findings reported that, a larger proportion of patients treated with cladribine tablets reported no subsequent treatment compared to those not exposed (50.3% vs. 26.8%), though this difference was not statistically significant. Patients exposed to cladribine tablets were also less likely to use additional DMTs during a median follow-up of 10.9 years (55.8% of the exposed vs. 26.8% of the non-exposed), with 58.1% of those receiving cladribine tablets at 3.5 mg/kg for 2 years using no further DMTs. Time-to-event analyses showed that cladribine-treated patients had a longer median time to the first subsequent DMT (12 years vs. 2.8 years for the non-exposed group), and better outcomes were observed in responder analyses over the 4 years following the last dose of the parent study.

3.3 *Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison*

3.3.1 Description of the NMA and individual primary studies

The company conducted a network meta-analysis (NMA) to assess the clinical effectiveness of cladribine tablets compared to other disease-modifying therapies (DMTs) licensed in the UK in adult patients with active relapsing-remitting multiple sclerosis (RRMS).

The NMA was based on the evidence identified from a company-conducted systematic literature review (SLR) whose objective was to synthesize the evidence from randomised controlled trials (RCTs) on efficacy, safety, health-related quality of life (HRQoL), and tolerability outcomes in relation to cladribine tablets and other active treatments used in adults with active RRMS, in accordance with the National Institute for Health and Care Excellence (NICE) decision problem. Further details of the SLR methodology (literature searches, data extraction, and risk of bias assessment strategies) are provided in the EAG report (section 2.1) and Appendix D (sections D.1.1.1-1.1.2 and section D.1.3, Table 18) of the company submission (CS).

The SLR searches identified 61 RCTs of which 38 were included in the NMA (Appendix D.1.1.1-1.1.3; Document B.2.9.2). Since the NMA focused on all NICE-approved DMTs for treatment of active RRMS in the UK, trials with intervention or comparator outside the NICE's scope of the submission were not included in the NMA.

Amongst 61 RCTs identified by the SLR searches, only one study CLARITY (n=1,326)[31] (Merck Group. CLARITY GEVD Re-Analysis. Data on file.; 2017.) A phase III trial evaluated cladribine tablets (3.5 mg/kg) as a monotherapy for the treatment of patients with active RRMS. Upon completion of CLARITY, patients were then eligible for entry into extension trial, CLARITY-EXT (n=806) (Merck Group. CLARITY-EXT GEVD Re-Analysis. Data on file.; 2017.) in which they were re-randomised to receive cladribine tablets 3.5 mg/kg or placebo. CLARITY and CLARITY-EXT trials were included in the marketing authorisation application to the Medicines and Healthcare products Regulatory Agency (MHRA) for cladribine tablets and the prior NICE submission (TA493/TA616).[14, 38] However, only the CLARITY study was included in the NMA. The company did not include the CLARITY-EXT study in the NMA due to the lack of a common treatment arm with competitor trials and heterogeneity of the study designs associated with studies evaluating long-term (> 2 years) data for active RRMS treatments. More detailed information about the design, methodological quality/risk of bias, population, treatment, and outcome characteristics of the CLARITY trial is provided in the EAG report (section 2.2), Document B (sections B.2.3-B.2.5), and Appendix D (section D.1.4) of the CS.

The EAG agree that in the absence of head-to-head RCT evidence comparing cladribine tablets with relevant licensed active comparators (i.e., other disease-modifying treatments), the NMA is an appropriate methodological option to indirectly compare the clinical efficacy of cladribine tablets to that of other DMTs licensed in the UK for treating patients with active RRMS.

The company assessed the availability of relevant reported data to assess the feasibility of NMA. Given the evidence available from the potentially relevant RCTs, the NMA focused on the assessment of 4 efficacy outcomes: annualised relapse rate (ARR), 3-month confirmed disability progression (3-month CDP), 6-month CDP, and treatment discontinuation. In individual trials, ARR was measured as the incidence rate (number of relapses within a treatment group per person-years), analysed as a Poisson distribution outcome, and expressed as incidence rate ratio (IRR) with 95% credible interval (95% CrI). The remaining NMA endpoints 3-month CDP, 6-month CDP, and treatment discontinuation assuming to follow exponential distribution, were analysed as 'time to event' outcomes, modelled as binomial likelihood with cloglog link function, and expressed as Cox proportional-hazards hazard ratios (HR) with 95% credible interval (95% CrI) (the CS Appendix D.1.1.4.4). Note that '6-month CDP' contributed by the CLARITY in the NMA was a post-hoc measured outcome.

The company performed NMAs using a hierarchical Bayesian approach with Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS. A summary of the methodological and statistical approach of taken by the company for the NMAs is provided in Appendix D (section D.1.1.4.4) of the CS. The company opted to run an arm-based rather than contrast-based model in order to maximise the amount of information contribution to the NMA for estimating RRs and HRs. These analyses were validated by comparing HRs and relative ARR reported across

the studies contributing to the analysis versus posterior estimates from the NMA. Both fixed and random effects models were considered as part of this analysis. The choice of random versus fixed effects model was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC). The model with lowest DIC and/or the closest total residual deviance to the number of data points in the model were considered the best fitting model. Based on the model fit statistics, heterogeneity in the patient population and trial design, the base case NMA for ARR, 3-month CDP, 6-month CDP and treatment discontinuations was analysed using a random effects model.

The company stated that an arm-based model over a contrast-based model was used to estimate the HRs and relative ARR to increase the amount of evidence contribution in the NMA. These analyses were validated by comparing HRs and relative ARR reported across the studies contributing to the analysis versus posterior estimates from the NMA. In order to further validate the output of the NMA, anchor-based indirect treatment comparisons were also conducted.

The summary of 38 trials included in the NMA by their contribution to each NMA outcome, are presented in Table 9 of the EAG report (from Table 21 of the CS Document B.2.9.2). As per the NICE scope and SLR inclusion criteria, the selected trials for the NMA were composed of adult patients (≥18 years) with a confirmed diagnosis of active RRMS. Although some studies specified RRMS as an inclusion criterion, they also included some patients with progressive disease. In this case, trials whose population was represented with more than 20% of progressive patients, were not included in the NMA.

The company assessed the risk of bias (RoB) of individual studies included in the NMA using NICE's checklist, which is provided in Appendix D (section D.1.3, Table 18) of the CS.

Table 9. Summary of trials included in the NMA of adults with active RRMS and reported outcomes (from Table 21 of the CS Document B.2.9.2)

Study name (author, year)	Intervention (N)	ARR (rate ratio)	3-m CDP (time to)	6-m CDP (time to)	Treatment discontinuation (time to)
ADVANCE (Calabresi 2014a) [39]	Peginterferon 125 µg Q2W (512)	✓		✓	
	Placebo (500)				
APEX 2019 (Saida et al. 2019) [40]	Dimethyl fumarate 240 mg (57)	✓			✓
	Placebo (58)				
APOLITOS 2022 (Kira et al. 2022) [41]	Ofatumumab 20 mg SC (43)	✓			✓
	Placebo (21)				
	Ofatumumab 20 mg SC (465)	✓	✓	✓	✓

Study name (author, year)	Intervention (N)	ARR (rate ratio)	3-m CDP (time to)	6-m CDP (time to)	Treatment discontinuation (time to)
ASCLEPIOS I 2020 (Hauser et al. 2020)[42]	Teriflunomide 14 mg PO (462)				
ASCLEPIOS 2 2020 (Hauser et al. 2020)[42]	Ofatumumab 20 mg SC (481)	✓	✓	✓	✓
	Teriflunomide 14 mg PO (474)				
BECOME trial (Cadavid 2009) [43]	Glatiramer acetate 20 mg QD (39)	✓		✓	✓
	Interferon beta-1b 250 µg QOD (36)				
BEYOND trial (O' Connor 2009) [44]	Glatiramer acetate 20 mg QD (448)	✓	✓		✓
	Interferon beta-1b 250 µg QOD (897)				
Bornstein 1987 [45]	Glatiramer acetate 20 mg QD (25)	✓	✓		
	Placebo (25)				
BRAVO trial (Vollmer 2014) [46]	Interferon beta-1a 30 µg IM QW (447)	✓	✓	✓	
	Placebo (450)				
Calabrese 2012 [47]	Glatiramer acetate 20 mg QD (55)	✓			
	Interferon beta-1a 44 µg SC TIW (55)				
	Interferon beta-1a 30 µg IM QW (55)				
CLARITY trial 2010 [31]	cladribine tablets 3.5 mg/kg (433)	✓	✓	✓	✓
	Placebo (437)				
CombiRx trial (Lublin 2013) [48]	Glatiramer acetate 20 mg QD (259)	✓		✓	
	Interferon beta-1a 30 µg IM QW (250)				
CONFIRM trial (Fox 2012)[49]	Dimethyl fumarate 240 mg BID (359)	✓	✓	✓	✓
	Glatiramer acetate 20 mg QD (350)				
	Placebo (363)				

Study name (author, year)	Intervention (N)	ARR (rate ratio)	3-m CDP (time to)	6-m CDP (time to)	Treatment discontinuation (time to)
Copolymer1 trial (Johnson 1995) [50]	Glatiramer acetate 20 mg QD (125)	✓	✓		
	Placebo (126)				
DEFINE Trial (Gold 2012) [51]	Dimethyl fumarate 240 mg BID (411)	✓	✓	✓	✓
	Placebo (410)				
Etemadifar 2006 [52]	Interferon beta-1a 30 µg IM QW (30)	✓			
	Interferon beta-1a 44 µg SC TIW (30)				
	Interferon beta-1b 250 µg QOD (30)				
European and Canadian Glatiramer trial (Comi 2001) [53]	Glatiramer acetate 20 mg QD (119)	✓			
	Placebo (120)				
EVOLVE-MS 2 2020 (Naismith et al. 2020) [54]	Dimethyl fumarate 462 mg PO (251)				✓
	Diroximel fumarate 240 mg PO (253)				
EVIDENCE trial (Schwid 2007) [55]	Interferon beta-1a 44 µg SC TIW (339)	✓			
	Interferon beta-1a 30 µg IM QW (338)				
Gala trial (Khan et al. 2013) [56]	Glatiramer acetate 40 mg TIW (943)	✓			✓
	Placebo (461)				
Gate trial (Cohen et al. 2015)[57]	Glatiramer acetate 20 mg QD (Generic) (355)	✓			✓
	Glatiramer acetate 20 mg QD (Branded) (357)				
	Placebo (84)				
IFNB MS trial (Duquette et al. 1993)[58]	Interferon beta-1b 250 µg QOD (124)	✓	✓		✓
	Placebo (123)				
IMPROVE trial (Stefano et al. 2012)[59]	Interferon beta-1a 44 µg SC TIW (120)	✓			
	Placebo (60)				

Study name (author, year)	Intervention (N)	ARR (rate ratio)	3-m CDP (time to)	6-m CDP (time to)	Treatment discontinuation (time to)
INCOMIN trial (Durelli et al. 2002)[60]	Interferon beta-1a 44 µg SC TIW (92)	✓		✓	✓
	Interferon beta-1b 250 µg QOD (96)				
Kappos 2011 [61]	Interferon beta-1b 250 µg Q1W(55)	✓			
	Placebo (54)				
Knobler 1993 [62]	Interferon beta-1b 250 µg TIW(6)	✓			
	Placebo (7)				
MS200527-0086 (Montalban et al. 2019) [64]	Dimethyl fumarate 120 mg BID for 7 days, then 240 mg BID daily PO (54)	✓			✓
	Placebo (53)				
MSCRG trial (Jacobs et al. 1996)[65]	Interferon beta-1a 30 µg IM QW (158)	✓		✓	
	Placebo (143)				
O`Connor 2006 (O'Connor et al. 2006)[66]	Teriflunomide 14 mg QD (57)	✓			✓
	Teriflunomide 7 mg QD (61)				
	Placebo (61)				
Opera I trial 2017[67]	Ocrelizumab 600 mg Q24W (410)	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW (411)				
Opera II trial 2017 [67]	Ocrelizumab 600 mg Q24W (417)	✓	✓	✓	✓
	Interferon beta-1a 44 µg SC TIW (418)				
OPTIMUM 2021 (Kappos et al. 2021) [68]	Ponesimod 20 mg PO (567)	✓	✓	✓	✓
	Teriflunomide 20 mg PO (566)				
PRISMS trial (Ebers et al.	Interferon beta-1a 44 µg SC TIW (184)	✓	✓	✓	✓

Study name (author, year)	Intervention (N)	ARR (rate ratio)	3-m CDP (time to)	6-m CDP (time to)	Treatment discontinuation (time to)
1998)[69]	Interferon beta-1a 44 µg SC TIW (189)				
	Placebo (187)				
REFORMS trial (Singer et al. 2012)[70]	Interferon beta-1a 44 µg SC TIW (65)	✓			✓
	Interferon beta-1b 250 µg QOD (64)				
REGARD trial (Mikol et al. 2008) [71]	Glatiramer acetate 20 mg QD (378)	✓		✓	✓
	Interferon beta-1a 44 µg SC TIW (386)				
TEMSO trial (O'Connor et al. 2011) [72]	Teriflunomide 14 mg QD (359)	✓	✓	✓	✓
	Teriflunomide 7 mg QD (366)				
	Placebo (363)				
TENERE Trial (Vermersch et al. (2014) [73]	Teriflunomide 14 mg QD (111)	✓			✓
	Teriflunomide 7 mg QD (109)				
	Interferon beta-1a 44 µg SC TIW (104)				
TOWER trial (Confavreux et al. 2014) [74]	Teriflunomide 14 mg QD (372)	✓	✓	✓	✓
	Teriflunomide 7 mg QD (408)				
	Placebo (389)				

3/6m=three/six month; ARR=annualised relapse rate; BID=twice daily; CDP=confirmed disability progression; IM= intramuscular; PO=oral; QD=once every day; QOD=every other day; QW=once a week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q24W=every 24 weeks; RRMS=relapsing-remitting multiple sclerosis; SC=subcutaneous; TIW= three times a week.

3.3.2 The general characteristics of studies included in the NMA

The general study characteristics (design, country, setting, blinding, diagnostic criteria, and trial duration) of the 38 studies included in the NMA are provided in Table 8 of the CS's Appendix D (1.1.4.1). Of the 38 studies, 27 (70%) were conducted as multi-centre involving settings of more than one country and 8 studies were conducted in a single country Iran (n=1),[52, 63] Italy (n=1),[60] and the US (n=5).[43, 50, 62, 65, 70] Most trials (n=31; 79%) were double-blind, 7 trials [43, 47, 52, 55, 70, 71, 73] were single-blind/open-label and blinding for one study (INCOMIN trial) [60] was unclear.

The majority of studies (n=27; 69%) for the diagnosis of RRMS used revised McDonald diagnostic criteria (2001, 2005, 2010) and 8 studies [45, 52, 53, 58, 60, 62, 65, 69] used Poser's criteria. The RRMS diagnostic criteria was unclear for 4 studies.[43, 50, 55, 72] The study duration across the 38 trials ranged from 12 weeks[70] to 260 weeks,[58] with most trials' duration of 96 weeks or longer (≥2 years).

EAG concurs with the company that overall study-specific general characteristics are comparable across the trials included in the NMA, with some variation in the duration of trials and the RRMS diagnostic criteria. EAG notes that the time of publication of the trials included in the NMA spans about 35 years (from 1987 to 2022), with 8 trials published 20 years ago (prior 2005).[45, 50, 53, 58, 60, 62, 65, 69] The trial characteristics such as RRMS diagnostic criteria (Poser's criteria), trial methodology (blinding, trial/treatment duration, relapse/disability progression outcome definition) reported in the older trials differ from those reported in newer trials. The heterogeneity with respect to these trial/design-specific features across the trials' networks may have introduced some bias in the NMA, and therefore threatens transivity assumption.

3.3.3 Inclusion and exclusion criteria of studies included in the NMA

The study participant inclusion and exclusion criteria for the 38 studies included in the NMA are provided in Table 9 of the CS's Appendix D (1.1.4.2).

To summarize, the study population inclusion criteria across the trials included in the NMA were generally comparable with slight variations (in diagnostic criteria), with most of which specified adult men and women aged 18 or older, diagnosed with RRMS (using revised McDonald diagnostic criteria 2001, 2005, or 2010), who must have had an Expanded Disability Status Scale (EDSS) score between 0.0 and 5.5 and should have experienced at least 2 relapses that had been medically documented within the last 3 years with at least one of these relapses or MRI activity (Gd-enhancing T1 lesions or new or enlarging T2 lesions) having occurred within the past 12 months prior to randomisation or study entry. Overall, the patient population in the included trials corresponds to that outlined in the scope of the decision problem. EAG would like to highlight several outlier trials. For example, in three trials,[42, 64, 68] patients with secondary progressive multiple sclerosis (SPMS) were also allowed. In one trial (INCOMIN trial),[60] only patients with EDSS between 1.0 and 3.5 were included. The inclusion criteria for one study (BEYOND trial) [44] was restricted to treatment-naïve RRMS patients. The inclusion of patients in the trial by Bornstein et al. (1987) [45] was restricted to age between 20 and 35 years.

Major exclusion criteria were diagnosis of primary progressive, secondary progressive, or progressive relapsing MS; history of any underlying conditions that could affect the CNS or interfere with the MRI results or any other evaluation in the study; use corticosteroids, interferon, other DMTs, immunosuppressive therapy with cytotoxic chemotherapy or lymphoid irradiation, insulin dependent diabetes, positive HIV or HTLV-I serology or required use of aspirin or chronic NSAID during the trial.

3.3.4 Patient baseline characteristics in studies included in the NMA

The patient baseline characteristics (age, ethnicity, MS duration, proportion of females) of the 39 studies included in the NMA are provided in Table 10 of the CS's Appendix D (1.1.4.3).

The patient mean age across the 38 studies included in the review did not notably differ. For example, the patient's mean age across the trials ranged from 28.4 [52] to 43.7 years old,[54] with the mean age in the majority of trials ranging between 30 and 40 years old.

Most trials recruited more females (range: 60%-75%) than males, with the proportion of females ranging from 33.3% [62] to 83.7% [41] across treatment arms.

The mean duration of RRMS at randomisation across trials ranged from 1.5 years [70] to 10.3 years,[66] with the mean disease duration in the majority of trials ranging from 5 to 8 years. The mean MS duration was not known for 13 trials.

The EDSS score was reported in many different ways across studies (mean and standard deviation, median and range). For the majority of trials, the mean or median EDSS score was between 2 and 3. The baseline EDSS score was not reported for 5 trials.[40, 46, 68, 70, 75]

The patients' demographic information particularly ethnicity was rarely reported in the published trial reports.

3.3.5 Risk of bias in studies included in the NMA

The risk of bias in studies included in the NMA is provided in Figure 1 (from Figure 2 of the CS Appendix D.1.1.5). Across the included studies, the method of generation of random sequence number was adequate in 64% (n=25) of the included trials, while in the remaining 36% (n=14) studies this information was unclear. Overall, 87% (n=34) of the included studies were associated with a low risk of bias in terms of blinding. In one of the included studies (REFORMS trial),[70] blinding was judged to be high risk and it was unclear for four studies. Across the included studies, reasons for withdrawals were adequately reported in 85% (n=33) of the studies. In 59% of the studies outcome reporting was associated with low risk of bias, while outcome selection and reporting was not clear in 41% of the studies.

All the RCTs except for one (Calabrese et al. 2012) [47] reported intention-to-treat (ITT) or modified ITT analysis for evaluating efficacy outcomes. The Calabrese trial reported Per Protocol (PP) analysis.

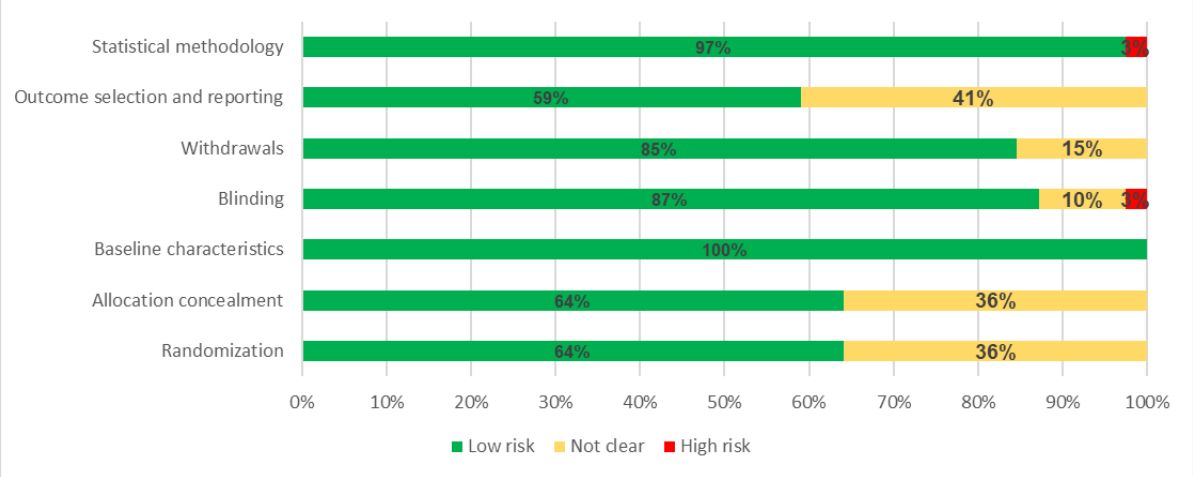


Figure 1. Risk of bias/methodological quality in studies included in the NMA using the NICE checklist (from Figure 2 of the CS Appendix D.1.1.5)

Overall, the ERG concurs with the risk of bias assessments accomplished by the company and believes that the majority of trials included within at least one NMA were generally of good quality. However, important design information regarding methods of randomisation or allocation concealment was not clear in 36% of the trial publications and the potential for selective outcome reporting bias might have taken place for 41% of the trial publications.

3.3.6 Publication bias

The company used funnel plots and contour-enhanced funnel plots of study results (DMTs compared to placebo) to assess the potential of publication bias for the following outcomes: ARR, 3-month CDP, 6-month CDP, and treatment discontinuation (CS, Appendix D.1.1.5, Figures 3-6). The funnel plots were plotted with log of rate ratio/RR (for ARR) and log of hazard ratio/HR (for 3-month CDP, 6-month CDP, and treatment discontinuation) on the x-axis and standard error on the y-axis.

The Figures 3-6 from the CS Appendix D are displayed in this EAG report below as Figure 2, Figure 3, Figure 4, Figure 5. They depict symmetry in the spread of studies in the funnel plot.

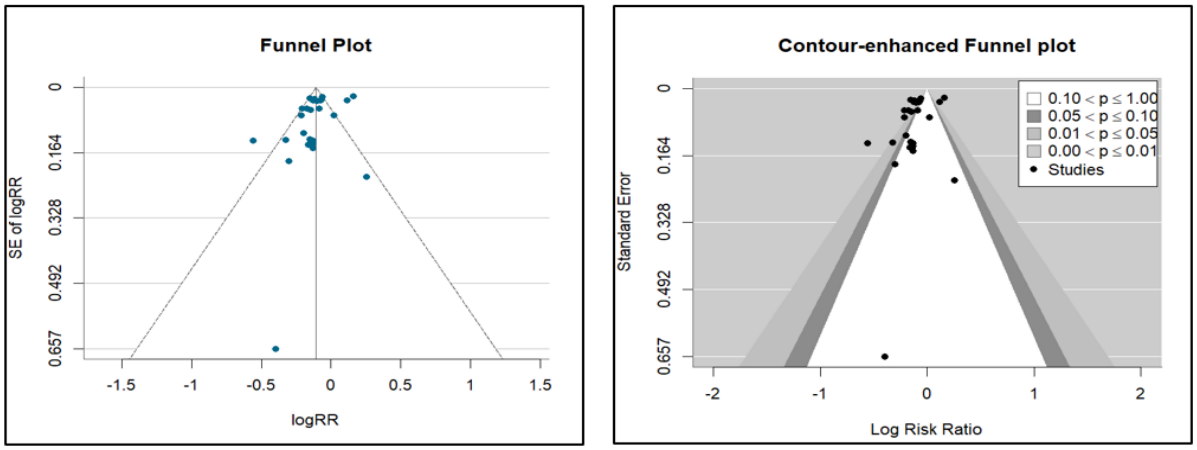


Figure 2. Funnel plot and contour-enhanced funnel plot for studies reporting ARR (Figure 3 from the CS, Appendix D.1.1.5).

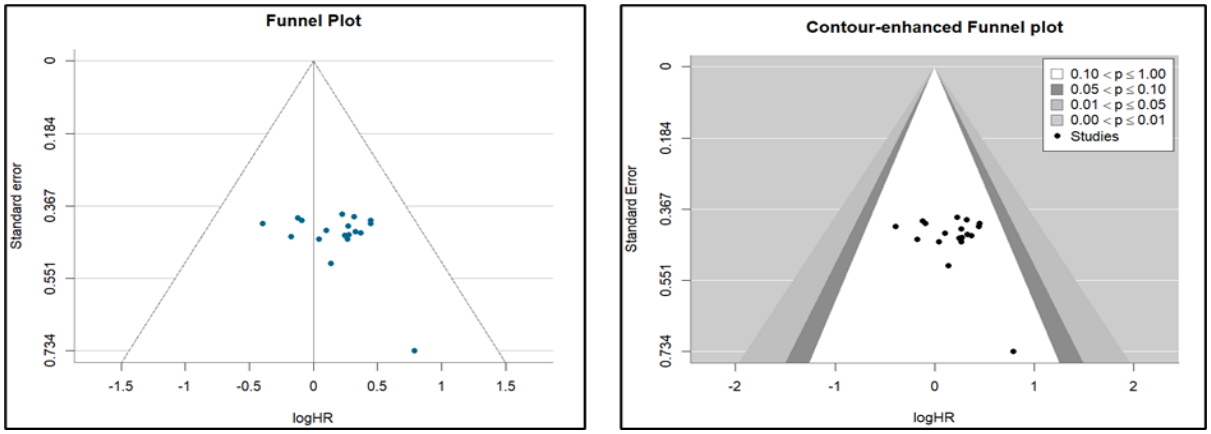


Figure 3. Funnel plot and contour-enhanced funnel plot for studies reporting 3-month CDP (Figure 4 from the CS, Appendix D.1.1.5).

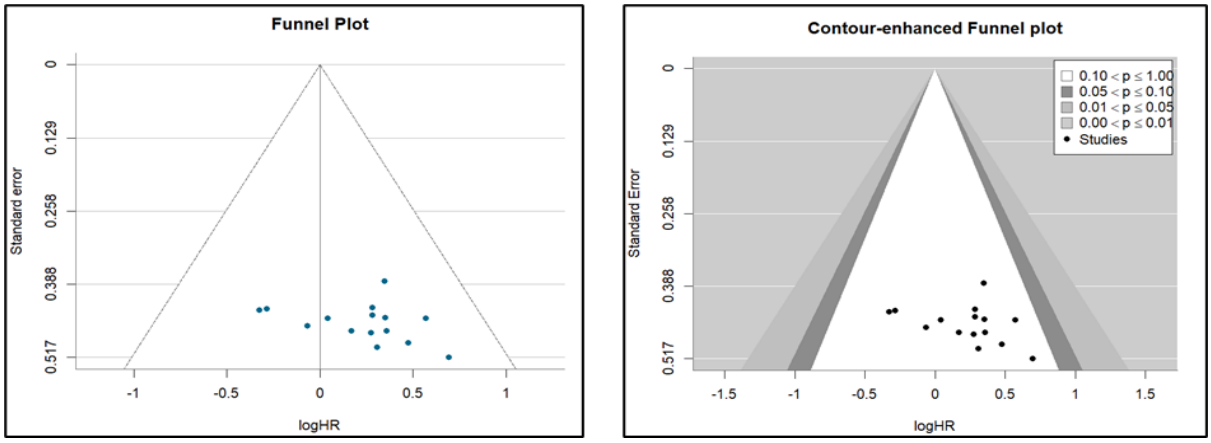


Figure 4. Funnel plot and contour-enhanced funnel plot for studies reporting 6-month CDP (Figure 5 from the CS, Appendix D.1.1.5)

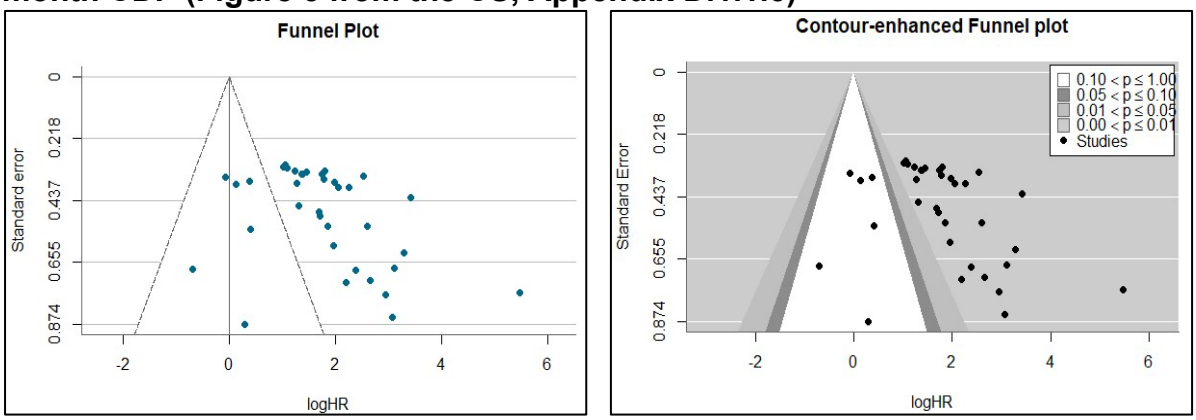


Figure 5.Funnel plot and contour-enhanced funnel plot for studies reporting treatment discontinuation (Figure 6 from the CS, Appendix D.1.1.5)

The study results for ARR, 3-month CDP, 6-month CDP, and treatment discontinuation located in the white (statistically non-significant) region of the contour-enhanced funnel plots, suggested that non-significant trials like those with significant results (in grey areas) were also published. The company concluded that the potential for publication bias with respect to the above-mentioned outcomes was less likely.

Given the funnel plot results and no additional trials meeting the company's eligibility criteria for inclusion in the NMA identified, the EAG concurs with the company that an impact of publication bias on the NMA's effect estimates is less likely.

3.3.7 Main treatment comparison results from the NMA (the base case)

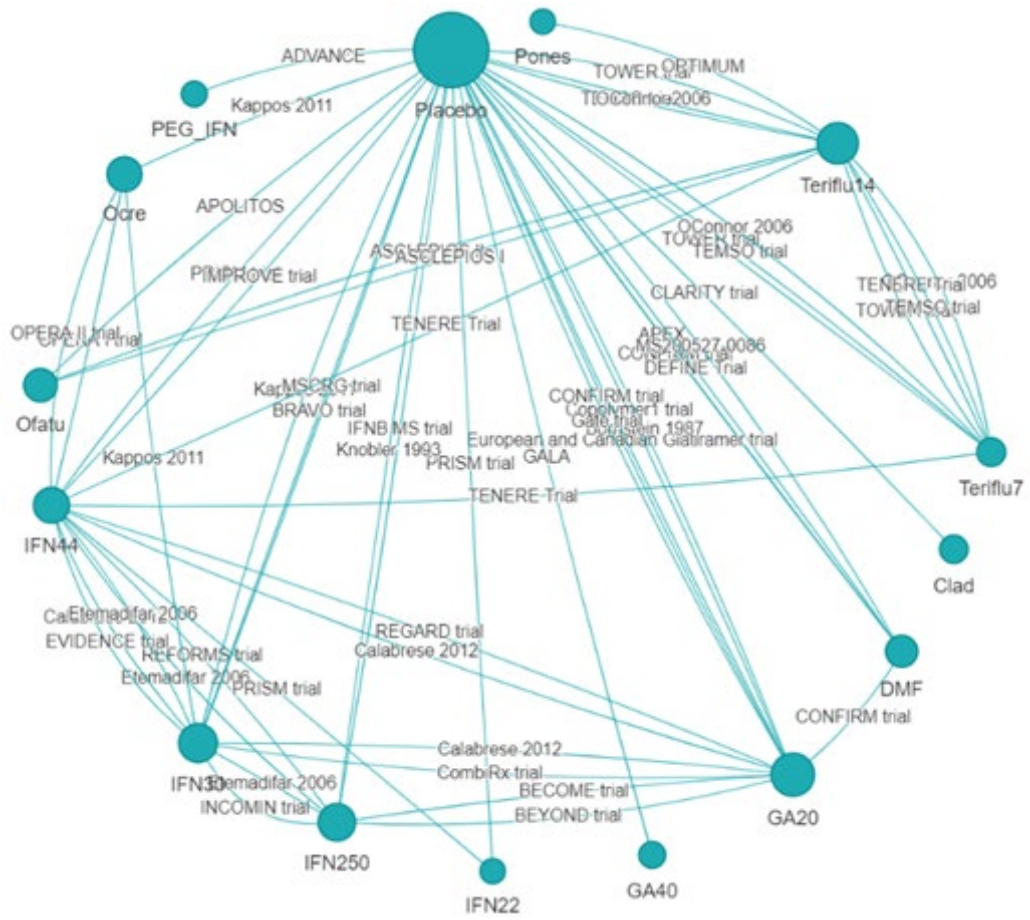
There were 38 RCTs included in the NMA. In the main analysis of the NMA (the CS Document B.2.9.3, Figures 10-17 and the CS Appendix D.1.1.6), the company evaluated the clinical efficacy of cladribine tablets relative to different DMTs approved in the UK and recommended by NICE for the treatment of patients with RRMS. The base case NMA results for ARR, 3-month CDP, 6-month CDP and all-cause treatment discontinuations are based on a random effects model given the best fit of the model to these data. According to the company, the same analyses based on the fixed-effects model showed similar results to the base case analysis.

When interpreting the NMA results, the company considered 'numerically favoured cladribine tablets' when RR or HR estimate (for the DMT/placebo vs. cladribine comparison) was not statistically significant and its magnitude was > 1.0. Conversely, statistically non-significant RR and HR estimates with magnitude < 1.0 were interpreted as 'DMT or placebo was numerically favoured over cladribine'. The EAG agrees that these interpretations are appropriate.

3.3.7.1 ARR

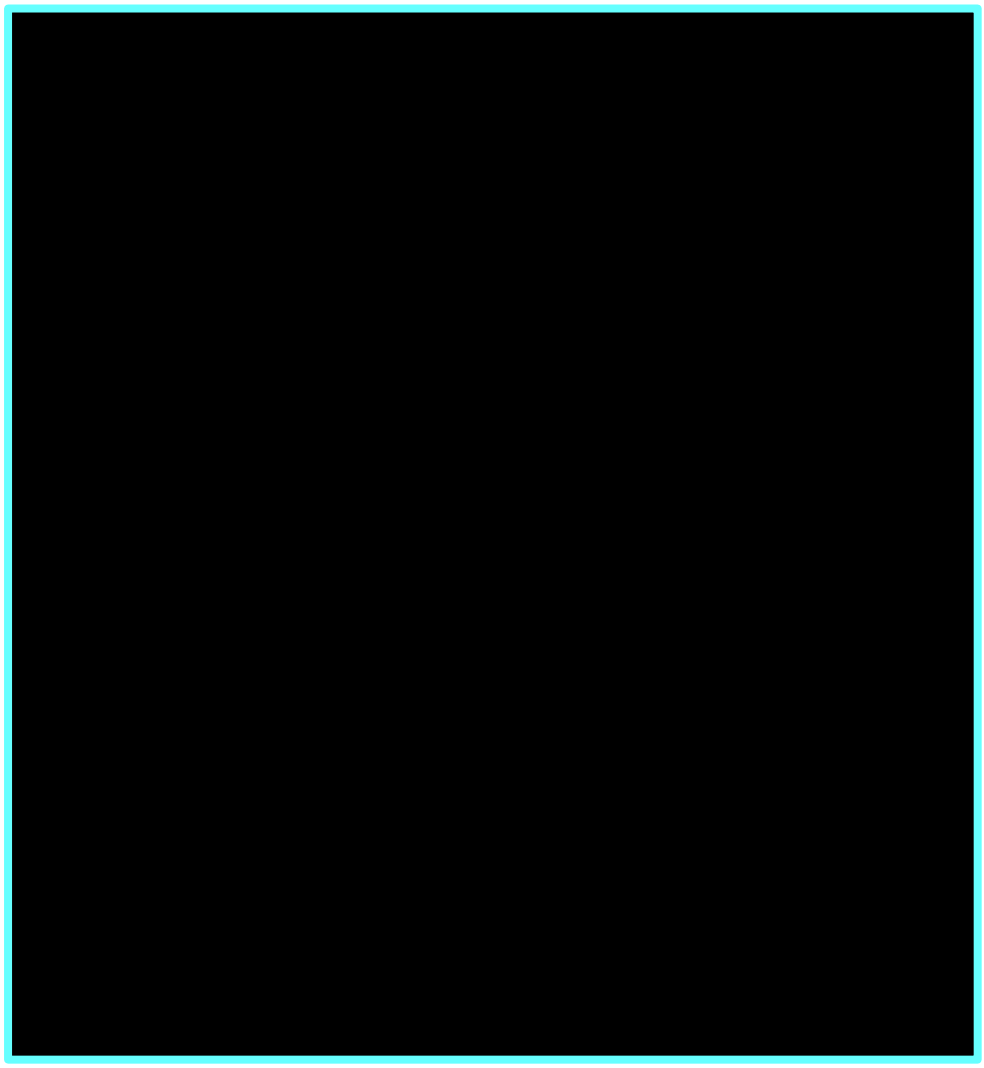
The NMA results for ARR based on the effects of cladribine tablets versus comparators in the ITT populations of the trials are presented in Figure 6, Figure 7(from Figures 10-11 of the CS Document B.2.9.3). The NMA for ARR was based on 37 RCTs and 15 regimens (including placebo).

According to Figure 7 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with a significantly greater reduction in fewest relapses, placebo (RR=[redacted]), teriflunomide 14 mg (RR=[redacted]), teriflunomide 7 mg (RR=[redacted]), glatiramer acetate 20 mg (RR=[redacted]), glatiramer acetate 40 mg (RR=[redacted]), peginterferon (RR=[redacted]), interferon beta-1a 22 µg (RR=[redacted]), interferon beta-1a 44 µg (RR=[redacted]), interferon beta-1a 30 µg (RR=[redacted]) and interferon beta-1b 250 µg (RR=[redacted]). Moreover, the NMA results numerically favoured cladribine tablets over dimethyl fumarate (RR=[redacted], 95% CrI: [redacted]) and ponesimod (RR=[redacted], 95% CrI: [redacted]). According to this network results for ARR, cladribine tablets ranked [redacted] following [redacted] (RR=[redacted], 95% CrI: [redacted]) and [redacted] (RR=[redacted], 95% CrI: [redacted]). Note that these differences were only numerical (i.e., statistically non-significant).



ARR=Annualised relapse rate; Clad=Cladribine tablets; DMF=Dimethyl fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre=Ocrelizumab; Ofatu=Ofatumumab; PEG_IFN=Peginterferon; Pones=Ponesimod; Teriflu=Teriflunomide

Figure 6. The base case NMA plot for ARR (from Figure 10 of the CS Document B.2.9.3)



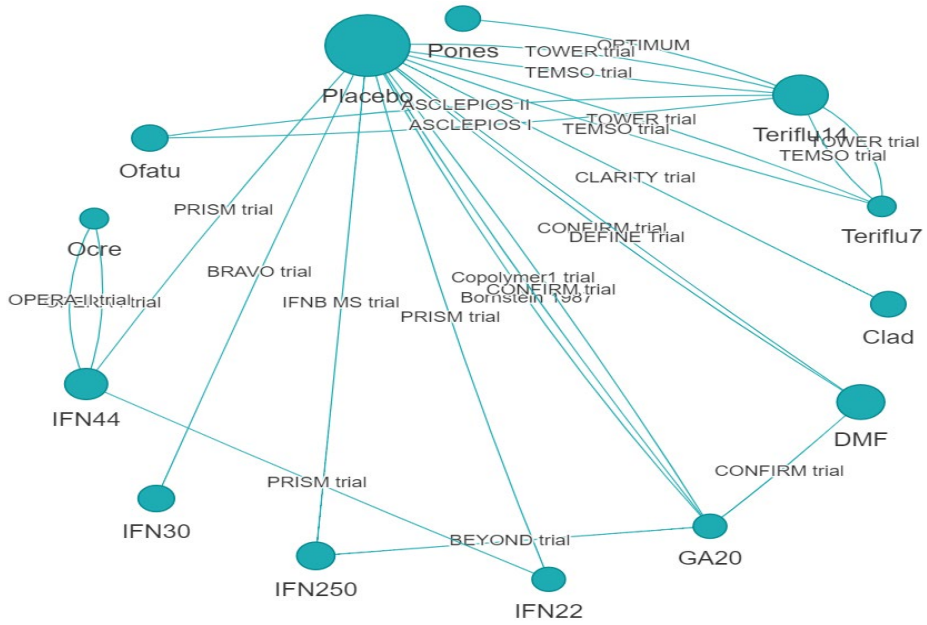
ARR=Annualised relapse rate; Crl=Credible interval; DMF=Dimethyl fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre= Ocrelizumab; Ofatu=Ofatumumab; PEG_IFN=Peginterferon; Pones=Ponesimod; Teriflu=Teriflunomide; ITT=Intention-to-treat; RR=Relative risk

Figure 7. Forest plot of DMT vs. cladribine tablets for ARR: the base case NMA (from Figure 11 of the CS Document B.2.9.3)

3.3.7.2 3-month CDP

The NMA results for 3-month CDP based on the effects of cladribine tablets versus comparators in the ITT populations of the trials are presented in Figure 8, Figure 9(Figures 12-13 from the CS Document B.2.9.3). The NMA for 3-month CDP was based on 15 RCTs and 13 regimens (including placebo).

According to Figure 9 (DMT comparator vs. cladribine), the risk for 3-month CDP was not statistically significantly different between treatment with cladribine tablets vs. all DMTs, but it was significantly lower for cladribine tablets vs. placebo (HR=[redacted], 95% CrI: [redacted]). The cladribine tablets were numerically favoured in terms of reduced risk of 3-month CDP compared to teriflunomide 14 mg (HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), interferon beta-1b 250 µg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), interferon beta-1a 22 µg (HR=1.08), interferon beta-1a 44 µg (HR=[redacted]), and dimethyl fumarate (HR=[redacted]). Compared to cladribine tablets, treatment with three DMTs: ocrelizumab (HR=[redacted]), ofatumumab (HR=[redacted]), and ponesimod (HR=[redacted]) were associated with numerically lower risk of 3-month CDP. Overall, cladribine tablets ranked [redacted] in the NMA for 3-month CDP. The EAG notes that this ranking is based on numerical differences.



Clad=Cladribine tablets; DMF=Dimethyl fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre=Ocrelizumab; Ofatu=Ofatumumab; Pones=Ponesimod; Teriflu=Teriflunomide

Figure 8. The base case NMA plot for 3-month CDP (Figure 12 from the CS Document B.2.9.3)

Crl=Credible interval; DMF=Dimethyl fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre= Ocrelizumab; Ofatu=Ofatumumab; PEG_IFN=Peginterferon; Pones=Ponesimod; Teriflu=Teriflunomide; ITT=Intention-to-treat; HR=hazard ratio

Figure 9. Forest plot of DMT vs. cladribine tablets for 3-month CDP: the base case NMA (from Figure 13 of the CS Document B.2.9.3)

3.3.7.3 6-month CDP

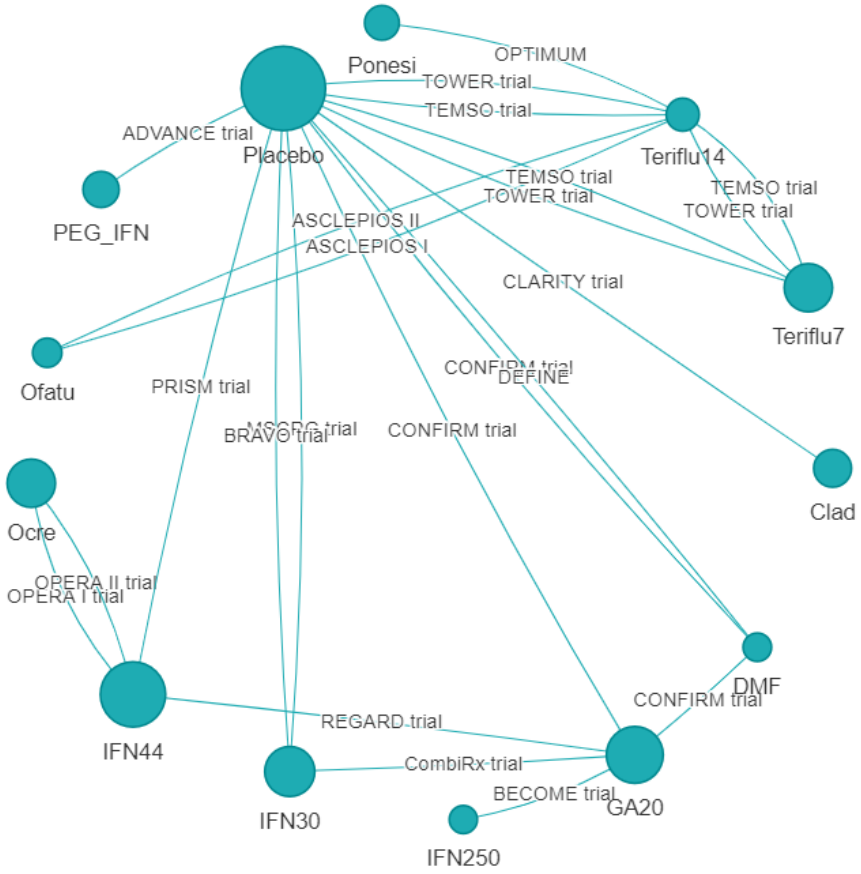
The NMA results for 6-month CDP based on the effects of cladribine tablets versus comparators in the ITT populations of the trials are presented in Figure 10, Figure 11(from Figures 14-15 of the CS Document B.2.9.3). The NMA for 6-month CDP was based on 17 RCTs and 13 regimens (including placebo).

According to Figure 11 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with numerically (although not statistically significantly different) lower risk of 6-month CDP compared to dimethyl fumarate (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), interferon beta-1a 44 µg (HR=[redacted]), teriflunomide 14 mg (HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), and ponesimod (HR=[redacted]). Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for 6-month CDP following [redacted] (HR=[redacted]), [redacted] (HR=[redacted]), [redacted] (HR=[redacted]) and [redacted] (HR=[redacted]). EAG notes that this ranking is based on numerical differences (i.e., statistically non-significant differences).

The EAG notes that for the 6-month CDP outcome, the company excluded one trial from the NMA base case even though this study (INCOMIN trial) reported 6-month CDP.[60] The company stated that the INCOMIN trial (interferon beta-1a vs. interferon beta-1b) demonstrated implausibly large benefits for 6-month CDP favouring interferon beta-1a over interferon beta-1b (HR=0.44, 95% CI: 0.25, 0.80).[60] The company noted that this result is inconsistent with clinical experience, which has established that individual interferon treatments have similar clinical effectiveness. This “outlier” trial has been reviewed in the literature [76] and in previous NICE appraisals (TA767 and TA699),[77, 78] and clinical experts have recommended exercising caution when interpreting these results. The company conducted a sensitivity analysis to compare the NMA results with and without INCOMIN trial included in the analysis (Table 10).

According to Table 10, the sensitivity analysis demonstrated that exclusion of INCOMIN trial did not influence the effect estimates for cladribine tablets or DMTs. With or without the INCOMIN trial in the analysis, IFN-β1b 250 µg was found to be numerically better compared with cladribine tablets when assessed for 6-month CDP, while the results for 3-month CDP indicated cladribine tablets to be better instead.

Moreover, the network for 6-month CDP includes only one trial (ADVANCE)[79] that included peginterferon as a treatment arm. Similarly the results of this study demonstrated implausibly large benefits for 6-month CDP favouring peginterferon beta-1a every 2 weeks over placebo (HR=0.46, 95% CI: 0.26, 0.81).[79] The company conducted sensitivity analyses by excluding the ADVANCE trial from the base case NMA of 6-month CDP. The results of NMA did not change with the removal of ADVANCE trial from the analysis (the CS Appendix D.1.1.6, Table 16).



Clad=Cladribine tablets; DMF=Dimethyl fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre=Ocrelizumab; PEG_IFN= Peginterferon; Ofatu=Ofatumumab; Pones=Ponesimod; Teriflu=Teriflunomide

Figure 10. The base case NMA plot for 6-month CDP (from Figure 14 of the CS Document B.2.9.3)

CrI=Credible interval; DMF=Dimethyl fumarate; GA=Glatiramer acetate; HR=Hazard ratio; IFN=Interferon; Ocre=Ocrelizumab; Ofatu=Ofatumumab; PEG_IFN=Peginterferon; Ponesi=Ponesimod; Teriflu=Teriflunomide

Figure 11. Forest plot of DMT vs. cladribine tablets for 6-month CDP: the base case NMA (from Figure 15 of the CS Document B.2.9.3)

Table 10. Summary table of 6-month CDP for DMT vs. cladribine tablets 3.5 mg/kg (random-effects model): sensitivity analysis with and without (the base case) INCOMIN trial (from Tables 15-16 of the CS Document D.1.1.6)

Treatment vs. cladribine tablets 3.5 mg/kg	HR (95% CrI) for 6-month CDP Excluding INCOMIN trial (the base case NMA)	HR (95% CrI) for 6-month CDP Including INCOMIN trial
Placebo	[redacted]	[redacted]
IFN-β1b, 250 µg, eod	[redacted]	[redacted]
GA, 20 mg, qd	[redacted]	[redacted]
IFN-β1a, 30 µg, q1w	[redacted]	[redacted]
DMF, 240 mg, bid	[redacted]	[redacted]
Ocrelizumab, 600 mg	[redacted]	[redacted]

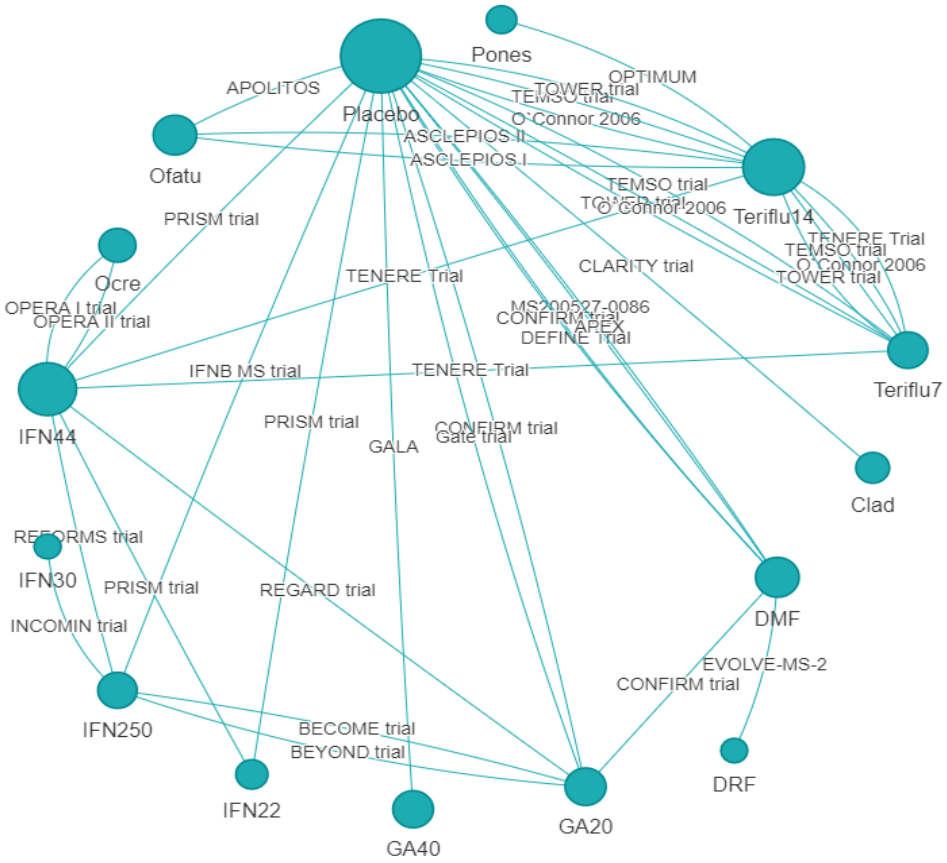
Treatment vs. cladribine tablets 3.5 mg/kg	HR (95% CrI) for 6-month CDP Excluding INCOMIN trial (the base case NMA)	HR (95% CrI) for 6-month CDP Including INCOMIN trial
IFN-β1a, 44 µg, tiw	[redacted]	[redacted]
Teriflunomide, 7 mg, od	[redacted]	[redacted]
Teriflunomide, 14 mg, od	[redacted]	[redacted]
Ofatumumab, 20 mg	[redacted]	[redacted]
Ponesimod, 20 mg	[redacted]	[redacted]
PEG-IFN-β1a, 125 µg, q2w	[redacted]	[redacted]

Bid=Twice a day; CrI=Credible Interval; DMF=Dimethyl fumarate; EOD=Every other day; GA=Glatiramer acetate; HR=Hazard ratio; IFN=Interferon; ITT=Intention to treat; kg=Kilogram; µg=Microgram; mg=Milligram; od=Once daily; qd=Per day; SD= Standard deviation; q1w=Once a week; q4w=very 4 weeks; tiw=Thrice a week

3.3.7.4 Treatment discontinuation (all-cause)

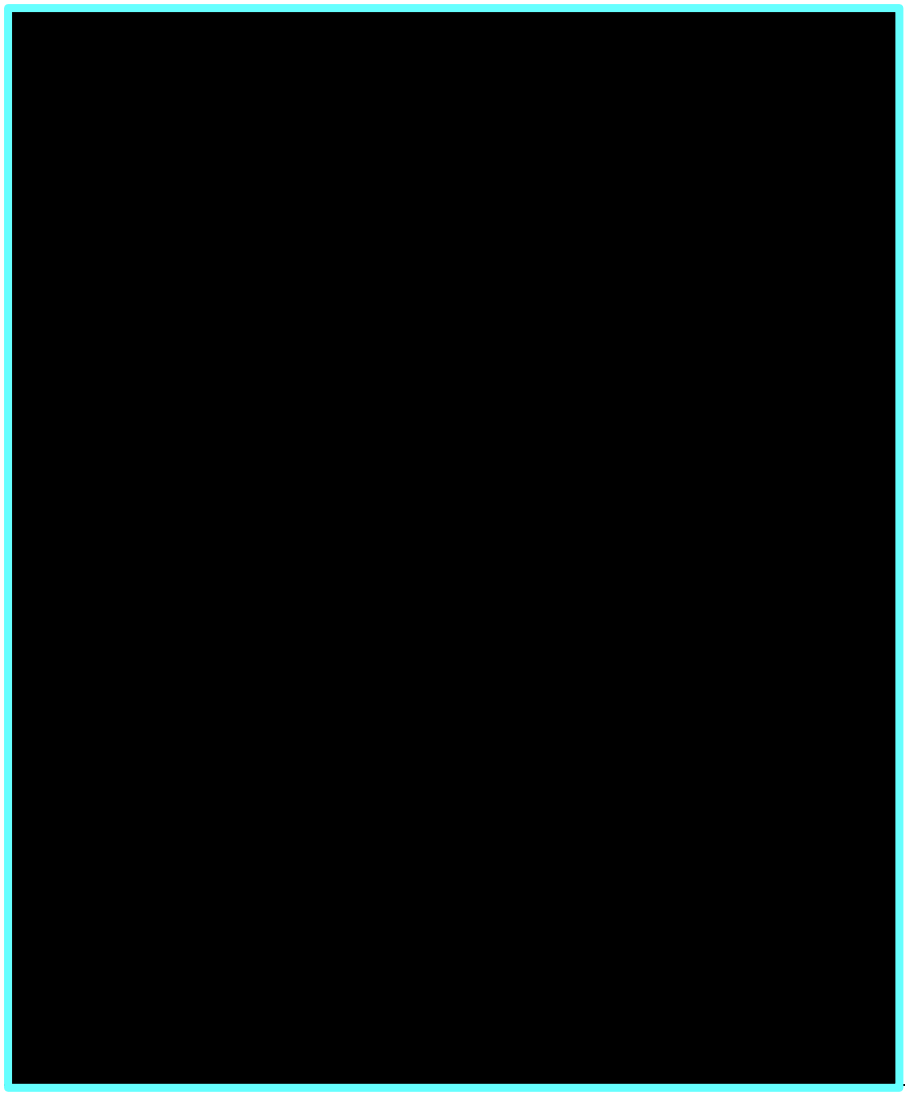
The NMA results for treatment discontinuation based on the effects of cladribine tablets versus comparators in the ITT populations of the trials are presented in Figure 12, Figure 13 (from Figures 16-17 of the CS Document B.2.9.3). The NMA for treatment discontinuation was based on 25 RCTs and 15 regimens (including placebo).

According to Figure 13 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with a significantly lower risk of treatment discontinuation than interferon beta-1a 44 µg (HR=[redacted], 95% CrI: [redacted] Moreover, treatment with cladribine tablets was associated with numerically (although not statistically significantly) lower risk of treatment discontinuation compared to dimethyl fumarate (HR=[redacted]), ofatumumab (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), glatiramer acetate 40 mg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), teriflunomide 14 mg (HR=[redacted]), interferon beta-1b 250 µg (HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), ocrelizumab (HR=[redacted]), placebo (HR=[redacted]), diroximel fumerate (HR=[redacted]), and ponesimod (HR=[redacted]). Overall, cladribine tablets ranked the first when evaluated in the NMA for all-cause treatment discontinuation. The EAG notes that this ranking is based on numerical differences (i.e., statistically non-significant differences).



Clad=Cladribine tablets; DMF=Dimethyl fumarate; DRF=Diroximel fumarate; GA=Glatiramer acetate; IFN=Interferon; Ocre= Ocrelizumab; Ofatu=Ofatumumab; Pones=Ponesimod; Teriflu=Teriflunomide

Figure 12. The base case NMA plot for treatment discontinuation (from Figure 16 of the CS Document B.2.9.3)



Crl=Credible interval; DMF=Dimethyl fumarate; DRF=Diroximel fumarate; GA=Glatiramer acetate; HR=Hazard ratio; IFN= Interferon; Ocre=Ocrelizumab; Ofatu=Ofatumumab; Pones=Ponesimod; Teriflu=Teriflunomide

Figure 13. Forest plot of DMT vs. cladribine tablets for treatment discontinuation: the base case NMA (from Figure 17 of the CS Document B.2.9.3)

3.3.7.5 NMA summary results for treatment comparisons

An overall summary of NMA results between cladribine tablets and the comparators of interest are presented for all efficacy outcomes in Table 11 (Table 11 from the CS Document D.1.1.6). Overall, the EAG opinion is that cladribine tablets showed a statistically significantly superior efficacy compared to teriflunomide, glatiramer acetate, peginterferon, interferon beta-1a/1b or placebo with regards to reductions in ARR. However, cladribine tablets were not significantly different from ofatumumab and ocrelizumab in reducing ARR. The results favouring cladribine tablets for reducing risk of all-cause treatment discontinuation were less convincing, indicating only numerical but non-significant advantage compared to other DMTs (and their regimens).

The NMA's results between cladribine tablets and comparators (DMT regimens) of interest in reducing the risk of disability progression were highly uncertain (non-significant wide confidence/credible intervals) and inconsistent (Table 11) between the results for 3-month CDP and 6-month CDP (for ponesimod 20 mg, interferon-β1a 44 µg, interferon-β1b, 250 µg, dimethyl fumarate 240 mg).

Table 11. Summary NMA efficacy outcomes results: cladribine tablets vs. DMTs or placebo (from Table 11 of the CS Document D.1.1.6)

Cladribine tablets, 3.5 mg/kg vs.	ARR	3-month CDP 24M	6-month CDP		Treatment discontinuation (all-cause)
			Without INCOMIN study	With INCOMIN study	
Placebo	↑	↑	↑	↑	↑
PEG-IFN-β1a, 125 µg, q2w	↑	-	↓	↓	-
DMF, 240 mg, bid	↑	↓	↑	↑	↑
DRF, 462 mg, bid	-	-	-	-	↑
Ofatumumab, 20 mg	↓	↓	↓	↓	↑
Teriflunomide,14 mg, qd	↑	↑	↑	↑	↑
GA, 20 mg, qd	↑	↑	↑	↑	↑
IFN-β1b, 250 µg, eod	↑	↑	↓	↓	↑
IFN-β1a, 30 µg, q1w	↑	↑	↑	↑	↑
IFN-β1a, 44 µg, tiw	↑	↓	↑	↑	↑
GA, 40 mg, tiw	↑	-	-	-	↑
Ocrelizumab, 600 mg	↓	↓	↓	↓	↑
Teriflunomide, 7 mg, qd	↑	↑	↑	↑	↑
Ponesimod, 20 mg	↑	↓	↑	↑	↑
IFN-β1a, 22 µg, tiw	↑	↔	-	-	↑

↑ Indicates better efficacy for cladribine tablets; ↓ indicates lower efficacy for cladribine tablets; "↔" indicates equivalent efficacy of cladribine tablets and comparator; Cells highlighted in green represent statistically significant results in favour of cladribine tablets, "-"indicates that analyses were not feasible for these comparisons considering limited evidence. ARR=Annualised relapse rate; bid=Twice a day; CDP=confirmed disability progression; CrI=Credible Interval; DMF=Dimethyl fumarate; eod=Every other day; GA=Glatiramer acetate; IFN=Interferon; ITT=Intention to treat; kg=Kilogram; µg=Microgram; mg=Milligram; qd=Once a day; q1w=Once a week; q2W=Every 2 weeks; q4w=Every 4 weeks; RF=Relapse-free; tiw=Three times a week

3.4 *Critique of the indirect comparison and/or multiple treatment comparison*

3.4.1 Summary of NMA methods and results

The company conducted a network meta-analysis to assess the comparative effectiveness of cladribine tablets vs. different comparator DMT regimens in patients diagnosed with active RRMS. The validity of NMA rests on the assumption that the trials included in the analysis are sufficiently similar in design, populations, outcomes.

The NMA included 38 trials of DMTs (up to 14 DMT regimens) approved for treating active RRMS in UK and aligned with the final NICE scope of the decision problem. The main outcomes assessed in the NMA were ARR, 3-month CDP, 6-month CDP, and treatment discontinuations (all-cause).

Overall, cladribine tablets showed a statistically significantly superior efficacy compared to several DMTs: teriflunomide, glatiramer acetate, peginterferon, interferon beta-1a/1b or placebo in terms of reducing ARR. However, cladribine tablets were not significantly different from ofatumumab, ocrelizumab, dimethyl fumarate, and ponesimod in reducing ARR. The NMA results comparing effects of cladribine tablets to DMT regimens for reducing risk of disability progression were inconclusive, owing to statistically non-significant estimates accompanied by wide and overlapping credible intervals. The effect on disability progression tended to numerically favour cladribine tablets compared to interferon, dimethyl fumarate, glatiramer acetate, teriflunomide, and ponesimod. Likewise, the results for all-cause treatment discontinuation showed numerical advantage of cladribine tablets compared to other DMTs and their regimens. However, the observed differences were statistically non-significant with wide overlapping 95% CrIs. Note that cladribine tablets were shown to significantly improve three (ARR, 3-month CDP, and 6-month CDP) of the four NMA outcomes compared to placebo.

Overall, the ERG concurs with the company that the majority of trials included the NMAs were generally of good quality and that a large impact of publication bias on the NMA results is unlikely.

The EAG notes that the NMA results nevertheless should be interpreted with caution due to statistically and/or clinically determined uncertainties.

The uncertainties in terms of statistical variability could be a result of a smaller number of RCTs that contributed data to NMAs for 3-month CDP, 6-month CDP, and all-cause treatment discontinuations (15, 17, and 25 RCTs, respectively) compared to ARR NMA that was based on 37 RCTs. Moreover, a relatively rare occurrence of CDP event (3- or 6-month) compared to ARR might have additionally contributed to this uncertainty if the length of follow-up of these trials was not long enough. Moreover, not all trials were designed to have had a power sufficient for detecting the outcomes of disability progression. The challenge of limited RCT evidence to support 3/6-month CDP and all-cause treatment discontinuations is universal across all NICE evaluations of treatments for RRMS. The approach to account for the

uncertainty in the results of NMA was handled through the usage of random effects model.

The EAG team agrees with the company that the results of this NMA are consistent to those in the previous NICE submission of cladribine in RRMS, demonstrating that cladribine tablets are statistically more effective or numerically favoured in reducing ARR compared to several other DMTs and their regimens (teriflunomide, glatiramer acetate, peginterferon, interferon beta-1a, interferon beta-1b, and dimethyl fumarate) in active RRMS (TA493/TA616).[14, 15] These results also agree in that there is a greater uncertainty around CDP outcomes (non-significant estimates with wide and overlapping 95% CrIs).

The company stated to have used a similar methodology to conduct the NMA to the previous NMAs that were accepted in recent NICE submissions of ocrelizumab (TA533),[80] ofatumumab (TA699),[78] and ponesimod (TA767) [77] for RRMS.

In general, the EAG considers the SLR (locating, selecting, extracting, and appraising primary studies) and NMA methodology (comparators included, the outcomes selected, and statistical approaches including the choice between random- and fixed-effects model) appropriate.

The reporting of NMA was not without gaps. The EAG listed these gaps in the clarification letter sent to the company and requested that the company provide the following information and response was submitted by the company:

i) Definition of the treatment discontinuation outcome in NMA (Q: A9)

ii) Timing of measurement of NMA outcomes 3-month and 6-month CDP (Q: A10)

iii) A priori selected treatment effect modifiers used in the NMA (Q: A11)

iv) Assessment of network connectivity (Q: A13)

v) Pairwise meta-analysis results (forest plots, primary studies and pooled study effect estimates with 95% CIs, I-square statistics) of trials included in the NMA (Q: A14)

vi) Addressing major NMA assumptions of heterogeneity, transitivity, and consistency (Q: A12, A15)

vii) Closed loops with mixed (direct and indirect comparisons pooled) treatments tested for consistency with inconsistency factor (IF) and 95% CIs provided (in table of forest plot) (Q: A16)

viii) Definition of the treatment discontinuation outcome in individual trials included in NMA (Q: A18)

ix) Trials excluded from the NMA and reasons for these exclusions (Q: A20)

x) Tabulated results for ARR, CDP, and treatment discontinuation in all primary RCTs included in the NMA (Q: A21)

xi) League tables and surface under the cumulative ranking curve area (SUCRA) (Q: A22-A23)

3.4.2 Major NMA assumptions

Conventionally, an NMA is conducted in the presence of studies with a common comparator arm (e.g., placebo or the same DMT regimen) and its validity relies on the connectivity of treatment nodes within an outcome-specific network and two key assumptions of transitivity (i.e., constancy or relative effects; similarity in cross-trial distribution of treatment effect-modifiers) and consistency (i.e., (dis)agreement between direct and indirect treatment effect estimates as a statistical manifestation of the transitivity assumption state). Differences in the distribution of effect modifiers (e.g., study design features, study patient inclusion/exclusion criteria, baseline patient characteristics, study outcomes) of the relative treatment effects and features of the common comparator (e.g., mode of administration, dose, or duration) across trials included in NMA could violate the transitivity-consistency assumption, and thus undermine the validity of an indirect comparison in a given NMA.

Initially, the EAG team assessed the connectivity of treatment nodes by comparing DMT regimen doses and modes of administration across 14 different DMT regimens included in the NMA. The posology and mode of administration of any given DMT regimen did not differ across the trials and corresponded to those recommended by NICE scope. This added an additional credibility to the connectivity of treatment nodes in this NMA.

The EAG compared study features/methods, patient inclusion/criteria, and baseline characteristics qualitatively by examining CS's Tables 8-10 (Appendix D 1.1.4.1). EAG concurs that overall general characteristics of most of the 38 studies are comparable with respect to design features (multi-national, multicentre, double-blind) with a variation in the duration of trials (range: 12 weeks-260 weeks) and diagnostic criteria for RRMS (not known for 4 trials; older Poser's criteria used in 4 trials). Given that the time of publication of the trials included in the NMA spans about 35 years with 8 trials published about 20 years ago (prior 2005), some heterogeneity in the study design (blinding technique, relapse and CDP definitions) and diagnostic criteria across the studies is expected. EAG notes that study population inclusion criteria were generally comparable (except for few outlier trials), i.e., men and women 18 years of age or older with RRMS and EDSS score ranging from 0 to 5.5. Likewise, the exclusion criteria reported across the trials were mostly uniform (e.g., primary/secondary progressive MS, serious underlying conditions, use of immunosuppressive therapy, use of DMTs, diabetes, HIV-positivity). Amongst patients' baseline characteristics, there were notable differences in the mean duration of MS (range: 1.5-10.3 years; not known for 13 trials) and EDSS score measurements (reported as mean range: 1.0-3.3; mean [SD] vs. median [range]). Most primary trial publications did not include information on ethnicity and prior treatment history across trials. Therefore, it is difficult to determine if there is any imbalance in these factors across the trials that might lead to biased estimates in the NMA.

The company did not discuss in the CS if the treatment node/network connectivity and the assumptions of heterogeneity, transitivity, and (in)consistency were examined before the NMA was conducted. The EAG in the clarification letter asked if the company assessed (Q: A11, A12, A13, A15 A16): a) a priori selected treatment effect modifiers and their effects, b) the treatment node/network connectivity, c) heterogeneity (by direct pair-wise meta-analysis), c) transitivity assumption, and d) (in)consistency assumption (statistical test for closed loops of mixed treatments). The company in the clarification letter response noted that they conducted tests for heterogeneity for pair-wise meta-analyses in regards to ARR, CDP3M, CDP6M and treatment discontinuations reported in placebo-controlled trials as well as DMT vs. DMT trials. The EAG examined the forest plots and noted a large heterogeneity across the trials reporting the ARR and treatment discontinuations (I^2=83%-88%, p<0.001). There was lower heterogeneity (<68%) with respect to CDP3M and CDP6M. This magnitude of heterogeneity was expected as the company presented different treatment and dose comparisons mixed in a single forest plot for each outcome without pooling (i.e., no meta-analytic estimate was provided). Visual inspection of the forest plots of the same treatments compared (potentially meta-analysable trials) did not reveal large heterogeneity, the effect estimates were mostly similar.

Regarding the network connectivity, the company noted that for different doses for DMTs available for the same treatment were treated as different comparators. The EAG and the company evaluated DMT dosages, which were similar across the trials. According to the company and EAG, placebo arms varied across the NMA in terms of mode, frequency, and blinding methods which may have influenced the comparability and treatment connectivity in the NMA. This may have violated the transitivity assumption. However, the company carried out the baseline risk-adjusted meta-regression NMA analysis (*Merck_Meta-Regression-Meta Analysis and Inconsistency", sheet named:"Beta_result_metaregression*") that demonstrated some degree of similarity between the beta coefficients (and 95% CrIs) of baseline risk-adjusted and random effects meta-regression models, thereby suggesting that the rates for ARR, CDP, and treatment discontinuations were not meaningfully different in the placebo arms across the trials.

The company also conducted a meta-regression to evaluate if a priori selected potential treatment effect modifiers such as mean EDSS score at baseline, proportion of female participants in each trial, disease duration, mean age at baseline had a significant effect on the NMA outcomes (Company's response to clarification questions file; Table 1, page 11). Almost all the estimates were statistically non-significant, suggesting that these covariates were not treatment effect modifiers. The company noted that there has been no firm agreement regarding the treatment effect modifiers for RRMS. The transitivity was also evaluated by comparison of the distribution of inclusion/exclusion criteria, baseline characteristics and outcome definitions.

The company checked the inconsistency assumption with results comparing indirect and direct evidence for the mixed treatment estimates presented in the forest plots (*Merck_Meta-Regression-Meta Analysis and Inconsistency", sheet named:"Beta_result_metaregression*"). The company stated that the test for

inconsistency between multiple closed loops were suggestive of low likelihood of inconsistency.

According to the EAGs visual inspection of the forest plots of closed loops in regards to direct, indirect, and mixed (pooled) HRs for all four NMA outcomes, most of the time there was consistency between the direct and indirect evidence, however few inconsistencies in HR magnitude were noted even if the corresponding 95% CIs overlapped. . Overlapping 95% CIs is not a necessary indication of consistency. If the CIs are wide because of statistical uncertainty, they will likely overlap even in the presence of major inconsistency.

Here are the examples of the inconsistency detected by EAG:

CDP-3 month (GA 20 mg vs. IFN-β1b 250 µg): [Direct HR: 0.69, 95% CI; 0.51, 0.94] vs. [Indirect HR: 1.25, 95% CI: 0.68, 2.32]

Treatment discontinuation (DMF 240 mg vs. PL): [Direct HR: 0.80, 95% CI: 0.55, 1.15] vs. [Indirect HR: 5.42, 95% CI: 1.18, 24.88]

Treatment discontinuation (IFN-β 1a 22 µg vs. PL): [Direct HR: 1.44, 95% CI: 0.48, 4.27] vs. [Indirect HR: 0.79, 95% CI: 0.14, 4.47]

ARR (PL vs. Teriflunomide 7 mg): [Direct HR: 1.38, 95% CI: 1.18, 1.60] vs. [Indirect HR: 0.74, 95% CI: 0.47, 1.17].

The company did not provide inconsistency factor (IF statistic), as EAG requested.

3.4.3 Limitations and uncertainties

- **Availability of relevant evidence**: A major limitation of the NMAs performed by the company is in the paucity of relevant evidence available for cladribine tablets vs. the comparators of interest particularly for the key efficacy outcomes of 3-/6-month CDP which had notably much smaller networks compared to ARR and treatment discontinuations. For example, the NMA results comparing effects of cladribine tablets to DMT regimens for reducing risk of 3-month CDP were not available for 23 (60.5%) of the 38 trials. Similarly, the outcome data for 6-month CDP were no available for 21 trials (55.3%). The outcome data for treatment discontinuations were not available for 13 (34.2%) of the trials included in the NMA. The resultant NMA effect estimates for these outcome were highly uncertain (i.e., statistically non-significant with wide and overlapping credible intervals), thereby rendering these findings inconclusive. The lack of relevant data could be explained by the fact that many trials were not sufficiently large (adequately powered) or long enough in follow-up length to capture and document progression of disability.

- **Definitions of NMA outcomes (ARR, CDP, treatment discontinuations)**: Only a limited number of RCTs reported a consistent and comparable outcome definitions. The uncertainties observed for the outcomes of ARR, CDP, and treatment discontinuation might have arisen due to differences in the outcome definitions and their time of measurement across trials included in the NMA, especially between the less vs. more recently published trials. As the company states, these trials were conducted over a period of 35 years (1987 to 2022) and

they differed in the outcome definitions, timing of their measurement, and length of follow-up. The company did not provide information if the trials used different definitions of ARR (any relapses, conformed relapses, or protocol-defined relapses). Likewise, the company did not discuss if the trials included in the NMA used similar or different definitions of 3-month and 6-month CDP outcomes as they may vary depending on the magnitude of EDSS score change (an increase of 1-point vs. increase of 1.5 points) and measurement time (e.g., at 12 months, at 24 months). Moreover, it was not clear whether or not the definition of treatment discontinuation was consistent across the trials. The definition could have been different based on its cause, i.e., all-cause, lack of efficacy-related, adverse event-related, related to mortality, or lost to follow-up. The company was requested in the clarification letter (Q: A1, Q: A9-A10, Q: A18) to provide this information. Also, the company was asked to provide an analysis if the risk of bias in more recently published trials differs from that in the earlier published trials (EAG clarification letter [Q: A25]). In their response to clarification questions, The NMA outcomes, 3-month and 6-month CDP were defined as being measured at 24-months of follow-up (Q: A10). The company noted that the treatment discontinuation in the NMA was defined as all-cause (Q: A9, A18). Although all-cause treatment discontinuation was available for the 25 RCTs included in the NMA (Company's response to clarification questions file; Table pages 14-15), for most of the trials the definition of this outcome was not reported. The definition reported for only three trials Vermersch 2014 (TENERE Trial), Durelli 2002 (INCOMIN trial), and Confavreux 2014 (TOWER trial) was not consistent.[60, 73, 74]

- **Risk of bias in more recent vs. less recent studies**. The company was asked to provide an analysis if the risk of bias in more recently published trials differs from that in the earlier published trials (EAG clarification letter [Q: A25]). The company stated that this analysis was performed for the previous NICE submission (TA493), which suggested that there was no important difference in the risk of bias between more recently vs. earlier published trials. Therefore, the analysis was not performed again.

- **Missing data:** Missing data on factors other than the key outcomes contributes additional uncertainty to NMA results. For example, most primary trial publications did not include information on ethnicity and prior treatment history across trials. Assuming that these factors are effect modifiers, it is uncertain whether or not the distribution of these factors across trials would have been comparable had these data been available.

- **Placebo arms:** The CS did not include the type, frequency and mode of administration of placebo regimens in the trials included in NMA. It is uncertain if the placebo arms were sufficiently uniform to be used as an anchor (common comparator) in the NMA. The EAG as well as the company noted (e.g., frequency, duration, mode of administration) in the placebo arms which could have modified the relative treatment effect and biased the NMA results. To check the degree of uniformity of the placebo arms, the EAG asked the company to provide a comparison of placebo rates of NMA outcomes from the trials included in the NMA (EAG clarification letter Q: A15). As stated earlier, outcome rates in

the placebo group did not significantly vary therefore the EAG did not identify a major concern.

- **Sensitivity analysis:** To remove INCOMIN trial,[60] the EAG team thinks that it is more prudent to include INCOMIN trial in the base case NMA for all outcomes given that on one hand its exclusion does not impact the NMA effect estimates noticeably and that on the other hand its inclusion contributes to the overall NMA model stability. The company provided a series of sensitivity analyses (*Merck_A25: Sensitivity analysis by year of publication 020824WA [NoCON]; Appendix A*) where it demonstrated robustness of the relative treatment effect on ARR, 3-month CDP at 24 months, and 6-month CDP at 24 months (no change in the direction compared to base-case scenario) for Cladribine vs. comparators with respect to diagnostic criteria (after excluding studies using Poser diagnostic criteria or studies for which diagnostic criteria was unclear), year of publication (after excluding studies published prior to the year 2000), blinding (after excluding open-label studies and studies for which blinding status was unclear), and study phase (after excluding phase II studies).

- **Post-hoc defined outcomes**: The present NMA includes post-hoc analysis-based 6-month CDP measurement for cladribine vs. placebo from CLARITY trial[31] and interferon beta-1a vs. placebo from the PRISMS trial.[69] These analyses were performed to improve the level of evidence available for 6-month CDP in active RRMS, and to improve the evidence connecting ocrelizumab which was studied versus interferon beta-1a, to the rest of the network.

- **Constancy of hazard ratio proportionality:** In the clarification letter (Q: A17), the EAG requested that the company provide their assessment of the hazard ratio proportionality assumption from the reports of individual trials. The company's response to EAG clarification letter indicated that there are no time-to-event data or KM curves available in the primary study reports to check the proportionality assumption. Therefore, EAG believe there is uncertainty in this regard. To this effect, the company stated that proportionality assumption validation was not required since both CDP and treatment discontinuation in the primary DMT study reports were provided in the form of a dichotomous data (i.e. number of patients with CDP or number of patients who discontinued the treatment). The hazard ratio was calculated in the NMA because a binomial clog-log model was used with the timepoint at which these data were measured.

- **Other outcomes:** The NMA did not measure/report other efficacy outcomes such as brain lesion count on magnetic resonance imaging (MRI) or no evidence of disease activity (NEDA). Likewise, no safety outcomes were reported. The company provided the league tables and SUCRA diagrams in their response to clarification questions file (Q: A22-23; Figures 2-9 and Figures 10-17, respectively; pages 18-29).

3.5 *Additional work on clinical effectiveness undertaken by the EAG*

The EAG conducted additional analysis of the clinical effectiveness evidence on DMTs for RRMS to verify accuracy and robustness, including generating new evidence when necessary to inform the economic model.

Firstly, the EAG replicated the NMAs performed by the company. Secondly, the EAG conducted survival analysis modelling to estimate the real-world persistence of DMTs, which was then used to inform EAG assumptions about treatment discontinuation in the model. The methods and outcomes of these analyses are reported in the below sections.

3.5.1.1 EAG Replication of the NMAs

The EAG replicated the NMAs on annualised relapse rate (ARR), 3-month confirmed disease progression (3m-CDP), 6-month CDP, and treatment discontinuation. To perform these analyses, the EAG requested the company's WinBUGS code used to fit the NMA models. However, the company was unable to provide the requested WinBUGS files, stating that the models described in the CS were run using proprietary software. Despite this, the company did provide the data in a format that allowed the EAG to replicate each NMA after further communication facilitated by the NICE Team. The EAG's analyses focused solely on fitting random effects models, running three chains for each model. Convergence and lack of autocorrelation were assessed as adequate using autocorrelation plots after a 100,000-simulation burn-in phase, with thinning applied every 5th sample.

The EAG successfully replicated the NMA for ARR, obtaining results consistent with those reported by the company. The company's estimates presented in Table 12 are sourced from Table 33 of CS document B.

Table 12. Relative Risk Ratios for ARR generated from EAG replication of the CS NMA (random-effect model)

	Median ARR (95%CrI)	
Treatment vs. Placebo	**CS Model (Table 33 of CS document B)**	**EAG Model**
Cladribine tablets	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	[redacted]
Interferon beta-1a 44µg	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]
Diroximel fumarate	[redacted]	
Glatiramer acetate 20mg		[redacted]
Teriflunomide 7mg		[redacted]

RR = Risk Ratio
CrI Credible Interval
Direximel fumarate did not have data on ARR. Assumed equal effectiveness to dimethyl fumarate in the model
Glatiramer acetate 20mg and Teriflunomide 7mg were not considered in the economic model

Table 13 presents the estimated hazard ratios for 6-month confirmed disease progression generated by the EAG's replication of the CS NMA. The figures are shown alongside those reported in Table 34 of CS document B. The results indicate a high level of agreement between the EAG's estimates and those provided in the company's submission. A good level of agreement was obtained for the 3-month CDP outcome (results not presented).

Table 13: EAG replication of the hazard ratios of 6-month CDP comparing DMT versus placebo (random effects model)

	HR for 6m-CDP (95% CrI)	
Treatment versus placebo	CS (Table 34, CS document B)	EAG
Cladribine tablets	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]
Glatiramer acetate	[redacted]	[redacted]
Interferon beta-1a 22µg	[redacted]	
Interferon beta-1a 44µg	[redacted]	[redacted]
Interferon beta-1a 30µg	[redacted]	[redacted]
Interferon beta-1b 250µg	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]
Diroximel fumarate	[redacted]	
Teriflunomide 7mg		[redacted]

For the NMA of treatment discontinuation, the EAG's replication of the CS analyses was only partially successful. While the EAG was able to generate hazard ratios for treatment discontinuation that align with those provided in the CS documents, some discrepancies remain. Table 14 compares the hazard ratios using cladribine as baseline treatment, in line with how the company presented its results (Table 17 of appendix accompanying CS). There is high level of agreement between the CS and EAG estimates of the treatment discontinuation hazard ratio.

Table 14: EAG estimate of the hazard ratio for treatment discontinuation for treatment versus cladribine tablets 3.5 mg/kg (random effect model)

	Median HR (95% CrI)	
Treatment versus Cladribine	CS HR[1]	EAG HR
Placebo	[redacted]	[redacted]
DMF, 240 mg, bid	[redacted]	[redacted]
Ofatumumab 20 mg	[redacted]	[redacted]

[1] Table 17 of CS appendix

Teriflunomide, 14 mg, od	[redacted]	[redacted]
GA, 20 mg, qd	[redacted]	[redacted]
IFN beta-1b, 250 mcg, eod	[redacted]	[redacted]
Diroximel Fumarate	[redacted]	[redacted]
GA, 40 mg, tiw	[redacted]	[redacted]
IFN beta-1a, 30 mcg, q1w	[redacted]	[redacted]
Teriflunomide, 7 mg, od	[redacted]	[redacted]
IFN beta-1a, 44 mcg, tiw	[redacted]	[redacted]
Ocrelizumab, 600 mg, once six months	[redacted]	[redacted]
Ponesimod, 20 mg	[redacted]	[redacted]
IFN beta-1a, 22 mcg, tiw	[redacted]	[redacted]

The hazard ratios for treatment discontinuation were converted into DMT-specific annual probability of stopping treatment, which were directly incorporated into the economic model (Table 37, CS document B). However, the EAG was unable to replicate the probabilities used in the model. During the clarification stage, the EAG requested the WinBUGS files that the company used to conduct its NMA to replicate their results (clarification question B11). Verifying the CS NMA estimates of treatment effect on ARR, 6-month CDP, and treatment discontinuation is crucial to this assessment, as these parameters are key to the cost-effectiveness analysis. Unfortunately, the company was unable to provide the required files due to proprietary reasons (as stated in the company's response to clarification question B11).

Based on the additional information provided by the company at clarification and Section B.3.4.3.5 of CS document B, which outlines the generation of treatment discontinuation probabilities, the EAG attempted to replicate the calculations.

The method essentially involves calculating the average weighted annual probability of treatment discontinuation across the placebo arms of trials included in the NMA that have a placebo arm, and then applying the hazard ratio relative to placebo to generate the DMT-specific probabilities. In the Bayesian framework, this process is implemented by a single line of code in the CS WinBUGS model, which has the advantage of automatically propagating uncertainty in the data through to the posterior estimate of the discontinuation probability.

The EAG fitted the models, but it was unable to produce estimates that match the company’s estimates of treatment discontinuation probability. Table 15 presents the two sets of estimates side by side for each comparison. For example, the mean 1-

year probability of treatment discontinuation is in the placebo group is [redacted] from the CS model and [redacted] from the EAG re-analysis of the company's data. Similar discrepancies between the EAG and CS estimates are evident across all DMTs. The EAG is unable to determine which of these estimates is correct or to elucidate the source of the discrepancy.

Table 15: Comparing EAG and CS estimate of the probability of DMT discontinuation

	CS estimates		EAG's estimates	
Treatment	Mean (95%CrI)	Median	Mean (95%CrI)	Median
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine tablets	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 40mg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 30 Âµg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44 Âµg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1b 250 Âµg	[redacted]	[redacted]	[redacted]	[redacted]
Interferon beta-1a 22 Âµg	[redacted]	[redacted]	[redacted]	[redacted]
Peginterferon	[redacted]	[redacted]		
Teriflunomide 14mg	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer acetate 20mg			[redacted]	[redacted]
Teriflunomide 7mg			[redacted]	[redacted]

3.5.1.2 Survival Modelling of DMT Treatment Persistence

The EAG disagrees with the company's approach to modelling treatment discontinuation in the economic model. The company estimated the probabilities of treatment discontinuation using RCT data that informed an NMA, from which the probability of stopping treatment was generated for the comparator DMTs in the economic model. The EAG is concerned that the use of RCT data may not

accurately reflect the real-world experience of RRMS patients and their clinicians with respect to stopping treatment.

To address this concern, the EAG sought real-world evidence on DMT treatment persistence in RRMS. A rapid literature review was conducted, focusing on observational studies that report real-world treatment persistence. Preference was given to studies reporting UK data but non-UK studies were also considered if they were well-conducted with moderate to large sample sizes and reported long-term persistence data. The review identified the following studies: Tallantyre et al. (2024),[81] Spelman (2023),[82] Reder (2019),[83] Zhornitsky (2015),[84] and Bucello (2021).[85] A published poster by Tai et al. (2023) [86] presented data on real-world persistence and adherence to ofatumumab versus ocrelizumab, based on an analysis of US medical insurance data. However, this data was not used to inform the model for ofatumumab because it is unpublished, not peer-reviewed, and based on US data, which may not reflect the experience of UK patients. The review did not find any studies reporting real-world data on treatment persistence for ponesimod.

The EAG selected the Tallantyre (2024) study as the most relevant source of data on DMT persistence. This study of UK patients with RRMS, included a reasonably large sample (4366 people with relapse-onset multiple sclerosis from 13 UK specialist centres in 2021), had the longest follow-up (up to 10 years for older DMTs such as glatiramer acetate and the interferons), and covered a reasonable proportion of the DMTs included cladribine considered in the economic model. Unfortunately, the Tallantyre data did not include ponesimod, ofatumumab, and diroximel fumarate.

From the Tallantyre study, the EAG digitised Kaplan-Meier (KM) plots for the reported DMTs (including cladribine, GLA, ocrelizumab, the interferon betas, teriflunomide, and dimethyl fumarate). Additional data for diroximel fumarate was sourced from Bucello (2021) based on Italian patients (n=1475), and Reder (2019) provided a second source of data on teriflunomide. These KM curves were digitised using an online tool, WebPlotDigitizer (https://automeris.io/), to obtain time-to-event data in the form of persistence probabilities for DMT treatment. Parametric survival curves were then fitted to the digitised data.

The available data consisted of survival probabilities derived from digitised Kaplan-Meier (KM) plots rather than raw time-to-event data. Therefore, a non-linear least squares (NLS) estimation algorithm implemented within the R package MINPACK [87] was employed to model the persistence probabilities directly rather than traditional endpoints. The method works by minimising the difference between the observed survival probabilities from the KM curves and the predicted probabilities generated by the parametric models. 95% confidence intervals were derived using bootstrapping.

Fitted models included the Exponential, Weibull, Gompertz, Lognormal, and Loglogistic. There were convergence problems with Generalized Gamma models, hence results for these were not reported.. Models were structured to predict the probability of remaining on treatment at specific time points. Initial parameter estimates were provided for each model, which were then adjusted to closely match the observed data. The best-fitting model to the observed data for each treatment was selected based on the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The model with the lowest AIC and BIC was chosen as it provided the best balance between fit and complexity. The selected models were used to extrapolate treatment persistence probabilities beyond the observed data to

2, 5, and 10 years. These extrapolated probabilities were critical for assessing long-term treatment effects and for informing the economic models. All analysis was done in R (R Core Team, 2023).[88] Table 16 presents the AIC and BIC statistics used to assess model fit to the observed data.

Table 16: Model fit statistics

Model	AIC	BIC		Model	AIC	BIC
***Cladribine*[1]**				*Teriflunomide*[1]		
exponential	-154	-152		exponential	-125	-122
weibull	-180	-176		weibull	-156	-152
gompertz	-176	-172		gompertz	-184	-180
lognormal	**-180**	**-177**		lognormal	-186	-182
loglogistic	-180	-176		loglogistic	-179	-174
Generalized **gamma**	-179	-174		**Generalized gamma**	**-187**	**-181**
***Dimethyl fumarate*[1]**				*Teriflunomide*[2]		
exponential	-228	-223		exponential	-242	-238
weibull	**-456**	**-449**		weibull	-348	-342
gompertz	-374	-368		**gompertz**	**-359**	**-352**
lognormal	-388	-382		lognormal	-301	-294
loglogistic	-435	-429		loglogistic	-328	-322
Generalized **gamma**	-460	-452		Generalized gamma	-355	-347
***Ocrelizumab*[1]**				*Diroximel fumarate*[3]		
exponential	-241	-238		exponential	-375	-370
weibull	-271	-266		weibull	-567	-560
gompertz	-284	-280		gompertz	-561	-554
lognormal	-277	-273		**lognormal**	**-589**	**-582**
loglogistic	-272	-267		loglogistic	-572	-565
Generalized gamma	**-281**	**-275**		Generalized gamma	-601	-592

[1]Tallantyre (2024); **[2]Bucello (2021)**; **[3]Lager 2023**

The fitted curves are displayed in Figure 14. Across all treatments, the exponential model yields the most pessimistic persistence predictions, while the Gompertz model tends to produce more optimistic estimates. The exception is teriflunomide, based on the Italian data (Bucello, 2021),[85] where the Gompertz model is more optimistic, and the exponential model is more pessimistic. The Weibull model predictions generally fall between these two extremes. Probability estimates of treatment persistence, based on observed data (where available) and predictions from the best-fitting model, are presented in Table 17.

Table 17: Probability of DMT treatment persistence

	Persistence probability (95% bootstrap confidence interval)		
Model	2 years[4]	5 years[4]	10 years[4]
***Cladribine*[1]**			
Exponential	0.959 (0.002)	0.899 (0.005)	0.809 (0.009)
Weibull	0.954 (0.002)	0.931 (0.008)	0.906 (0.016)
Lognormal*	0.954 (0.002)	0.933 (0.005)	0.912 (0.008)
Loglogistic	0.954 (0.002)	0.931 (0.005)	0.907 (0.009)
Gompertz	0.952 (0.002)	0.945 (0.006)	0.945 (0.007)
Dimethyl fumarate[1]			
Exponential	0.76 (0.004)	0.503 (0.006)	0.253 (0.006)
Weibull*	0.713 (0.012)	0.519 (0.014)	0.339 (0.037)
Lognormal	0.704 (0.002)	0.519 (0.002)	0.374 (0.004)
Loglogistic	0.708 (0.001)	0.518 (0.002)	0.367 (0.003)
Gompertz	0.71 (0.002)	0.514 (0.002)	0.396 (0.007)
Ocrelizumab			
Exponential	0.943 (0.002)	0.865 (0.004)	0.747 (0.006)
Weibull	0.942 (0.001)	0.888 (0.004)	0.817 (0.009)
Lognormal	0.942 (0.001)	0.893 (0.003)	0.841 (0.006)
Loglogistic	0.942 (0.001)	0.889 (0.003)	0.823 (0.008)
Gompertz*	0.941 (0.001)	0.906 (0.003)	0.89 (0.007)
Teriflunomide[1]			
Exponential	0.693 (0.008)	0.4 (0.011)	0.16 (0.009)

Weibull	0.668 (0.004)	0.427 (0.008)	0.223 (0.012)
Lognormal*	0.654 (0.003)	0.434 (0.005)	0.277 (0.007)
Loglogistic	0.659 (0.003)	0.431 (0.006)	0.271 (0.007)
Gompertz	0.655 (0.003)	0.436 (0.006)	0.312 (0.014)
Teriflunomide[2]			
Exponential	0.782 (0.004)	0.541 (0.007)	0.292 (0.008)
Weibull	0.823 (0.008)	0.482 (0.013)	0.138 (0.032)
Lognormal	0.821 (0.006)	0.501 (0.005)	0.245 (0.012)
Loglogistic	0.824 (0.005)	0.493 (0.004)	0.229 (0.008)
Gompertz*	0.822 (0.003)	0.466 (0.006)	0.03 (0.008)
Diroximel fumarate[3]			
Exponential	0.702 (0.006)	0.412 (0.009)	0.17 (0.007)
Weibull	0.781 (0.003)	0.656 (0.007)	0.532 (0.012)
Lognormal*	0.791 (0.002)	0.698 (0.005)	0.618 (0.007)
Loglogistic	0.784 (0.003)	0.674 (0.006)	0.574 (0.009)
Gompertz	0.826 (0.004)	0.821 (0.005)	0.821 (0.005)

[1]Tallantyre (2024); [2]Bucello (2021); [3]Lager 2023 [81, 85, 89]
[4]Time sine DMT initiation

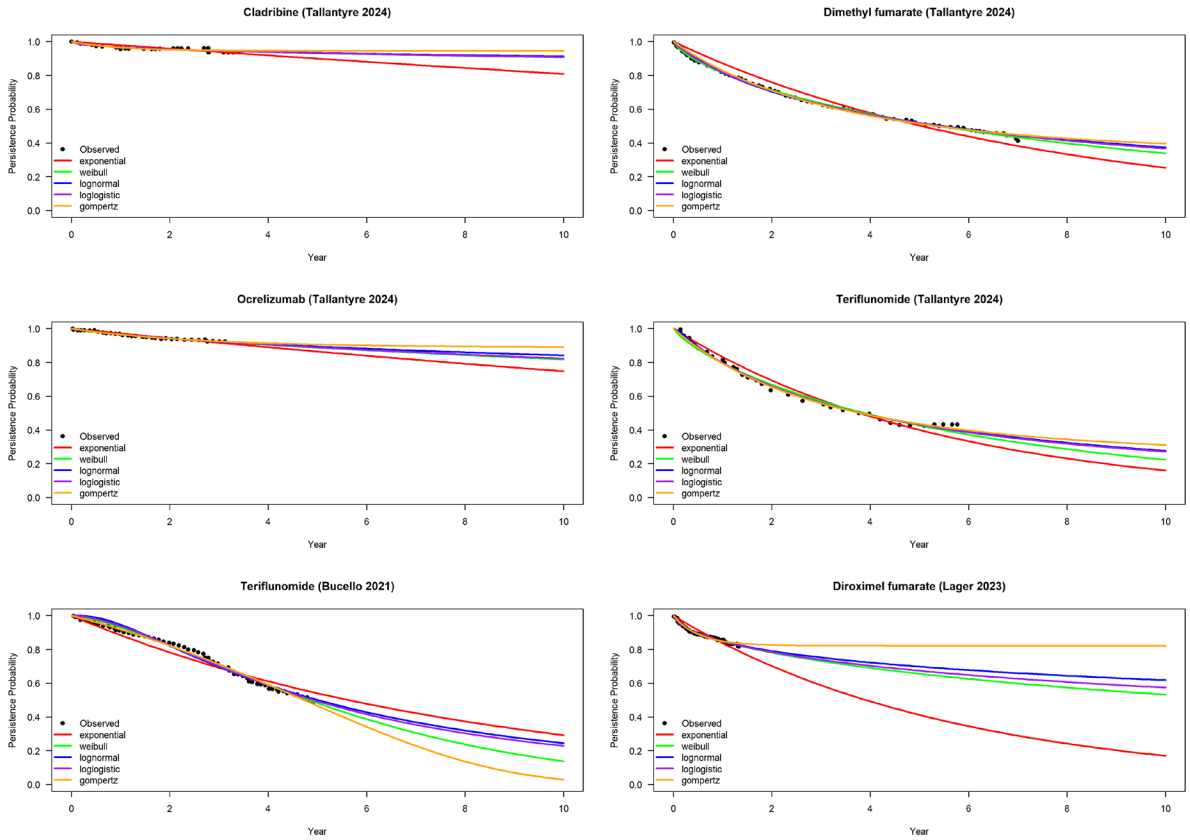


Figure 14. Parametric survival extrapolation of DMT treatment persistence

For cladribine, only two years of follow-up data are reported and available from Tallantyre (2024), with the best fit model to the observed persistence probabilities being the log-normal model. The data are immature, and the median survival (in this case, persistence) has not been reached, so caution is warranted when extrapolating beyond the observed data. Because of this, the probabilities predicted beyond the observed data by all the parametric survival models will be highly uncertain, with the degree of uncertainty increasing as the extrapolation period extends.

When faced with uncertainties in long-term extrapolation of survival data, one approach to addressing this uncertainty is to compare the predictions to external reference data. The survival curve that generates predictions closest to the external reference data could be preferred on this basis. One potential external data source is the Tallantyre (2024) study, which also reported up to 10 years of treatment persistence data for alemtuzumab, an older immune-reconstituting DMT with a short-course administration similar to that of cladribine. Note that alemtizumab was not considered as a comparator in the CS. The data suggest probabilities of persistence of 96.4% at 2 years, decreasing to 89.8% at 5 years and 80% at 10 years. Notably, more people remained on alemtuzumab at 2 years (96.4%) compared to cladribine (95.5%).

Given this information, and if it is reasonable to use the alemtuzumab data as an external reference to guide the selection of a long-term extrapolation model for cladribine, the exponential curve (Figure 13) would appear to generate predicted probabilities for cladribine that most closely match the alemtuzumab data. The

predicted probabilities of persistence on DMT for cladribine from the exponential model are Figure 13 at 5 years and 80.9% at 10 years (see Table 17).

The EAG's work on estimating the probability of treatment discontinuation has several limitations. Due to time and resource constraints, the EAG could not conduct a comprehensive systematic literature review for real-world evidence on the persistence of DMTs in RRMS. Instead, it performed a rapid review, identifying the Tallantyre (2024) study, which offers real-world evidence on the use of DMTs among UK patients.

However, the Tallantyre (2024) study does not cover all comparators relevant to the NICE decision problem, such as ofatumumab, ponesimod, and diroximel fumarate. Like the company's NMA data, the definitions of treatment discontinuation or persistence in the Tallantyre study are inconsistent for cladribine and other DMTs. For example, cladribine's persistence is defined as the time to the first DMT switch or the time to the last known follow-up if no subsequent DMT was prescribed, while other DMTs use the duration a patient remained on a single DMT.

Additionally, the EAG recognises challenges in using alemtuzumab data as an external reference when choosing its preferred model for extrapolating cladribine's treatment persistence. This approach introduces significant uncertainty due to the immature cladribine data and the differences in safety profiles between the two treatments. Furthermore, the analysis did not involve randomization or stratification, and only three baseline characteristics—gender ratio, mean age at the start of DMT, and mean disease duration—were compared, making this a naïve comparison.

Despite these challenges, the EAG considers the Tallantyre data to be the best currently available real-world evidence on the persistence of DMTs among UK patients with RRMS. It remains valuable in exploring uncertainties regarding the long-term persistence of DMTs in RRMS.

3.6 *Conclusions of the clinical effectiveness section*

The company conducted a network meta-analysis (NMA) to assess the comparative effectiveness of cladribine tablets vs. different comparator DMT regimens in patients with active RRMS. The NMA included 38 trials of DMTs approved for treating active RRMS in UK and aligned with the final NICE scope of the decision problem. The

main outcomes assessed in the NMA were ARR, 3-month CDP, 6-month CDP, and treatment discontinuations (all-cause).

In general, the EAG considers the SLR (locating, selecting, extracting, and appraising primary studies) and NMA methodology (comparators included, the outcomes selected, and statistical approaches including the choice between random- and fixed-effects model) appropriate.

The EAG believe that the patient population in the included in NMA trials generally corresponds to that outlined in the scope of the decision problem. The ERG concurs with the company that most the trials included the NMAs were of good quality.

Overall, the EAG opinion is that cladribine tablets showed a statistically significantly superior efficacy compared to teriflunomide, glatiramer acetate, peginterferon, interferon beta-1a/1b or placebo with regards to reductions in ARR. But cladribine tablets were not significantly different from ofatumumab and ocrelizumab in reducing ARR. The NMA results comparing effects of cladribine tablets to DMT regimens in terms of 3-month or 6-month disability progression were inconclusive given statistically non-significant estimates accompanied by wide and overlapping credible intervals. The results for all-cause treatment discontinuation showed some numerical advantage of cladribine tablets compared to other DMTs and their regimens, but again the observed differences were presented as non-significant estimates with wide overlapping 95% CrIs. Cladribine tablets significantly improved ARR, 3-month CDP, and 6-month CDP (but not treatment discontinuations) compared to placebo.

Given the visual inspection of the funnel plots suggested that a large impact of publication bias on the NMA results is unlikely.

The EAG agrees with the company that the results of this NMA are consistent to those in the previous NICE submission of cladribine in RRMS, demonstrating that cladribine tablets are statistically more effective or numerically favoured in reducing ARR compared to several other DMTs and their regimens in active RRMS (TA493/TA616). These results also agree in that there is a greater uncertainty around CDP outcomes.[14, 15] The EAG advises that the NMA results should be interpreted with caution due to both statistical and clinical uncertainties. Notably, the EAG was unable to replicate the probabilities of treatment discontinuation generated by the company from its NMAs. Furthermore, due to time constraints, the EAG could not perform additional checks to validate the NMA and survival modelling it conducted for this appraisal. The company did not assess the validity of underlying assumptions, such as the consistency assumption, and the EAG was unable to implement these assessments due to time constraints and the extensive volume of data and analyses in the company's submission.

The EAG notes that the NMA results should be interpreted with caution owing to statistically and/or clinically determined uncertainties. Statistical uncertainty could be a result of a smaller number of RCTs that contributed data to the CDP and treatment discontinuations compared to ARR outcomes. Not all trials were designed to have had a power or length of follow-up sufficient for detecting the outcomes of disability progression. Other uncertainties might have arisen due to differences in the outcome definitions (ARR, CDP, and treatment discontinuation), their time of measurement, and the duration of trials included in the NMA. The EAG notes that the RRMS diagnostic criteria has evolved (e.g., addition of magnetic resonance imaging results) during the time span of 35 years (from 1987 to 2022), when the included in NMA

trials were published. For example, the trials published before 2007, used Poser's criteria, whereas trials published in later years used McDonald's criteria. Furthermore, there were notable differences in the duration of MS and EDSS score measurements. The placebo arms could have been different with respect to frequency and mode of administration that would violate the connectivity and transitivity assumptions. Most primary trial publications did not include information on ethnicity and prior treatment history across trials. Therefore, it is difficult to determine if there is any imbalance in these factors across the trials that might lead to biased estimates in the NMA. There is a great uncertainty in the definition and consistency of the NMA outcomes across the trials, especially for CDP and treatment discontinuations. All this may have led to inconsistencies between the direct and indirect treatment comparisons in the closed NMA loops thereby suggesting that the transitivity assumption may have been violated.

4 COST EFFECTIVENESS

4.1 *EAG comment on company's review of cost-effectiveness evidence*

The company conducted three separate SLRs for cost-effectiveness studies, health-related quality of life (HRQoL) studies, and cost and resource use studies. The majority of searches were conducted on 6th February 2024.

Search strategies

Cost-Effectiveness Studies SLR (Appendix G)

Searches for cost-effectiveness studies in relapsing-remitting multiple sclerosis (RRMS) were carried out independently from those for HRQoL and cost/resource use. There are inconsistencies between the databases reported in the introduction (Appendix G.1.1) and the search strings provided (Appendix G, Tables 32-34). The search strings indicate searches were conducted in MEDLINE and Embase (via Embase.com) on February 6, 2024; the Cochrane Database of Economic Evaluations (January 2017); and MEDLINE In-Process (February 6, 2024). The introduction also mentions EconLit and NHS EED/DARE databases, which were not reflected in the search strings. The company clarified in response to question C2. Appendix G: Q1 that "searches conducted in NHS EED, DARE, and EconLit were conducted before 2015. Due to archiving issues (decommissioning of one of the vendor's systems), we can no longer access files containing the specific search strings for these databases." And "It is worth noting that this particular aspect of the submission has been evaluated in the previous NICE appraisal for cladribine tablets (TA493)."

The search terms were broad, although some spelling errors were noted in the search strings (e.g., "chariot diease" and "neuromtelitis" instead of correct terms). Additional sources, including conference proceedings and HTA websites, were reportedly searched, but not enough detail is provided for the EAG to critique the search methods. Search results were subsequently limited to articles and reports published since 2017, following the initial NICE appraisal for cladribine (TA493/TA616), and relevant to the UK. The SR ultimately included 11 cost-effectiveness studies and six economic models from NICE submissions since 2017. A list of excluded studies (199 according to the flow diagram) was provided in response to clarification question C2. Appendix G: Q3.

HRQoL SLR (Appendix H):

The HRQoL search aimed to identify published utility studies in RRMS, particularly those relevant to decision-making in England. The databases searched included MEDLINE and Embase (via Embase.com), MEDLINE In-Process (via PubMed), and CENTRAL/ CDSR (via Cochrane Library), with searches conducted in February 2024. The search strings employed a broad filter, but a language limit applied to the MEDLINE In-Process search caused recently added records not yet indexed by language to be missed, reducing the total from 2,439 to 441. The Cochrane search has a significant error in line #30; line #17 is combined with line #2 instead of line #29, but it is unclear if this is in the reporting or in the actual search, and the searching of other related databases helps to mitigate any effect of this. The search strategy included additional sources, such as conference proceedings and HTA websites. Ultimately, 143 studies (from 160 publications) were included, alongside

six HTA submission documents. A list of excluded studies with reasons was not initially available (239 exclusions at full-text). In response to a clarification question, a list of some excluded publications (those dated 2015-2023) was provided.

Cost and Resource Use SLR (Appendix I):

A broad search for cost and resource use studies was conducted in February 2024. Despite minor discrepancies between the databases listed in the introduction and those in the search strings, relevant studies were captured. MEDLINE and Embase were searched, as well as MEDLINE In-Process (via PubMed), with the PRISMA flow diagram also listing EconLit and Cochrane.

The search initially identified 151 publications (135 studies). Six studies were eventually selected for inclusion in the cost-effectiveness model, including two key studies (Hawton et al. and Tyas et al.) used to derive costs by EDSS state and relapse, both inflated to the 2023 cost year. In total, 1,162 articles were excluded at the full-text stage. A full list of these with reasons was not available, but in response to a clarification question, lists of excluded publications with reasons dated 2017-2023 were provided. The company noted that evidence for cladribine tablets prior to 2017 had been evaluated in a previous NICE submission (TA493).

Summary

Overall, the search strategy for the economic evidence (cost-effectiveness, HRQoL, and cost and resource use) SLRs in RRMS was generally acceptable to the EAG, but there were a few areas of concern. In particular, the incorrect use of a language limit in one database in the HRQoL review may have resulted in recently added studies being missed. There were also some discrepancies between the databases listed in the introductions of the appendices and those in the search strings, and a few minor typographical errors were found in the search terms. Additionally, for the HRQoL and cost and resource use reviews, excluded studies were not fully listed, making it difficult to assess comprehensiveness. Despite these issues, the EAG considers the overall search strategy to be adequate for capturing relevant studies for the cost-effectiveness analysis, although full details of the original and supplementary searches would have been beneficial.

4.2 *Summary and critique of the company's submitted economic evaluation by the EAG*

The EAG assessment of the company economic evaluation against the NICE reference case checklist is provided in Table 18.

Table 18. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes. The company's base case includes the quality-of-life effects on carers
Perspective on costs	NHS and PSS	Yes.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes.

Element of health technology assessment	Reference case	EAG comment on company's submission
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes.
Synthesis of evidence on health effects	Based on systematic review	Yes. NMA of annualised relapse rates, 6m-CDP and all-cause treatment discontinuation. The EAG believes that the NMA estimates of discontinuation probabilities are not appropriate for the model, primarily because they are derived from RCT data. The EAG was unable to replicate them in it's re-analyses of the NMA data. The EAG considers real-world evidence to be more reflective of the actual experiences of RRMS patients regarding the discontinuation of DMTs.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes. CLARITY trial baseline EQ-5D-3L
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes. CLARITY trial baseline EQ-5D-3L mapped to UK 3L tariff
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.1 Model structure

The company developed a Markov state cohort simulation model to estimate the cost-effectiveness of cladribine tablets compared to best supportive care (BSC) and other disease-modifying therapies (DMTs) for patients with relapsing-remitting multiple sclerosis (RRMS). The model has a cycle length of 1-year, a time lifetime horizon of 50-years, and comprises of two key components: a natural history reference model, which uses data on the disability and relapse status of patients receiving BSC, and a treatment-adjusted model, which integrates the natural history

data with comparative efficacy and safety data of DMTs versus placebo. Both components utilise a core 11-health state structure that categorises patients based on their Expanded Disability Status Scale (EDSS) scores to model disease progression, along with a single health state for death from all causes Table 15 depicts the model structure presented the company's submission document B.

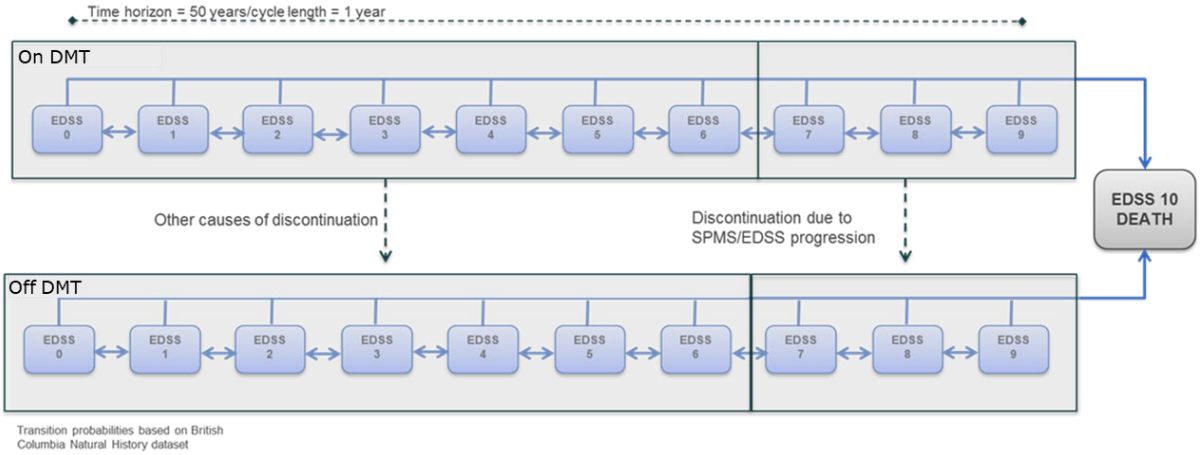


Figure 15: Health state structure of the 11-state model including periods on and off DMT

EAG comment

The EAG agrees that the 11-health state structure is appropriate for the decision problem at hand namely estimating the cost-effectiveness of cladribine compared with Best Supportive Care (BSC) and other Disease Modifying Therapies (DMTs) in people with RRMS. It has been used in the previous appraisal of cladribine (TAs TA493/TA616).[14, 38] It is a simplification of a more complex and comprehensive 21-health state model previously used in RRMS appraisals by excluding secondary progressive multiple sclerosis (SPMS)-specific states. The EAG agrees with the company's preference for a simplified 11-state model over the 21-state model, citing challenges in clearly identifying the transition from RRMS to SPMS in clinical practice and concerns about the reliability of data from the London Ontario registry. The company considered this data flawed due to post-hoc censoring and the absence of individual patient-level information. As a result, the company's economic model does not distinguish between RRMS and SPMS, instead treating SPMS as a continuation of RRMS, with disease progression primarily indicated by changes in EDSS scores.

Upon entering the model, patients receiving BSC or a DMT (including cladribine) are distributed across the 10 EDSS states based on the baseline EDSS distribution observed in the CLARITY trial (placebo and the 3.5mg cladribine arm) population (16, taken from Table 29 of CS document B). Throughout the annual cycle periods, the patient cohort may:

- Experience progression in disability, resulting in a transition to a higher EDSS state,
- Show improvement in disability status, leading to a transition to a lower EDSS state,

- Remain in their current EDSS state without any change in disability level, or
- Death.

Table 19. Baseline distribution of CLARITY population according to EDSS

EDSS category	CLARITY ITT population at baseline (N=870)
EDSS 0	[redacted]
EDSS 1.0	[redacted]
EDSS 2.0	[redacted]
EDSS 3.0	[redacted]
EDSS 4.0	[redacted]
EDSS 5.0	[redacted]
EDSS 6.0	[redacted]
EDSS 7.0	[redacted]
EDSS 8.0	[redacted]
EDSS 9.0	[redacted]

For patients receiving Best Supportive Care (BSC), the probability of transitioning between EDSS states is modelled based on natural history transition matrices derived from the British Columbia Multiple Sclerosis (BCMS) registry assuming a median age at disease unset of 28 years and median disease duration of 5.18 years. Specifically, the transition matrices published in Palace et al.[90] were applied. These matrices were developed using continuous-time multi-state methods, both with and without baseline covariates, to accurately reflect the progression of the disease in the patient cohort. For patients receiving disease-modifying therapies (DMTs), including cladribine tablets, the effect is to slow disease progression from lower to higher EDSS states. This effect is modelled by applying a DMT-specific hazard ratio (Table 20), derived from a random-effects network NMA of RCT data on 6-month confirmed disability progression (CDP), to the BCMS transition matrices underlying disease progression in the BSC arm.

Table 20. Hazard ratios of 6-month CDP comparing DMT versus placebo (random effects model)

Treatment vs. placebo	Median hazard ratio of 6-month CDP
Cladribine tablets	[redacted]
Dimethyl fumarate	[redacted]
Glatiramer acetate	[redacted]
Interferon beta-1a 22 µg	[redacted]
Interferon beta-1a 44 µg	[redacted]
Interferon beta-1a 30 µg	[redacted]
Interferon beta-1b 250 µg	[redacted]
Peginterferon	[redacted]
Teriflunomide	[redacted]
Ocrelizumab	[redacted]
Ofatumumab	[redacted]
Ponesimod	[redacted]
Diroximel fumarate	[redacted]

Consistent with previous RRMS appraisals assessments (TA527,[91] TA533,[80] TA624,[92] TA699,[78] and TA767 [77]), the modelled cohort may also experience one or more acute relapse events during each cycle. These events are treated independently from disability progression associated with EDSS and are calculated by applying a time-dependent Annual Relapse Rate (ARR) modelled to the number of patients alive in the model.

For patients in the BSC arm, the number of acute relapse events in each cycle of the Markov model is determined by multiplying the number of patients alive in each cycle by the annualised relapse rate (ARR) for active RRMS of [redacted] (95% CI: [redacted] to [redacted]) observed in the placebo arm of the CLARITY trial. The company stated that this approach differs from previous assessments of disease-modifying therapies (DMTs), where the relapse rate was modelled based on the EDSS scores using data from UK multiple sclerosis (MS) surveys conducted nearly two decades ago. However, the company argues that this older method results in double counting the benefits of DMTs, as it accounts for their effects on both disease progression and relapse rates. For patients in the DMT arms, the number of relapse events is calculated using an annualised relapse rate ratio derived from the company's network meta-analysis (NMA) of randomised controlled trials (RCTs). This ratio is applied to the time-dependent ARR estimated for the BSC arms, based on the CLARITY trial's placebo relapse rate.

Finally, the model allows patients to discontinue treatment for reasons such as the development of significant side effects, progression to non-relapsing secondary progressive multiple sclerosis (SPMS) (i.e. move to EDSS states >6), and pregnancy. The company stated that these reasons for discontinuation are based on the 2015 revised Association of British Neurologists (ABN) guidelines for prescribing disease-modifying therapies (DMTs) in relapsing-remitting multiple sclerosis (RRMS), which recommend clinicians consider stopping treatment under these circumstances. Notably, it appears that the model does not allow for discontinuation due to a lack of efficacy of a DMT, which would typically necessitate switching to another DMT. Not permitting patients and their clinicians to consider changing treatment if discontinuation of their current DMT is warranted is a main concern of the EAG with the model structure. People simply move to BSC arm on treatment discontinuation. This is unlikely to represent current NHS practice. Given that several DMTs exist for RRMS and the progressive nature of the disease, it is likely that patients and their clinicians would consider the possibility of changing to another DMT given a need to discontinue their current treatment. However, the EAG agrees with the company's position that modelling treatment switching was not included due to the absence of an established clinical pathway for treatment switching sequences in the NHS and the complexity this would entail, citing previous Single Technology Appraisals (STAs) of RRMS that also did not include treatment switching. Overall, the EAG thinks the model structure is appropriate for decision making.

4.2.2 Population

The population modelled consists of adults with active relapsing-remitting multiple sclerosis (RRMS), based on characteristics from the CLARITY ITT population. This includes a sample size of 870, with a mean age of 38.7 years, a female to male ratio of 1.933 (equivalent to 70% female), and a mean of [redacted] relapses in the prior 12 months. The data combines the placebo and the 3.5mg cladribine arms of CLARITY

rather than just the placebo arm, as suggested in the CS document B (Table 29). Patient weight is crucial to this assessment because of cladribine dosing and therefore acquisition costs are weight-dependent. The weight distribution appears approximately d withith a mean weight of around [redacted] kg (Figure 16).

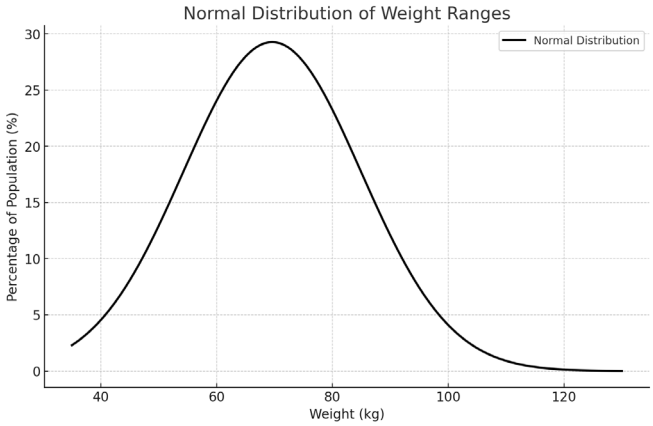


Figure 16. Distribution of body weight at baseline for modelled population

The distribution of the EDSS health states at baseline also appears to be approximately normal with a median EDSS score of 3 and mean of 3.14 (Figure 17). This distribution is critical for assessing the initial health status of the patient cohort and forecasting potential impacts of treatments on disease progression within cost-effectiveness analyses.

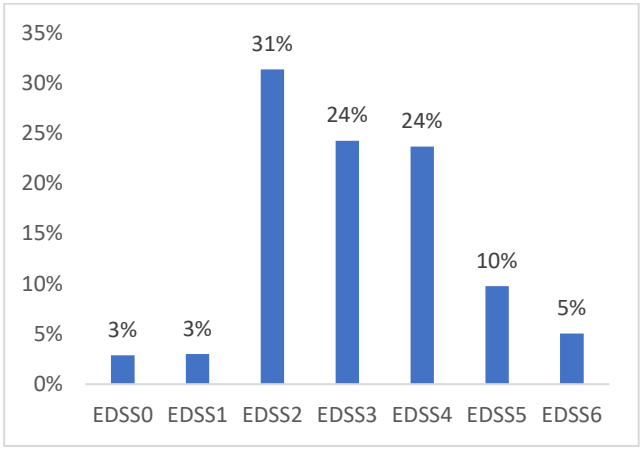


Figure 17. Baseline distribution of patients across EDSS states in the modelled population

EAG comment

The modelled population aligns with the population specified in NICE's final scope,[93] which includes "adults with active relapsing multiple sclerosis" but excludes adults with the highly active form of RRMS that was previously appraised in TA616. The EAG agrees that the CLARITY ITT population is generalisable to RRMS populations in the UK. The characteristics of CLARITY study participants are comparable to those of patients enrolled in the UK Multiple Sclerosis Risk Sharing Scheme [90], as shown in Table 21.

Table 21. Characteristics of modelled population

Characteristic	CLARITY ITT (n=870)	UK **MS r**isk sharing scheme **(n=898)**
Average age at baseline (years)	38.7	37.2
Age at unset of MS (years)		29.3
% female	65.9%	74.2%
Average patient weight (kg)	[redacted]	
Average number of relapse in prior 12 months	[redacted]	
Disease duration at baseline, mean		7.9

4.2.3 Interventions and comparators

The intervention involves administering 3.5mg cladribine tablets, dosed according to body weight, to individuals with active relapsing-remitting multiple sclerosis (RRMS). The comparators include:

- Optimised standard care without any disease-modifying therapy (BSC)
- Interferon beta-1a (Rebif® 22ug)
- Interferon beta-1a (Rebif® 44ug)
- Interferon beta-1a (Avonex®)
- Interferon beta-1b (Extavia®)
- Interferon beta-1a (Plegridy®)
- Dimethyl fumarate (Tecfidera®)
- Diroximel fumarate (Vumerity®)
- Glatiramer acetate 20mg (Copaxone®)
- Teriflunomide (Aubagio®)
- Ocrelizumab (Ocrevus®)
- Ofatumumab (Kesimpta®)
- Ponesimod (Ponvory®)

EAG comment

The company's economic modelling includes all relevant comparators specified in the NICE scope. However, Siponimod, beta-interferon, and autologous haematopoietic stem cell transplant—treatments specifically mentioned in the scope for secondary progressive multiple sclerosis (SPMS) with evidence of active disease—were excluded. This is because the company's modelling focused solely on the RRMS population, for which cladribine has received marketing authorisation in the UK.

For glatiramer acetate, only the 20mg dose was included in the modelling. The 40mg dose was excluded due to a lack of evidence on its effectiveness for the 6-month CDP outcome (the GALA trial, which tested the 40mg dose, did not report on 6-month CDP). Similarly, teriflunomide 7mg was excluded, with the explanation provided in the CS that the 7mg dose is not a recommended adult dosage according

to its SmPC [94]. The EAG agrees with the company's approach to inclusion of comparator DMTs and that all relevant comparators were appropriately captured in the CS economic model.

4.2.4 Perspective, time horizon and discounting

The company's base case analysis is conducted in accordance with NICE methods guidelines for technology appraisals [95]. It adopts the following perspective: the National Health Service (NHS) and Personal Social Services (PSS) for cost considerations, and the patient and caregiver for quality-adjusted life years (QALYs). The analysis uses a lifetime horizon of 50 years, assuming a starting age of 38. Both costs and QALYs are discounted at an annual rate of 3.5%. The EAG notes that about 20% of patients remain alive in the model after 50 years. Therefore, the EAG recommends extending the time horizon to 60 years, by which point less than 1% of patients would be alive under the company's base-case assumptions. While this change is unlikely to significantly impact cost-effectiveness, it ensures that all costs and benefits of DMTs are fully captured by the model.

4.2.5 Treatment effectiveness and extrapolation

4.2.5.1 Natural history relapses and transition between EDSS probabilities: BSC

Relapsing-Remitting Multiple Sclerosis (RRMS) is characterised by episodes of acute relapses and progressively worsening disability of increasing severity over time. As an incurable disease, the aim of Disease Modifying Therapies (DMTs) for RRMS is twofold: to reduce the frequency of relapses and to slow the progression of disability.

For patients receiving Best Supportive Care (BSC) and not on DMTs, the occurrence of active acute relapse events is modelled as a function of time independently of EDSS (Expanded Disability Status Scale) state. According to the CS, this approach avoids double-counting the benefit of DMTs by incorporating an additional indirect effect of DMTs on the relapse rate through their impact on the progression rate. The number of relapses in the first year is based on the observed annualised relapse rate in the placebo arm of the CLARITY study (mean [redacted], 95% CI: [redacted]). The number of acute relapses in subsequent years is modelled to decrease, on average, by 17% every 5 years based on data by Trimlett et al. 2008 (Figure 18).

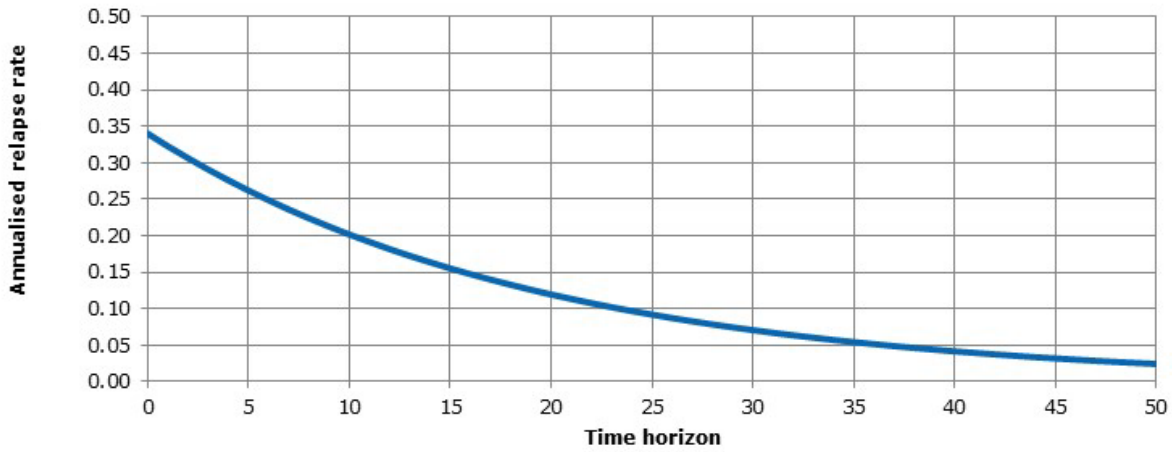


Figure 18. ARR over time for a BSC population using data from CLARITY in the first year combined with an estimated 5.07% decline in relapse rate per year thereafter

Disease progression in MS is typically measured using the EDSS scale. For patients receiving BSC, the natural history of RRMS progression is modelled based on transition probabilities that govern movement between EDSS states over time. In the company's base-case analysis, the probabilities were derived from the British Columbia Multiple Sclerosis (BCMS) dataset [90].

EAG Comment

The EAG is satisfied with the company's approach to modelling the natural history of MS, including that of the relapses and disease progression over time. The choice of data used to inform the natural history model is appropriate. The decline in relapse rates over time and across EDSS states aligns with clinical practice evidence. The EAG sought clarification from its clinical advisors. Consistent with the company's model depicted in Figure 19, the EAG clinicians advises that as relapsing-remitting multiple sclerosis (RRMS) progresses and patients age, the frequency of relapses generally decreases, shifting from frequent inflammatory episodes in the early stages to fewer relapses and a more steady progression of disability, often transitioning into secondary progressive multiple sclerosis (SPMS).

The EAG also agrees with the company's use of BCMS data to inform transitions between EDSS states under natural history conditions. This data has previously been used in the UK MS risk-sharing scheme model [90] and in previous appraisals of MS treatments, including cladribine tablets (TA493/TA616). Figure 19 shows the simulated distribution of state occupancy over time, based on the BCMS data, in the absence of DMT treatment. The plot illustrates how the distribution of patients across various EDSS states changes over time, highlighting the progression of disability and the eventual transition of patients to higher EDSS states or death as the simulation progresses.

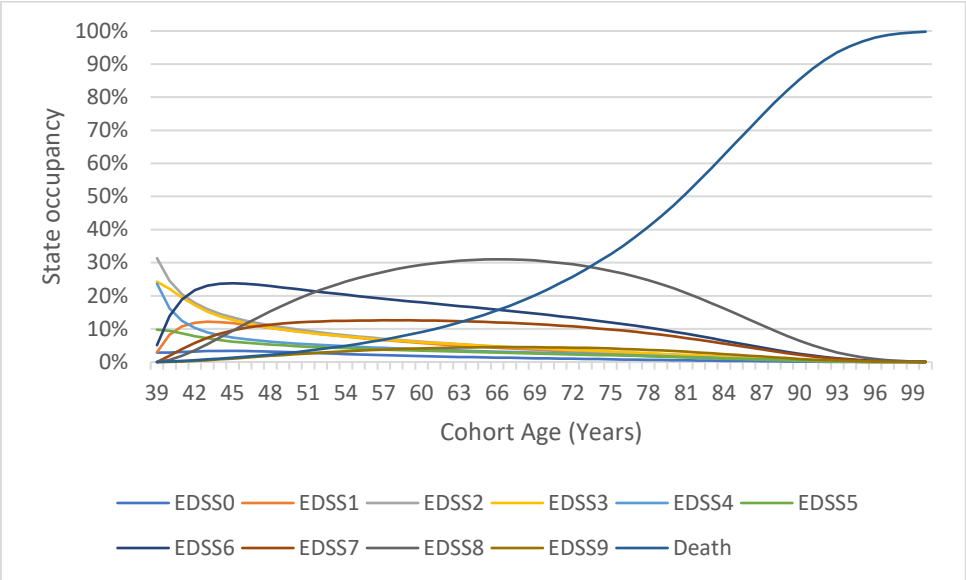


Figure 19. State occupancy over time in the BSC arm

4.2.5.2 Clinical effect of cladribine and other DMTs

The aim of treatment in relapsing-remitting multiple sclerosis (RRMS) is to reduce the frequency of relapses and slow disability progression. In the CS, the clinical effects of cladribine and competitor DMTs is driven by relative treatment effects estimated from a company's sponsored network meta-analysis (NMA) of RCT data. For relapses, the NMA produced risk ratios (RR) comparing DMTs to one another and placebo (Table 22).

Table 22. Central estimate of the annualise relapse rate ratio: DMT versus placebo

DMT	***Mean RR***
Ofatumumab	[redacted]
Ocrelizumab	[redacted]
Cladribine Tablets	[redacted]
Ponesimod	[redacted]
Dimethyl fumarate	[redacted]
Diroximel fumarate	[redacted]
Glatiramer Acetate	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]
IFNβ-1a (Peginterferon beta-1a)	[redacted]
IFNβ-1b (Betaferon/Extavia)	[redacted]
Teriflunomide	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]
IFNβ-1a (Avonex)	[redacted]

In the model, the risk ratios generated by the NMA are applied to the simulated number of relapses for the BSC arm Figure 20 to estimate the number of relapses for each DMT. Figure 20 plots the company's data. As expected, the BSC arm showed evidence of early worsening relapses, while cladribine is the most effective at reducing relapses. At first, the EAG is concerned with the cladribine's superior performance compared to other DMTs predicted by the modelling. EAG thinks this inconsistent with the risk ratios for DMTs versus placebo generated from the company's NMAs (Table 22). Ofatumumab (RR=[redacted]) and Ocrelizumab (RR=[redacted]) are, on average, better were at reducing relapses than Cladribine (RR=[redacted]) compared with placebo. However, this is not reflected in the model as shown in graphs displayed in Figure 20, where Cladribine appears to perform better on average in reducing relapses. Although the credible intervals suggest that the rate ratios for Cladribine versus Ocrelizumab or Ofatumumab are not statistically significant (see Table 33, CS document B, page 114), the discrepancies between the relapse rates for different comparators indicate that efficacy alone may not be the sole driver of treatment benefit in the company's economic modelling.

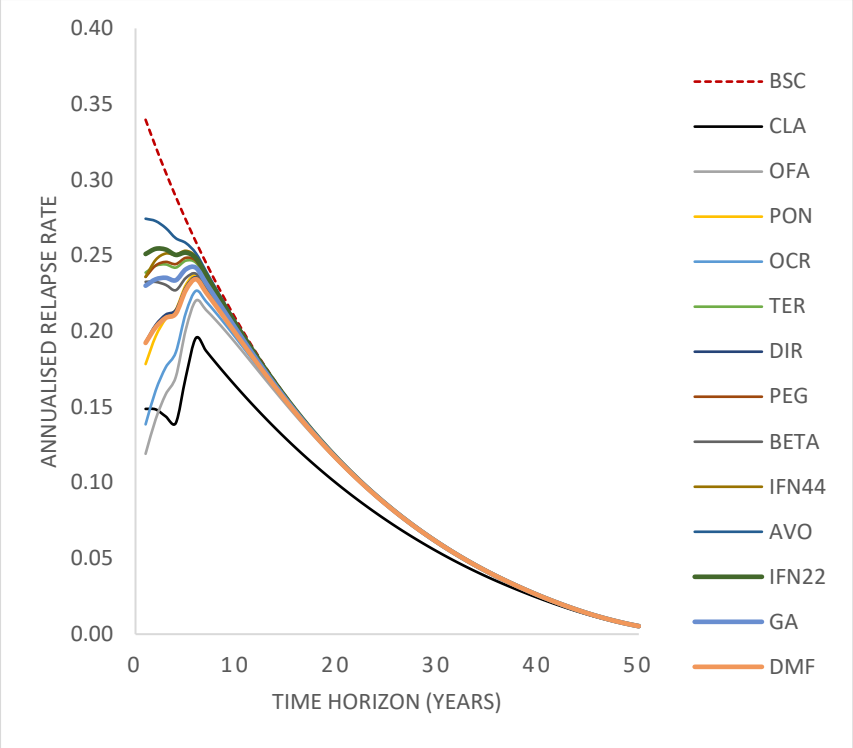


Figure 20. Predicted number of relapses over the modelled time horizon

Another clinical effect of DMT is to slow disability progression from better EDSS health states to worse EDSS states. This is captured in the model through a treatment effect hazard ratio for DMT versus placebo estimated by the company's NMA for a confirmed disease progression over a 6-months period of assessment (Table 23). Ocrelizumab (HR versus placebo [redacted]), IFNβ-1a (HR=[redacted]), IFNβ-1b (HR=[redacted]) and ofatumumab (HR=[redacted]) all appear more effective on average than cladribine tablets (HR=[redacted]) at reducing disability progression.

Table 23. Central estimate of the Hazard ratio for 6m-CDP: DMT versus placebo

Treatment	***HR for 6m-CDP: DMT versus placebo***
Ocrelizumab	[redacted]
IFNβ-1a (Peginterferon beta-1a)	
IFNβ-1b (Betaferon/Extavia)	
Ofatumumab	
Cladribine Tablets	
IFNβ-1a (Avonex)	
Dimethyl fumarate	
Diroximel fumarate	
Ponesimod	
Glatiramer Acetate	
IFNβ-1a (Rebif 22µg)	
IFNβ-1a (Rebif 44µg)	
Teriflunomide	

EAG critique

The company's model base-case assumptions predicts that cladribine will perform better on average in reducing relapses and disease progression compared to all the comparator DMTs. However, this is not consistent with the clinical efficacy data generated by the company's NMA. Based on the NMA results for ARR and 6-month CDP outcomes alone, the EAG would expect high-efficacy comparator DMTs such as ocrelizumab and ofatumumab to perform better on average than cladribine in reducing relapses and disease progression. Where this is not the case, then the only other factor that might influence treatment efficacy is treatment discontinuation. In the model, patients automatically move to BSC after discontinuing DMT. Highly effective therapies could have their long-term clinical efficacy compromised if a significant number of patients discontinue treatment.

4.2.5.3 Treatment discontinuation

The model captured the impact of stopping treatment on relapses and disease progression. Cladribine, with its less frequent dosing regimen consisting of two consecutive courses over 4-5 days at the beginning of the first and second years, is uniquely different from other DMTs regarding treatment discontinuation. In the company's model, patients who complete the two courses were assumed to remain on cladribine without continuously receiving the drug and were therefore no longer considered at risk of discontinuation. This contrasts with the other DMTs, which typically require frequent dosing, such as daily, weekly, or monthly administrations, and continuous treatment throughout the year, thus remaining at risk of discontinuation as long as patients remain on treatment.

In the model, the probability of stopping treatment is modelled independently of EDSS progression, based on data from the company's NMA of RCTs that generated odds ratios comparing different DMTs (including cladribine) with each other and placebo. The outcome, all-cause treatment discontinuation, is not uniquely defined in the CS but is understood to be defined as per each trial included in the discontinuation NMA. The EAG requested clarification from the company on how treatment discontinuation is defined in its economic model and how it is measured in the studies included in the NMA (clarification questions A9 and A18). In response, the company stated that all-cause treatment discontinuation is considered in both its NMA and economic model. The company provided a table summarising how treatment discontinuation outcomes were reported in the trials included in the NMA. The data indicate that discontinuation is reported inconsistently across trials, with many not providing a clear definition at all.

The annual absolute probability of treatment discontinuation was derived for each DMT, including cladribine, from the NMA hazard ratios and the observed probability of discontinuation in the placebo arm of included trials. The predicted probability of discontinuation for cladribine from the NMA was [redacted] However, for patients on cladribine, the company chose not to use the probability of treatment discontinuation predicted by the NMA. The company stated this was to avoid overestimating discontinuation for this therapy, as in the model, tolerability events are only assumed to occur between the first and second courses of treatment. Instead, the company used an estimated probability of 4.85% which is much lower than [redacted]% value generated by the NMA, based on data from the CLARITY study, and applied it in the first two years of the model time horizon. For the other DMTs, the annual probability of treatment discontinuation applied in the model ranged from [redacted]% for ofatumumab to [redacted]% for interferon beta-1a 44 µg (Table 24).

Table 24. Probability of treatment discontinuation in the company's base case model. Estimates were generated from the random effects NMA model of treatment discontinuation

Treatment vs. placebo	Mean
Placebo	[redacted]
Cladribine tablets*	[redacted]
Dimethyl fumarate	[redacted]
Glatiramer acetate	[redacted]
Interferon beta-1a 30 µg	[redacted]
Interferon beta-1a 44 µg	[redacted]
Interferon beta-1b 250 µg	[redacted]
Interferon beta-1a 22 µg	[redacted]
Peginterferon	[redacted]
Teriflunomide	[redacted]
Diroximel fumarate	[redacted]
Ocrelizumab	[redacted]
Ofatumumab	[redacted]
Ponesimod	[redacted]

*Not considered in the economic model

The CS stated on page 119 of document B that *"Patients who complete the two courses were assumed to remain 'on DMT' without actively receiving the drug, and hence were no longer considered at risk of discontinuation."* The EAG disagrees with this statement, as patients who complete the 2-course treatment may still switch to another DMT at a later date, which can be considered discontinuation from cladribine.For the other DMTs, patients were assumed to remain at risk of treatment discontinuation over the modelled time horizon. The only time that patients were no longer at risk of discontinuation was when they progressed to EDSS states ≥ 7, which applies equally to cladribine.

Following treatment discontinuation, patients move to BSC and this applies to all DMTs including cladribine. Figure 21 illustrates the effect of applying the company's preferred base-case assumptions about the probability of treatment discontinuation on the proportion of the cohort that remains in treatment, accounting for mortality, for cladribine and competitor DMTs. It is evident that company's base-case assumptions about treatment discontinuation leads to substantially higher number of patients continuing to benefit from cladribine over the modelled time horizon compared to the other DMTs. Since cladribine is administered only during the first and second years of treatment, the company's assumptions about treatment discontinuation imply that patients on cladribine accrue benefits without accruing the cost of the drug beyond the second year. This is unlike other DMTs that require continuous treatment until discontinuation is warranted or mortality occurs.

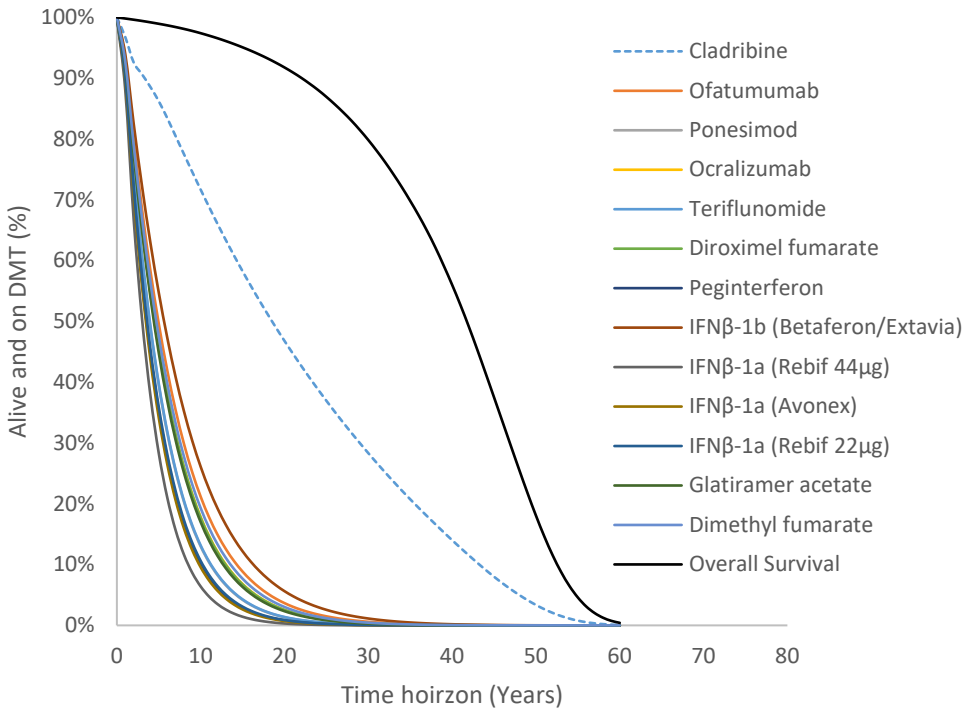


Figure 21. Overall survival and the probability of being on a DMT

4.2.5.4 EAG critique: Treatment discontinuation

The EAG has significant reservations about the company's approach to modelling treatment discontinuation. Firstly, the EAG was unable to replicate the probability of treatment discontinuation used in the CS base-case (Table 37 of CS document B) when it reanalysed the NMA data (Section 2.5.1.1 of the EAG report). Secondly, the data source used to inform the discontinuation probabilities in the economic model raises concerns. The company derived these probabilities from an NMA of RCT data, which the EAG believes may not accurately reflect the real-world experiences of MS patients using DMTs. While the CS references previous NICE appraisals where discontinuation probabilities based on RCT data were accepted, relying solely on RCT data for estimating treatment discontinuation probabilities in RRMS may not capture the complexities of real-world conditions. RCTs are conducted in highly controlled environments with strict protocols and selective patient criteria, which often do not represent the diverse populations encountered in clinical practice. This selection bias can lead to the underestimation or overestimation of discontinuation rates when applied to the broader RRMS population.

The EAG suggests an alternative approach that better reflects clinical practice is to additionally assume that treatment discontinuation (both observed and unobserved) occurs if patients switch to another DMT. This view is supported by recent evidence on real-world persistence of multiple sclerosis DMTs from Welsh data (Tallantyre, 2024).[81] In this study, Tallantyre et al. calculated treatment persistence for several DMTs, including cladribine and alemtuzumab, based on UK data from 4,366 people with relapse-onset MS. Persistence probabilities were calculated based on reasons for stopping treatment (Table 25), with adverse events (34.8%) and lack of efficacy (30.1%) being the most common. Notably, Tallantyre (2024) reported that in cases

where alemtuzumab or cladribine was followed by another DMT, the most common reason was lack of efficacy (48%).

Table 25. Reasons for stopping DMT reported in Tallantyre (2024) study

Reasons for stopping (n=3362 DMT stops)	Date of DMT commencement			Total (%)
	pre-2012	2012-2016	2017-2021	
Adverse events,	444	439	287	1170 (34.8%)
Disease Progression	133	49	14	196 (5.8%)
Drug holiday,	60	18	14	92 (2.7%)
Increased risk of adverse event	66	102	60	228 (6.8%)
Lack of efficacy	382	410	220	1012 (30.1%)
Patient choice	94	100	49	243 (7.2%)
Pregnancy	105	97	56	258 (7.7%)
Other	9	7	9	25 (0.7%)
Unknown	36	44	58	138 (4.1%)
Total				**3362 (100%)**

If it is reasonable to assume that patients experiencing an increase in relapse rates would switch to another DMT due to lack of efficacy, the EAG believes that the data and reasons for stopping treatment reported by Tallantyre et al. (2024) [81] more accurately reflect clinical practice with cladribine. Since the company's economic analysis does not explicitly model treatment switching, patients who discontinue by switching to another treatment are moved to the BSC arm, losing the benefits of their initial treatment. This assumption applies to all DMTs, including those with short treatment durations, such as cladribine, as well as those requiring continuous treatment.

In the economic model, treatment discontinuation is modelled with different probabilities across three time periods: the first 2 years, the next 2-10 years, and beyond 10 years within the model's time horizon. Therefore, the model requires discontinuation probabilities that cover these specific periods. Tallantyre (2024) does not provide discontinuation probabilities for all the comparator DMTs of interest in this appraisal. For the DMTs that are reported, particularly newer ones, long-term data up to 10 years is limited, with only 2-year probabilities available for all. Glatiramer Acetate and the interferon beta group have up to 10 years of data in Tallantyre (2024), but cladribine and ocrelizumab only have two years of data. Dimethyl fumarate has 8 years of treatment discontinuation data, and Teriflunomide has 5 years of data, with a second source from Italian patients (Bucello, 2021) [85] also reporting 5 years. Table 26 presents the probability estimates of treatment discontinuation based on the Tallantyre (2024) data and other published sources identified by the EAG. Note that the data reported in Tallantyre (2024) are for treatment persistence, and the EAG assumed the probability of discontinuation equals 1 minus the probability of persistence.

Table 26. Probability of treatment discontinuation for DMTs

DMT	Treatment discontinuation probabilities (CS base-case)			Treatment discontinuation probabilities (EAG preferred values)			
	Year: 0-2	**Year: 2-10**	**Year: 10-lifetime**	**Year: 0-2**	**Year: 2-10**	**Year: 10-lifetime**	**Source**
Cladribine Tablets	4.9%	0.0%	0.0%	4.5%	**10.0%[a]**	**19.1%[a]**	Tallantyre (2024)
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	28.4%	48.6%	**66.1%[b]**	Tallantyre (2024)
Glatiramer Acetate	[redacted]	[redacted]	[redacted]	49.5%	67.6%	81.9%	Tallantyre (2024)
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]	39.9%	63.9%	81.9%	Tallantyre (2024)
IFNβ-1a (Rebif 44µg)	[redacted]	[redacted]	[redacted]	39.9%	63.9%	81.9%	Tallantyre (2024)
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]	39.9%	63.9%	81.9%	Tallantyre (2024)
IFNβ-1b (Betaferon/Extavia)	[redacted]	[redacted]	[redacted]	39.9%	63.9%	81.9%	Tallantyre (2024)
IFNβ-1a (Peginterferon beta-1a)	[redacted]	[redacted]	[redacted]	39.9%	63.9%	81.9%	Tallantyre (2024)
Teriflunomide	[redacted]	[redacted]	[redacted]	36.1%	56.8%	**72.3%[c]**	Tallantyre (2024)
Ocrelizumab	[redacted]	[redacted]	[redacted]	5.8%	**13.5%[d]**	**25.3%[d]**	Tallantyre (2024)
Ofatumumab	[redacted]	[redacted]	[redacted]	5.8%	**13.5%[e]**	**25.3%[e]**	Assumed same as ocrelizumab
Ponesimod	[redacted]	[redacted]	[redacted]				
Diroximel fumarate	[redacted]	[redacted]	[redacted]	**21.9%[f]**	**34.4%[f]**	**46.8%[f]**	Lager (2023)

Note that all interferon beta's are assumed to have same treatment discontinuation rate.[84] Predicted values are highlighted and in bold font, whilst observed values are not.

[a,d]Predicted from the exponential distribution based on EAG's modelling of treatment persistence data in Tallantyre et al. (2024). See Section 5.1.1. The exponential was selected because its generates predictions that closely align with the observed data for Alemtuzumab, an immune reconstituting therapy with similar short-course posology as cladribine.

[b]Weibull EAG modelling of treatment persistence data in Section 5.1.1. This model was selected based on its fit to 8 years of observed data, considering that a 10-year extrapolation is not significantly beyond the observed period. With 8 years of data available, the best-fitting model was chosen.

[c]Predictions are based on extrapolating the digitized Kaplan-Meier curves of persistence probabilities from the Tallantyre (2024) data using log-normal parametric survival models. The log-normal model was selected based on best fit to observed data.

[e]Ofatumumab is assumed to have similar probability of discontinuation as ocrelizumab

fWeilbull predictions of digitised KM plots from Lager (2023). Only, 16 months of follow-up data was available, so predicted probabilities were used for the 0-2, 2-10 and >10-year periods.

For DMTs without10 years of treatment persistence data, the EAG extracted time-to-event data on treatment persistence by digitising Kaplan-Meier survival curves. It then fitted parametric survival curves to this data, allowing for extrapolation of treatment persistence over a 15-year period. From these extrapolated curves, predicted probabilities of persistence and treatment discontinuation (calculated as 1 - probability of persistence) were generated. Note that Tallantyre (2024) does not include data on ponesimod and ofatumumab, and the EAG could not find published real-world evidence on persistence for these two DMTs. Therefore, the EAG assumed that ofatumumab would have similar persistence to ocrelizumab, as noted by the committee in NICE's technology appraisal TA699 [78] which evaluated the clinical and cost-effectiveness of ofatumumab. However, for ponesimod, the EAG found no evidence to support such assumptions, and as a result, this treatment was not included in the EAG's analysis.

Figure 22 illustrates the impact of the EAG's assumptions about treatment discontinuation on the proportion of the cohort that remains on treatment over the modelled time horizon. For cladribine, the graph compares the company's base-case (red grey line) with the EAG predictions of treatment persistence beyond the observed data (dotted line), which are based on a log-normal, Weibull and exponential extrapolation of the Tallantyre (2024) data. The EAG believes parametric extrapolation of the Tallantyre (2024) data predicts treatment discontinuation that is more consistent with observations for other DMTs based on real world-evidence. While cladribine still shows a higher proportion of patients remaining on treatment compared to other DMTs, the EAG's model presents a more conservative advantage for cladribine than the company's base-case assumptions.

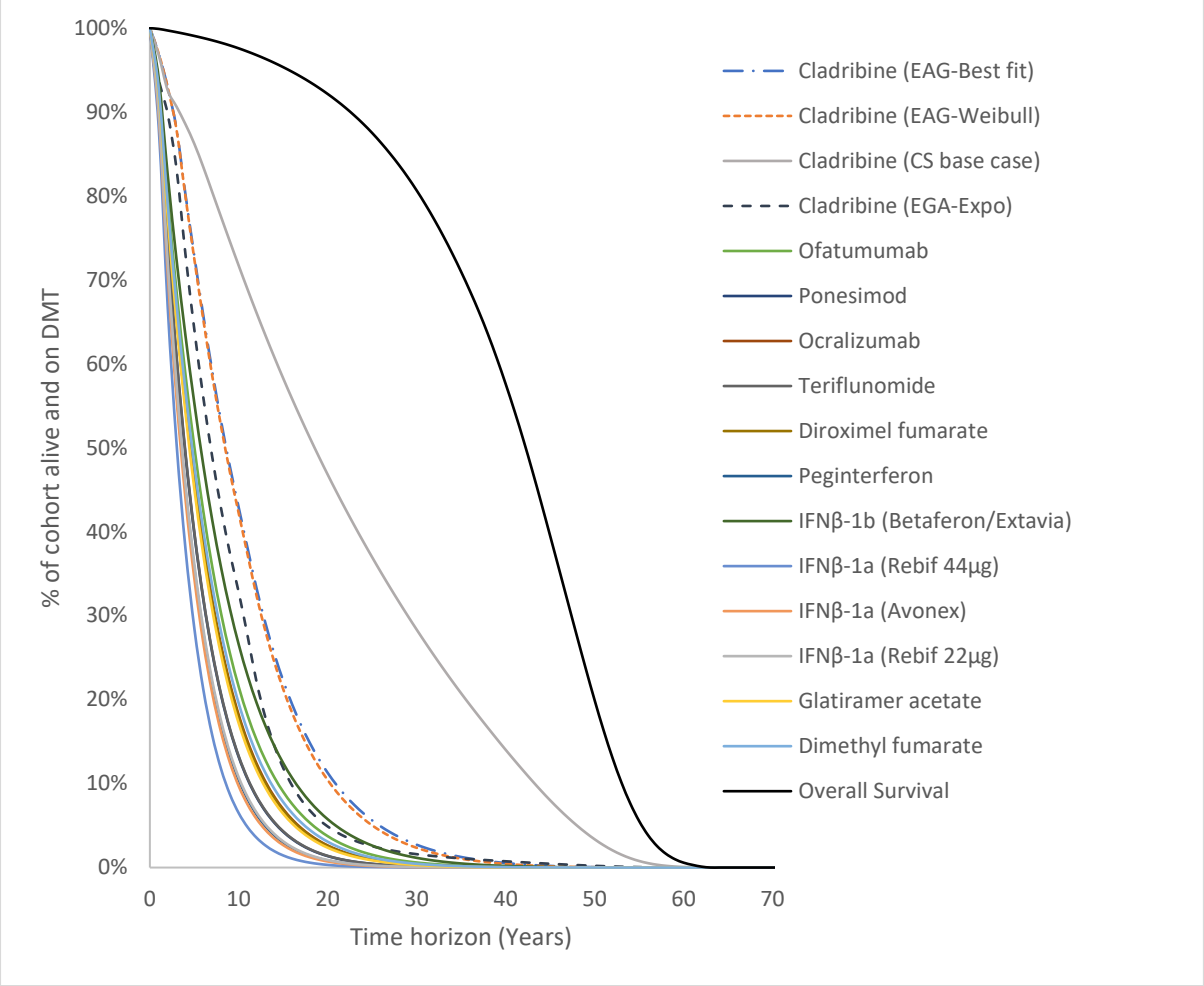


Figure 22. Proportion of Cohort alive and on DMT based on data generated from EAG modelling of DMT discontinuation (Table 23)

4.2.5.5 EAG critique: Predicting DMT persistence based on model fit statistics

The EAG's modelling of the Tallantyre (2024) data suggests that the best fit for the observed data is the log-normal model for cladribine, teriflunomide, and diroximel fumarate, Weibull for dimethyl fumarate and Gompertz for ocrelizumab (Table 13, Section 5.1.1). Table 27 presents the probability estimates of discontinuation based

on the best fit model for cladribine and competitor DMTs. Probability of discontinuation were derived from corresponding estimate of DMT persistence (Table 10, Section 5.1.1) that the EAG generated from it's modelling of DMT treatment persistence. Note: probability of discontinuation is calculated as 1-probability of treatment persistence.

Table 27. Probability of treatment discontinuation, best model fit

DMT	**Treatment discontinuation probabilities (EAG preferred values)**			
	Year: 0-2	**Year: 2-10**	**Year: 10-lifetime**	**Source**
Cladribine Tablets	0.045	**0.067**	**0.088**	Tallantyre (2024)
Dimethyl fumarate	0.28	0.49	**0.339**	Tallantyre (2024)
Glatiramer Acetate	0.50	0.68	0.82	Tallantyre (2024)
IFNβ-1a (Rebif 22µg)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Rebif 44µg)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Avonex)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1b (Betaferon/Extavia)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Peginterferon beta-1a)	0.40	0.64	0.82	Tallantyre (2024)
Teriflunomide	0.36	0.57	**0.72**	Tallantyre (2024)
Ocrelizumab	0.06	**0.094**	**0.11**	Tallantyre (2024)
Ofatumumab	0.06	**0.094**	**0.11**	Assumed same as ocrelizumab
Ponesimod				
Diroximel fumarate	**0.209**	**0.302**	**0.382**	Lager (2023)

Predicted values are in bold

Using the predicted probability of treatment discontinuation from the model that best fit the observed data (note: predicted values are used only if the observed data is not available) increases the company's base-case deterministic ICER from [redacted] to [redacted] per QALY gained for cladribine tablets compared with BSC. Cladribine remains dominant over ofatumumab, while the ICER compared to ocrelizumab rises to [redacted] per QALY lost (incremental costs [redacted] and incremental QALY loss of [redacted]). The ICERs compared with the other DMTs ranged from [redacted] and [redacted] per QALY gained compared with teriflunomide and IFNβ-1b (Betaferon/Extavia) respectively.

It is important to note that the ICER for ofatumumab was generated under the assumption that it is in the same class as ocrelizumab. A previous NICE appraisal of ofatumumab (TA699 [78]) took the view that the two treatments may be equivalent in their mode of action. However, it was not possible to generate an ICER for ponesimod due to a lack of data, and the EAG does not have prior knowledge to inform plausible assumptions about its treatment persistence.

4.2.5.6 EAG critique: Weibull predictions of DMT persistence

The EAG's survival modelling highlights the immaturity of the Tallantyre (2024) data, which includes only two years of data on treatment persistence for ocrelizumab and

cladribine. The median survival has not been reached for either treatment, as indicated by the KM curves (Figure 13, Section 5.1.1). Extrapolating such limited data over the long term is likely to produce highly uncertain estimates of treatment persistence at 5 and 10 years. In scenarios with immature data, all survival extrapolations based on limited data will be subject to significant uncertainty, and the best-fitting model to the observed data may not yield the most accurate long-term predictions.

When examining the fitted survival curves, it is evident that the Exponential model, which assumes a constant hazard rate and leads to a steady, exponential decline, fits the early data reasonably well but may oversimplify the persistence pattern, especially in later years. The Weibull model offers a reasonable compromise between the exponential fit and other models. It balances fitting the observed data with making plausible long-term predictions. Table 28 presents the probability of treatment discontinuation based on the observed data (where available) and predicted from the Weibull model (where observed data is not available).

Table 28. Probability of treatment discontinuation, Weibull distribution

DMT	**Treatment discontinuation probabilities (EAG preferred values)**			
	Year: 0-2	**Year: 2-10**	**Year: 10-lifetime**	**Source**
Cladribine Tablets	0.045	**0.069**	**0.094**	Tallantyre (2024)
Dimethyl fumarate	0.28	0.49	**0.339**	Tallantyre (2024)
Glatiramer Acetate	0.50	0.68	0.82	Tallantyre (2024)
IFNβ-1a (Rebif 22µg)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Rebif 44µg)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Avonex)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1b (Betaferon/Extavia)	0.40	0.64	0.82	Tallantyre (2024)
IFNβ-1a (Peginterferon beta-1a)	0.40	0.64	0.82	Tallantyre (2024)
Teriflunomide	0.36	0.57	**0.78**	Tallantyre (2024)
Ocrelizumab	0.06	**0.12**	**0.183**	Tallantyre (2024)
Ofatumumab	0.06	**0.12**	**0.183**	Assumed same as ocrelizumab
Ponesimod				
Diroximel fumarate	**0.219**	**0.344**	**0.468**	Lager (2023)

Predicted values are in bold

Applying the Weibull model's predictions for cladribine's treatment discontinuation, based on the Tallantyre (2024) data, increases the company's base-case deterministic ICER for cladribine from [redacted] to [redacted] per QALY gained compared to BSC. Cladribine remains dominant over ofatumumab among high-efficacy DMTs, but the ICER rises to [redacted] per QALY lost (incremental costs [redacted] and incremental QALY loss of [redacted]; ICER lies in South-West quadrant of CE-Plane) per QALY lost when compared to ocrelizumab. The ICERs compared with the other DMTs ranged from [redacted] and [redacted] per QALY gained compared with teriflunomide and IFNβ-1b (Betaferon/Extavia) respectively.

4.2.5.7 EAG critique: Comparisons of DMT persistence to external data

As mentioned earlier, parametric survival extrapolations are subject to a degree of uncertainty. This issue becomes more pronounced when the data is immature and the median survival has not been observed. In such cases, a sensible approach is to compare survival predictions to external data and choose a plausible fit based on those reference sources.

In the EAG's survival modelling, Tallantyre (2024) provides up to 10 years of treatment persistence data for alemtuzumab, an immune reconstituting therapy which has a similar posology to cladribine (both are administered intermittently in courses over a shorter time period rather than continuously). The exponential model predictions for cladribine, showing 10% persistence at 5 years and 19.1% at 10 years, are close to the 5- and 10-year discontinuation rates observed for alemtuzumab in the Tallantyre (2024) data (Table 14 and Figure 13 of Section 5.1.1). Therefore, the EAG considers it useful to assess the impact of assuming the exponential model's treatment discontinuation predictions on the ICER. Applying this assumption increases the base-case deterministic ICER to [redacted] per QALY gained for cladribine compared with BSC. When compared with high-efficacy DMTs, cladribine remains dominant over ofatumumab, while the ICER compared to ocrelizumab increases to [redacted] per QALY lost (incremental costs [redacted] and incremental QALYs [redacted], south-west quadrant of cost-effectiveness plane). The ICERs compared with the other DMTs ranged from [redacted] and [redacted] per QALY gained compared with teriflunomide and IFNβ-1b (Betaferon/Extavia) respectively.

4.2.5.8 Treatment waning

The CS base-case applied a "same waning" assumption in which the efficacy of cladribine and competitor DMTs waned at 0% in the first 0-4 years of treatment initiation, 25% in Years 4-5 and 75% beyond year 5. Waning is used to explore the impact of uncertainty because of the lack of long-term efficacy data for DMT treatments in RRMS. The company justified the no waning assumption for cladribine in the 0-4 Year period based on evidence from the CLARITY extension study[96] which showed that the effectiveness of cladribine is maintained over a 4-year period following treatment initiation. The same waning assumption is extended to comparator DMTs for consistency whilst alternative waning assumptions allowed for the impact of "no waning" and differential or DMT specific waning assumptions to be explored in sensitivity analyses.

4.2.5.9 EAG critique: Treatment waning

The EAG has verified that the treatment waning formula is correctly implemented in the model (Company's response to clarification question B12). The EAG align with the company that evidence from the cladribine extension study supports maintaining cladribine's efficacy over the first four years of treatment, justifying the decision not to model treatment waning during Years 0-4 for cladribine users [96]. The EAG notes that the EAG notes that during the appraisal of ofatumumab (TA699 [78]), the manufacturer successfully demonstrated no waning in relapse frequency for up to four years. Therefore, the EAG agrees with the company's base-case of applying no waning for all DMTs in years 0-4. Beyond four years, there is no evidence to support cladribine's long-term effectiveness, so the EAG agrees with the company's approach of applying a waning rate after this period.

The EAG does, however, have concerns the concurrent modelling of treatment discontinuation and treatment waning. The EAG believes that both approaches serve to address uncertainty in the long-term effectiveness of DMTs and notes that the application of treatment waning has been inconsistent across previous appraisals.[97] For example, in the appraisals of ocrelizumab (TA533 [80]) and ofatumumab (TA699 [78]), treatment waning was not applied, and the committee accepted that treatment discontinuation could serve as a proxy for waning in the absence of evidence. Despite these concerns, the EAG considers it reasonable to take a conservative approach and apply both treatment discontinuation and waning in the modelling, as the company has done. This is particularly relevant for cladribine, given its unique dosing regimen, where the medication is administered only during the first two years but is assumed to confer long-term benefits, despite the lack of evidence supporting its effectiveness beyond four years.

4.2.5.9.1 Mortality

Age- and gender-specific background mortality rates for the UK general population were sourced from official UK government statistics. Standardised mortality rate ratios (SMRs) for RRMS populations were then applied to these rates to generate RRMS-specific mortality rates, accounting for the excess mortality associated with RRMS. In the company's base case, a single SMR sourced from the UK study by Jick et al. [98] was applied, irrespective of EDSS status. Sensitivity analyses were conducted to explore the impact of allowing the SMR to vary as a function of EDSS using historical UK data analysed by Sadovnick et al [99 185] and Pokorski et al [100]. Figure 23 shows the impact of assuming that mortality remained the same independent of EDSS state and form of MS (company's base-case) compared with allowing the mortality rate in the MS population to vary with EDSS score and form of MS.

Figure 23. Assumptions about mortality rate used in the economic model. Survival gain from moving from fixed to variable mortality

Not allowing the mortality in MS population to vary with EDSS and form of MS (company's base-case) implies there is no survival advantage from slowing disease progression from using DMTs. The alternative assumption of allowing the mortality to vary with EDSS state (Figure 24). For example, the variable SMR assumption leads to a difference in survival of about [redacted] (dotted red line in the figure) for cladribine versus BSC which peaks at round about 35 years in the model time horizon.

4.2.5.10 EAG critique: Mortality

The EAG agrees with the company's approach to mortality risk in the model, noting that the age and gender adjustment of background mortality is appropriately applied and the sources for background mortality and SMR are well-suited to the UK and RRMS populations. However, the EAG believes that the fixed mortality assumption, where mortality in RRMS does not vary with EDSS progression, oversimplifies reality, as patients in higher EDSS states are likely to have a higher mortality risk than those in lower EDSS states. That's because, in the course of RRMS, as patients experience greater levels of disability, their overall health often deteriorates, leading to a higher risk of mortality. This aligns with an assumption that a variable standard mortality rate (SMR), which adjusts for levels of disability, provides a more realistic and nuanced depiction of mortality compared to a fixed SMR. The model submitted by the company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b).

The impact of constant versus variable mortality assumptions on overall cost-effectiveness is likely minimal, as the survival gain when moving from a constant mortality assumption (0%) to a variable mortality assumption based on EDSS state (4%) is small. However, the EAG prefers the variable mortality assumption, as it better reflects the natural history of untreated RRMS, where mortality increases with higher EDSS states associated with worse disease progression. Adjusting the mortality to vary with EDSS state and form of RRMS slightly increased the company's base-case deterministic ICER from [redacted] to [redacted] per QALY gained compared with BSC. Cladribine remained dominant in comparisons with teriflunomide, ocrelizumab, ofatumumab, ponesimod, and diroximel fumarate. For the remaining competitor DMTs, the ICER ranged from [redacted] (compared with IFNβ-1b (Betaferon/Extavia)) and [redacted] compared with IFNβ-1a (Avonex).

4.2.6 Health related quality of life

The economic model incorporated health-related quality of life by assigning an annual utility weight to each RRMS health state, defined by EDSS score, to reflect disease progression. It also accounted for annual utility decrements associated with the transition to SPMS health states (regardless of EDSS), event-based disutility from relapse events, event-based utility decrements due to treatment side effects/adverse events, and annual carer disutility associated with caring for someone with MS.

4.2.6.1 Quality of life in RRMS

Quality of life associated with disease severity and progression in RRMS, as defined by EDSS score, was derived from EQ-5D-3L data collected from CLARITY trial participants at baseline. Health utility values were calculated using

this data and the general UK population tariff (Ref: Kind et al., 1997). Utility values were available for EDSS scores 0-5 only, as the trial excluded patients with EDSS scores ≥6.

To supplement the trial data, the company conducted a systematic literature review and selected three studies [101-103] that it deemed most suitable for providing quality of life estimates for the appraisal. A comparison of the CLARITY baseline data with these three studies showed similar quality of life values by EDSS state between the CLARITY trial (mean age 38.3 years) and the Heather study (mean age 55.3 years), while the corresponding values in the Orme and Hawton studies were considerably lower (see Table 39 on page 124 of CS document B).

Only the Orme study [102] reported utility values across EDSS states 0-9. Therefore, for the base case, utility values from the CLARITY trial were used for EDSS states 0-5, as the trial excluded patients with EDSS scores ≥6 (Table 29). For higher EDSS states, the study by Hawton et al. [101] was used to inform EDSS state 6, while the Orme study [102] provided data for EDSS states 7-9. Sensitivity analyses explored combinations of utilities from Hawton plus Orme, Heather plus Orme, and Orme only.

Table 29. Quality of life values applied in the company's base-case

EDSS score	**Utility**	***Source***
EDSS 0	0.906	CLARITY Baseline data
EDSS 1	0.845	
EDSS 2	0.804	
EDSS 3	0.701	
EDSS 4	0.655	
EDSS 5	0.565	
EDSS 6	0.496	Howton et al (2016)
EDSS 7	0.392	Orme et al (2007)
EDSS 8	0.025	
EDSS 9	-0.195	

4.2.6.2 SPMS disutility

Moving from an RRMS to SPMS health state incurs an annual utility decrement regardless of EDSS state. In the company's , 21-health state model structure scenarios SPMS disutility is set at [redacted] and is estimated from the Orme et al 2006 study [102] (Section H.1.3.4 of Appendix H of CS) as the regression coefficient associated with SPMS compared with RRMS. Table 30 displays the utility values derived for SPMS health states stratified by EDSS score.

Table 30. Quality of life values used in the company's 21-health state model structure scenarios

EDSS state	RRMS				SPMS		
	Patient (utility)	Carer (disutility)	Combined utility		Patient (utility)	Carer (disutility)	Combined utility
EDSS 0	[redacted]	-0.002	[redacted]		[redacted]	-0.002	[redacted]
EDSS 1	[redacted]	-0.002	[redacted]		[redacted]	-0.002	[redacted]
EDSS 2	[redacted]	-0.002	[redacted]		[redacted]	-0.002	[redacted]

EDSS 3	[redacted]	-0.045	[redacted]	[redacted]	-0.045	[redacted]
EDSS 4	[redacted]	-0.142	[redacted]	[redacted]	-0.142	[redacted]
EDSS 5	[redacted]	-0.16	[redacted]	[redacted]	-0.16	[redacted]
EDSS 6	0.496	-0.173	0.323	0.451	-0.173	0.278
EDSS 7	0.392	-0.03	0.362	0.347	-0.03	0.317
EDSS 8	0.025	-0.095	-0.07	-0.02	-0.095	-0.115
EDSS 9	-0.195	-0.095	-0.29	-0.24	-0.095	-0.335

4.2.6.3 Carer disutility

The disutility associated with caring for a person with MS is captured by applying a carer disutility value that is stratified by EDSS state, reflecting the increasing burden of care as disability and disease severity progress. Unlike patient health-related quality of life, carer disutility was not measured in the CLARITY trial. Instead, carer disutility values were sourced from a UK observational online survey study that assessed the quality of life of 200 caregivers of people with MS, compared to non-caregivers, and stratified by the severity of MS [104].

4.2.6.4 Relapse disutility

In the company's base-case, a daily disutility of -0.071, sourced from the Orme study [102], was applied to each relapse event for BSC and all comparator DMTs including cladribine. For sensitivity analysis, a disutility of -0.066, sourced from another UK study of MS patients [105], was used. Relapses were modelled as either hospitalisation events ([redacted] with an average duration of [redacted] days or non-hospitalisation events ([redacted]) with an average duration of [redacted] days, based on data from the 3.5mg cladribine arm of the CLARITY trial (Merck Group. *CLARITY GEVD Re-Analysis. Relapses Duration by Hospitalization Status. Data on file.*; 2017.) This resulted in a calculated event disutility of [redacted] for hospitalised relapses and [redacted] for non-hospitalised relapses in the company's base-case model.

4.2.6.5 Adverse event disutility

The CS modelled QALY loss associated with treatment-related adverse event from combining estimated number of days and utility decrement associated with each of the adverse event specific to each DMT. Adverse events profile differs between DMTs due to their mode of administration (tablets, infusions and injections), chemical properties and mode of action. Relevant adverse event profile is obtained from their summary of product characteristics. AEs ranged from -0.0002 (infusion site reaction) to -0.116 (malignancy) as reported in Table 44 on page 129 of CS document B. Events that had a large impact on total QALY were malignancy (-0.116) and thyroid related events (-0.110). Severe infections, influenza-like symptoms and gastrointestinal disease had a significant impact on the person's HSU but persisted for a shorter period of time (e.g., 14 days) than malignancy and thyroid events, and hence had a reduced impact on total QALYs.

4.2.6.6 EAG critique: Health related quality of life

The company's approach to incorporating health utility in the model is appropriate, and the EAG believes the model effectively captures the relevant disutilities (RRMS and SPMS health states, relapses, and carer burden) associated with the health effects of DMTs in RRMS. The CLARITY trial and its extension studies collected long-term quality of life data for patients on cladribine. These data could have been

used to validate or compare the model's quality of life predictions against the observed outcomes in the CLARITY trials. Since the EAG did not request these data during the clarification stage, it cannot validate the model's health-related quality of life predictions against the observed trial data.

4.2.7 Resources and costs

4.2.7.1 Intervention and comparators' costs

The total cost of cladribine and comparator DMTs is calculated based on costs associated with drug acquisition, administration, and monitoring. Note that BSC is assumed to incur zero treatment costs. The acquisition cost for each DMT is determined by the frequency of administration (Table 32). For cladribine, acquisition costs are incurred only in the first and second years of treatment, with the number of tablets required in each treatment window dependent on the patient's weight. In the company's base-case, 100% treatment with cladribine is assumed in Year 1 and Year 2 for the proportion of the cohort eligible for treatment (EDSS <7.0). No re-initiation of treatment is allowed. The patient weight distribution taken from 3.5mg cladribine arm of CLARITY (mean weight [redacted]). Based on the mean body weight, each patient would thus require a total of 50 of the 10mg cladribine tablets (25 tablets per year) to complete the course of treatment.

Table 31. Annual acquisition costs of cladribine tablets based on assumptions about then weight distribution in the CLARITY trial

Weight class	Weight used in CS base-case (kg)	ITT proportion (n=870)	Total required dose in mg	Number of 10mg cladribine tablets	Number of 10mg cladribine tablets by patient weight	Total acquisition costs (CS base-case)	Total acquisition costs (ERG assumption)
40-50 kg	45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-60 kg	55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-70 kg	65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70-80 kg	75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80-90 kg	85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90-100 kg	95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100-110 kg	105	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>115kg	110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						[redacted]	[redacted]

[at]Total annual acquisition cost of cladribine tablets based on midpoint of each weight interval except for the weight band >110 kg where it was assumed equals to 110kg.
[b]Total annual acquisition cost of cladribine based on weight distribution in CLARITY but assuming weight in >110kg group is 115kg.

Table 31 shows the acquisition costs of cladribine based on the weight distribution observed in the cladribine trial. The weights are grouped into bands, and it seems that the CS calculations use the midpoint value for each band. This method was applied to all weight bands except for the >110kg group, where no midpoint was available. In the company's base case, a weight of 110kg was assumed for this group, leading to an estimated per-patient total acquisition cost of approximately £25,986 (£25,953 according to the company's calculations). However, the ERG believes this calculation is flawed because it assumes that the central estimate for patients with a body weight >110kg is 110kg. When a more conservative central estimate of 115kg is used for this group, the total annual acquisition cost of cladribine tablets increases to £26,017 (Table 31).

4.2.7.2 EAG critique: Intervention and comparator costs

Since the acquisition costs of the tablets are sensitive to patient weight in the model, the EAG would prefer to use individual patient data from the CLARITY trial to estimate the exact weight distribution observed at study entry for this appraisal of cladribine's cost-effectiveness. However, as this information is not currently available, the EAG's preference is to calculate the acquisition costs based on the mean weight of the trial participants. This approach would effectively reflect the total acquisition costs for the modelled population (assuming the population on cladribine does not change due discontinuation of treatment or mortality occurs), as total costs equal the mean weight multiplied by the unit costs.

Changing the total acquisition cost per patient of cladribine from £25,986 (CS base-case) [redacted] (EAG's estimate) increased the base-case deterministic ICER slightly [redacted] to [redacted] per QALY gained compared with BSC. Cladribine remained dominant in comparison with teriflunomide, ocrelizumab, ofatumumab, ponesimod, and diroximel fumarate.

4.2.7.3 Drug administration and monitoring

The model includes treatment administration costs such as admissions for infusions, medications provided alongside therapy, patient training for self-injection, and costs associated with nurse-led or neurologist follow-up visits for monitoring purposes. Administration costs for tablets (cladribine and dimethyl fumarate for example) are set to zero. For injectables, the company assumed that training for self-administration requires 3 hours of nurse time as a one-off session. Monitoring costs as assumed to vary between the first and subsequent years on DMT to account for increased monitoring required on initiation of DMT. Monitoring costs are estimated based on resources consumed and include Monitoring costs comprise biochemistry tests, complete blood counts, human papilloma virus (HPV) tests, MRI scans, thyroid function tests, tuberculin skin tests, urinalysis, hepatitis B and C virus testing, John Cunningham's (JC) virus testing, and visits to health care practitioners to support the monitoring of DMT. The costs of drug monitoring were assumed to vary between the first and subsequent years.

Monitoring costs are assumed to differ between the first and subsequent years on DMT to account for the increased monitoring required during the initiation phase. These costs are based on the resources consumed and include biochemistry tests,

complete blood counts, HPV tests, MRI scans, thyroid function tests, tuberculin skin tests, urinalysis, hepatitis B and C virus testing, JC virus testing, and visits to healthcare practitioners for DMT monitoring. The company indicates specific monitoring requirements for cladribine, such as lymphocyte counts at set intervals, baseline MRI scans, and various infection tests.

4.2.7.4 EAG critique: Monitoring costs

To verify that the company's assumptions regarding resource use for each DMT are appropriate, the EAG consulted its clinical advisors (Table 32). For cladribine, the EAG received clinical advice indicating that the current monitoring practices, both radiological and clinical, are effective and generally do not require additional safety or efficacy monitoring. However, it was noted that cladribine is an immune reconstitution therapy (IRT), similar to alemtuzumab, another IRT used for RRMS. Once the two-year course is complete, patients are monitored regularly with clinical and MRI assessments. The treatment is not currently licensed for repeat use in cases of MRI activity or relapse, but the company can provide a repeat dose free of charge if needed in years 3-5. Based on this advice, the EAG interpreted that MRI scans and regular neurology visits are necessary for monitoring disease activity in cladribine-treated patients. However, the company's model included one MRI scan and two neurology visits in the first year of treatment only. The EAG believes that these monitoring practices (1 MRI and 2 neurology visits per year) should extend beyond the first year of treatment, covering the entire period during which the patient remains on cladribine. This increased the total discounted monitoring costs of cladribine under the company's base-case assumptions from [redacted] to [redacted] over the modelled 50-year time horizon. The corresponding impact on the ICER for cladribine versus BSC is to increase it from [redacted] per QALY gained to [redacted] per QALY gained. For the other DMTs, the ICER ranged from cladribine being dominant to a high of [redacted] per QALY gained compared with Peginterferon beta-1a.

Table 32: Resources associated with DMT monitoring (Table 50 of CS document B)

			First year on DMT		Subsequent years on DMT	
Therapy	**Administration**	**Source**	**Monitoring resources consumed**	**EAG's clinical advisors comment**	**Monitoring resources consumed in subsequent years**	**Clinical advisors comment**
Cladribine tablets	Oral	Based on the CLARITY study and appropriate assumptions	1 x MRI scan 3 x complete blood counts 2 x neurology visits 1 x tuberculin skin test 1 x hepatitis C test 1 x hepatitis B test	The current monitoring both radiology and clinical are in place and work well and satisfactory. In general, real world experience is consistent with no real need for any additional monitoring for safety or efficacy.	3 x complete blood counts 1 x neurology visits 1 x tuberculin skin test 1 x hepatitis C test 1 x hepatitis B test	The treatment is an immune reconstitution treatment (IRT) (same as Alemtuzumab, another IRT licensed for use in RRMS. Once the two year 'course' is complete then patients are monitored regularly with clinical and MRI assessments. Currently the treatment is not licensed for repeat use in case of MRI activity or a relapse but can be used on a

			First year on DMT		Subsequent years on DMT	
						company provided free of charge basis if a repeat dose is required in years 3-5.
Dimethyl fumarate	Oral	NICE TA320: Dimethyl fumarate for treating RRMS	1 x MRI scan 4 x biochemistry test 5 x complete blood counts 3 x urinalysis tests with microscopy 3 x neurology visits		1.5 x biochemistry test 4 x complete blood counts 1.5 x urinalysis tests with microscopy 1 x neurology visits	
Glatiramer acetate	S/C	NICE TA312: Alemtuzumab for treating RRMS	2 x neurology visits 2 x biochemistry tests	In the document enclosed table 22, both for Glatiramer acetate, beta interferon and teriflunomide there are two neurology visits listed in year 1, this is not routine practice. Injection techniques are taught by	2 x neurology visits 2 x biochemistry tests	
Interferon beta-1a 22 µg	S/C	NICE TA312: Alemtuzumab for treating RRMS	4 x biochemistry tests 2 x complete blood count 2 x neurology visits 4 x urinalysis tests 1 x thyroid function test		2 x biochemistry tests 2 x complete blood count 2 x neurology visits	
Interferon beta-1a 44 µg	S/C					
Interferon beta-1a 30 µg	I/M					
Interferon beta-1b 250 µg	S/C					
Peginterferon	S/C					
Teriflunomide	Oral	NICE TA303: Teriflunomide for treating RRMS	8 x biochemistry tests 2 x neurologist visit 1 x complete blood count		2 x biochemistry test 2 x neurology visits	

			First year on DMT		Subsequent years on DMT	
				company led nurses. Hence this may need further clarification to find out why this has been included.		
Ocrelizumab	I/V	Summary of product characteristics	2 x complete blood count 1 x neurology visit 1 x hepatitis B test		2 x complete blood count 1 x neurology visit	
Ofatumumab	S/C	Summary of product characteristics	1 x complete blood count 1 x neurology visit 1 x hepatitis B test		1 x neurology visit	
Ponesimod	Oral	Summary of product characteristics	2 x electrocardiograms 1 x biochemistry tests 3 x complete blood count 1 x neurology visit 1 x ophthalmology		2 x complete blood count 1 x neurology visit	
Diroximel fumarate	Oral	Summary of product characteristics	4 x biochemistry tests 5 x complete blood count 3 x urinalysis tests 3 x neurology visit 1 x MRI		1.5 x biochemistry tests 4 x complete blood count 1.5 x urinalysis tests 1 x neurology visit	

Further clinical advice (Table 33) suggests that standard practice for patients on glatiramer acetate, beta interferon, and teriflunomide does not typically include two neurology visits in the first year of treatment. Instead, injection techniques are taught by company-led nurses, not neurologists. Since this training is provided by company-led nurses, the associated costs should not represent an opportunity cost for the NHS and, therefore, should not be included in the modelling. Table 23 shows that removing nurse visits to train patients and neurology appointments has a minimal impact on the ICER for cladribine compared with the affected DMTs.

Table 33. Impact of setting first-year nurse visit and neurology appointments to zero on company's base-case ICER

Intervention	ICER vs. Cladribine (QALY gained)		
	CS base-case	Nurse-visit to train patients to self-administer set to zero	Set 1st year nurse and neurology visits to zero
Dimethyl fumarate	Cladribine dominant	Cladribine dominant	
Glatiramer Acetate	£9,707.81	£9,879.11	£10,089.27
IFNβ-1a (Rebif 22µg)	£9,362.80	£9,519.04	£9,709.61
IFNβ-1a (Rebif 44µg)	£6,543.51	£6,691.05	£6,871.00
IFNβ-1a (Avonex)	£9,776.81	£9,947.07	£10,154.73
IFNβ-1b (Betaferon/Extavia)	£2,448.79	£2,783.28	£3,191.25
IFNβ-1a (Peginterferon beta-1a)	£13,304.40	£13,525.74	£13,795.72
Teriflunomide	Cladribine dominant	Cladribine dominant	Cladribine dominant
Ocrelizumab	Cladribine dominant		
Ofatumumab	Cladribine dominant	Cladribine dominant	
Ponesimod	Cladribine dominant		
Diroximel fumarate	Cladribine dominant	Cladribine dominant	

Note: ICER compared with ocrelizumab lies in the south-west quadrant of the cost-effectiveness plane
Only comparators that are relevant to the sensitivity analysis are shown with ICERs

4.2.7.5 Health states and relapse costs

EAG comment

The EAG is satisfied with the company's approach to estimating health state costs in its economic modelling. The company conducted a systematic literature review and identified two UK studies (Hawton et al., 2016,[106] and Tyas et al., 2007 [107]) that reported direct medical care costs for RRMS patients. These data were adjusted to current prices and used in the model. Both studies showed a similar cost distribution, with higher costs at EDSS 0 due to initial diagnosis and treatment initiation. Costs decreased from EDSS 0 to EDSS 3, likely reflecting a peak in resource use around diagnosis, followed by stabilisation. As MS progresses and walking impairment develops (EDSS > 4.0), costs increase due to the need for more intensive medical support. The company chose the more recent Hawton study for its base-case, as it required less adjustment for inflation compared to the older Tyas study. Additionally, the cost of treating relapses was estimated at £4,959 for hospitalised events and £733 for non-hospitalised events, based on Hawton et al.'s data.

4.2.7.6 Adverse events costs

EAG comment

The adverse events considered in the analysis include infusion site reactions, injection site reactions, severe infections, macular oedema, gastrointestinal issues, hypersensitivity, autoimmune thyroid-related events, influenza-like symptoms, and malignancy. The costs associated with these events were derived from various literature sources, including NICE appraisals of DMTs, and were weighted by the probability of their occurrence. Due to time constraints and the large volume of material submitted by the company, the EAG was unable to thoroughly review all the costs associated with adverse events included in the model. However, the EAG sensitivity analysis suggest overall impact of adverse event modelling is likely minimal on the company's cost-effectiveness results. Overall, the EAG is satisfied with the company's approach to modelling adverse events and calculating the associated costs.

4.2.8 Severity

No severity modifiers were applied in the model and the company did not submit a case for such in the CS.

5 COST EFFECTIVENESS RESULTS

5.1 *Company's cost effectiveness results*

The company's base case estimates showing undiscounted overall survival and discounted QALYs.

Table 34. CS deterministic base-case patient benefits

			Total discounted QALY by item at 50 years				
	Life Years	Total relapses	AE	Relapse	EDSS - Patient	EDSS - Caregiver	Total
Cladribine Tablets	[redacted]						
Dimethyl fumarate	[redacted]						
Glatiramer Acetate	[redacted]						
IFNβ-1a (Rebif 22µg)	[redacted]						
IFNβ-1a (Rebif 44µg)	[redacted]						
IFNβ-1a (Avonex)	[redacted]						
IFNβ-1b (Betaferon/Extavia)	[redacted]						
IFNβ-1a (Peginterferon beta-1a)	[redacted]						
Teriflunomide	[redacted]						
Ocrelizumab	[redacted]						
Ofatumumab	[redacted]						
Ponesimod	[redacted]						
Diroximel fumarate	[redacted]						
BSC	[redacted]						

The model predicts that cladribine will result in the fewest relapses, averaging [redacted] per patient, and will accumulate the highest number of QALYs ([redacted]) discounted over a 50-year model time horizon, compared to BSC and other DMTs, including high-efficacy DMTs like ocrelizumab and ofatumumab. The total accumulated discounted survival of [redacted] life-years is estimated to be the same for all treatments, indicating no survival advantage for DMTs compared to BSC. This suggests that cladribine's QALY advantage over competitor treatments stems entirely from improved quality of life. This improvement is associated with slower disease progression, allowing patients to spend more time in healthier states, experiencing fewer relapses, and benefiting from enhanced caregiver quality of life.The company's deterministic base case estimates the discounted costs presented in Table 35.

Table 35. CS deterministic base-case cost estimates

	Total discounted drug cost				**Total discounted cost by item**				
	Acquisition cost	Admin cost	Monitoring cost		AE cost	Relapse and rescue	EDSS - direct	EDSS - indirect	Total
Cladribine Tablets	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dimethyl fumarate	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Glatiramer Acetate	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 22µg)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Rebif 44µg)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Avonex)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1b (Betaferon/Extavia)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFNβ-1a (Peginterferon beta-1a)	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The primary cost components include the acquisition of cladribine, as well as the costs associated with monitoring and managing adverse events, totalling [redacted] at list prices when discounted over a 50-year time horizon. Compared to best supportive care (BSC), there are significant cost savings from avoided relapse costs and the direct medical and social care expenses related to managing disability, amounting to [redacted]. Overall, cladribine is estimated to increase the average cost per patient by [redacted] compared with BSC (Table 36). For the other DMTs, the increase in costs ranged from [redacted] for IFNβ-1a (Rebif 22µg) to [redacted] for ocrelizumab.

Table 36. Company's base-case deterministic cost-effectiveness estimates at list prices

	Total discounted				
Intervention	Cost (£)	QALY	Cost (£)	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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

At list prices, the deterministic ICER is [redacted] per QALY gained when compared with BSC, and it ranges from [redacted] to [redacted] per QALY gained when compared with the interferon group of DMTs. For the newer and more expensive high-efficacy DMTs, such as ocrelizumab, ofatumumab, and ponesimod, cladribine is dominant, as it is both cheaper and more effective in terms of QALY gains.

The probabilistic modelling yields a similar central cost-effectiveness estimate of [redacted] per QALY compared with BSC, with cladribine having a [redacted] probability of being cost-effective at a £20,000/QALY threshold and a [redacted] probability at a £30,000/QALY threshold (Figure 24 and Figure 25).

Figure 24. Cost-effectiveness acceptability curves cladribine versus BSC at list price

[redacted]

Figure 25. Cost-effectiveness plane: Cladribine versus BSC

In comparisons with other DMTs, cladribine dominates ocrelizumab. The probability that cladribine tablets are cost-effective versus ponesimod, ofatumumab, and ocrelizumab in the active RRMS population is [redacted] at a £20,000/QALY threshold and [redacted] at a £30,000/QALY threshold (Figure 26). In contrast, the probability that ponesimod, ofatumumab, or ocrelizumab are the optimal cost-effective strategies in this population ranges from [redacted] to [redacted] at the same thresholds.

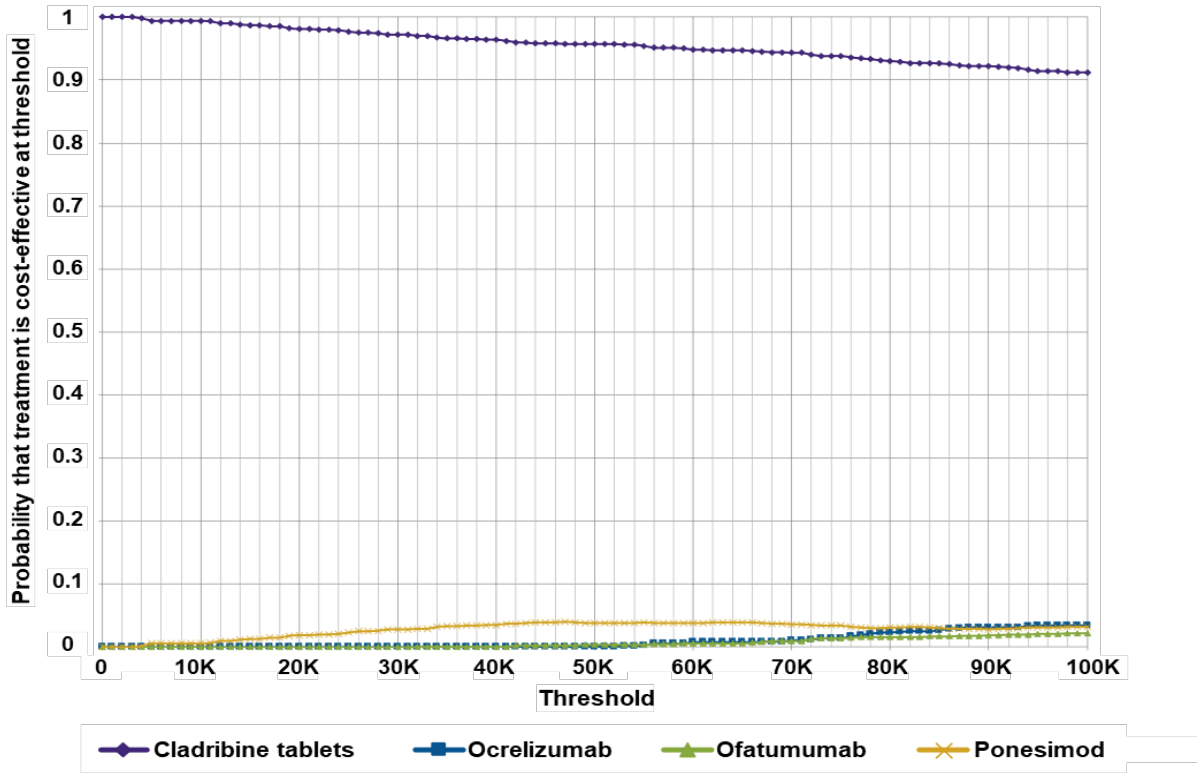


Figure 26. Multi-way cost-effectiveness acceptability curve for active RRMS at list price

5.2 *Company's sensitivity analyses*

The company conducted a series of one-way sensitivity analyses to evaluate the impact of varying individual model parameters on the incremental net health effects of cladribine tablets compared to high-efficacy DMTs. The input values and the resulting ICERs for the comparison with Ponesimod are presented in Table 37.

Table 37. One-way sensitivity analysis for the comparison with Ponesimod

		Input value		ICER[1]	
Variable	Default	Low	High	Low	High
Effect on DP - Cladribine	[redacted]	[redacted]	[redacted]	Dominant	[redacted]
Effect on DP - Ponesimod	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Effect on ARR - Cladribine	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Effect on ARR - Ponesimod	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Cladribine - discontinuation	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Ponesimod discontinuation 0-2	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Ponesimod discontinuation 2-10	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Ponesimod discontinuation 10+	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Mortality multiplier	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Baseline age	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Baseline female to male	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Baseline relapse in prior year	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Baseline weight	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Discounting: Costs -0-30 years	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Discounting: Costs - 30 years plus	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Discounting: Outcome - 0-30 years	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Discounting: Outcome - 30 years plus	[redacted]	[redacted]	[redacted]	Dominant	Dominant

[1]**Dominant implies cladribine is dominant**

Cladribine tablets remained dominant over Ponesimod in all sensitivity analyses, except when the hazard ratio for 6-month CDP for cladribine versus placebo increased from [redacted] (base-case value) to [redacted] (the upper limit of the 95% confidence interval). In this case, the ICER shifted from dominance to [redacted] per QALY gained compared to Ponesimod. The resulting tornado diagrams (Figure 27) indicate that the analysis is most sensitive to changes in the effect of DMTs on 6-month CDP, the discount rate for costs and outcomes, and the discontinuation rate for comparator DMTs. Other factors, such as the mortality multiplier, the impact of cladribine tablets on ARR, and the discontinuation rate for cladribine tablets, had a lesser impact on the results..

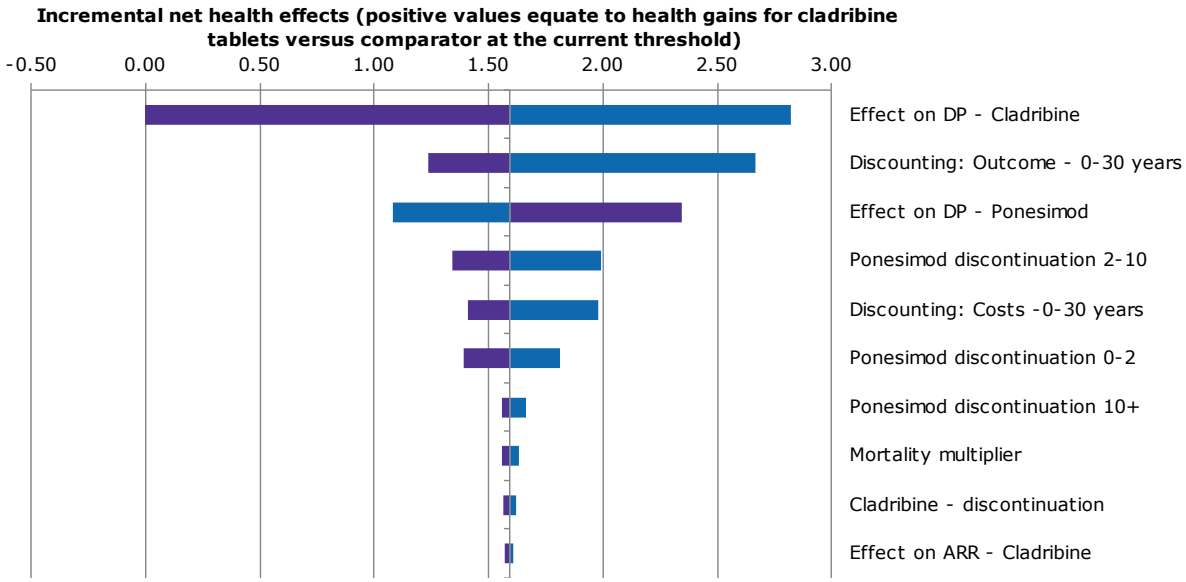


Figure 27. Tornado diagrams of incremental net health effects

The company also presents a range of scenarios in Table 61 of CS Document B, focusing on the comparison with high-efficacy DMTs (Ponesimod, ofatumumab and ocrelizumab). For completeness, the results of the company's scenario analyses are reproduced below in Table 38.

Table 38. Company's scenario analyses results for the comparison between cladribine versus high-efficacy DMTs

Scenario	Scenario description	ICER: Ponesimod	ICER: Ocrelizumab	ICER: Ofatumumab
Base case	Base case	Dominant	Dominant	Dominant
S1a	Model structure: 21-state with British Columbia data for RRMS	Dominant	Dominant	Dominant
S1b	Model structure: 21-state with London Ontario data for RRMS	Dominant	Dominant	Dominant
S2	Relapse by EDSS	Dominant	Dominant	Dominant
S3	NMA: Fixed effect models	Dominant	Dominant	Dominant
S4a	Mortality by EDSS	Dominant	Dominant	Dominant
S4b	Mortality by Lalmohamed (2012)	Dominant	Dominant	Dominant
S5a	Discontinuation: pooled data from trials	Dominant	Dominant	Dominant
S5b	Discontinuation: rates halved after 2 years for comparators	Dominant	Dominant	Dominant
S6a	Waning: No treatment waning	Dominant	Dominant	Dominant
S6b	Waning: Differential waning	Dominant	Dominant	Dominant
S7a	Utility (Hawton 2016 plus Orme 2007)	Dominant	Dominant	Dominant
S7b	Utility (Orme 2007 only)	Dominant	Dominant	Dominant
S7c	Utility (Heather 2023)	Dominant	Dominant	Dominant
S8	Utility – Relapse (Ruutiainen 2016)	Dominant	Dominant	Dominant
S9	Direct medical costs – (Tyas 2007)	Dominant	Dominant	Dominant

5.3 *Model validation and face validity check*

The company undertook measures to ensure both the internal and external validity of the model, as detailed in their submission. The 11-state model structure, which had been previously accepted by the committee in earlier cladribine appraisals (TA493/TA616), was employed in this assessment. According to the company's submission (CS), the model structure and data sources were reviewed and validated by clinical experts and external health economists from the UK who specialise in RRMS. These experts confirmed that the base case assumptions used in the cost-effectiveness model were appropriate. Additionally, the company visually inspected the predicted changes in mean EDSS, comparing them with predictions from the British Columbia registry, to verify the correct implementation of the natural history model.

Furthermore, the Evidence Review Group (EAG) conducted its own validation checks to ensure that the model's predictions were consistent with the data. The structure was also reviewed by EAG's clinical experts, who agreed that it was suitable for the decision problem at hand [EAG clinical input required]. This validation process included verifying that more effective treatments, as indicated by better annualised relapse rate ratios and 6-month confirmed disability progression (6m-CDP), led to fewer annual relapses and slower disease progression compared to less effective treatments. In instances where discrepancies were identified, the EAG pinpointed the sources of these inconsistencies. For example, despite cladribine having a numerically worse annualised relapse rate ratio and 6m-CDP compared to ocrelizumab, the model predicted that cladribine was more effective in preventing relapses and slowing disease progression over the 50-year modelled time horizon. The EAG's investigation suggested that this discrepancy was due to the assumptions and data used to inform treatment discontinuation in the model.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 *Based on the EAG critique of the company's preferred assumptions and analysis*

6.1.1 EAG revised base-case

The following changes were made by the EAG to the company's base-case

EAG01: In the company's base case, the probability of treatment discontinuation was informed by evidence from NMA RCT data. However, the EAG prefers to use probabilities of treatment discontinuation based on published UK data that provide real-world evidence on the persistence of DMTs among people with multiple sclerosis.

EAG02: In the company's base case, a fixed standardised mortality rate (SMR) was assumed, meaning that mortality did not vary with the EDSS state, which characterises disease progression in RRMS. The EAG believes this is an oversimplification, as mortality increases with disease progression. Therefore, the EAG revised this assumption to a variable SMR, allowing mortality to vary with disease progression.

EAG03: Corrected an error in calculating the acquisition cost of cladribine, increasing the cost from [redacted].

EAG04: Based on EAG's clinical advice, the resources and costs associated with treatment monitoring for cladribine changed from no MRI scan and 1 neurology visits beyond the first year of treatment initiation to 1 MRI scan and 2 neurology visits.

EAG05: Based on the EAG's clinical advice, the time required for nurses to train patients on using the self-administration injection device has been reduced from 3 hours to zero.

EAG06: Number of neurology appointments in the first-year changed from not routine practice in the NHS for patients on glatiramer acetate and beta interferons.

Table 39. Impact of individual EAG preferred model assumptions on ICER compared with BSC

Preferred assumption	EAG report sections	Incremental costs	Incremental QALYs	ICER	Change in ICER versus CS base-case
Company base case versus BSC		[redacted]	[redacted]	[redacted]	[redacted]
EAG01: treatment discontinuation sourced from real-world evidence (exponential distribution)	2.5.1.2, 3.2.5.3, 3.2.5.4 & 3.2.5.7	[redacted]	[redacted]	[redacted]	[redacted]
EAG02: Variable SMR	3.2.5.9.1 & 3.2.5.10	[redacted]	[redacted]	[redacted]	[redacted]
EAG03: Corrected error in acquisition cost of cladribine	3.2.7.1	[redacted]	[redacted]	[redacted]	[redacted]
EAG04: Monitor of patients on cladribine beyond first-year updated to include 1 MRI and 2 neurology appointments each year	3.2.7.3 & 3.2.7.4	[redacted]	[redacted]	[redacted]	[redacted]
EAG05: Nurse time to train self-administration reduced from 3 to 0 hours	3.2.7.3 & 3.2.7.4	[redacted]	[redacted]	ICER vs. BSC not affected. ICER compared with affected DMTs increased very slightly	[redacted]
EAG06: Number of neurology appointments in the first-year changed from not routine practice in the NHS for patients on glatiramer acetate and beta interferons.	3.2.7.3 & 3.2.7.4	[redacted]	[redacted]	ICER vs. BSC not affected. ICER compared with affected DMTs increased very slightly	[redacted]

6.1.2 EAG's Deterministic Base-case

The cumulative impact of the EAG changes on the company's deterministic base case is presented in Table 40. Cladribine tablets shows incremental costs of [redacted] and an increase of [redacted] QALYs compared with BSC. The ICER for the base case is [redacted] per QALY gained. Cladribine continue to dominate

ofatumumab and diroximel fumarate. For the comparison with ocrelizumab, cladribine was cheaper (incremental costs [redacted]) but also less effective (incremental QALYs [redacted]) with an ICER of [redacted] per QALY lost. For all other DMTs, the ICER ranged from [redacted] for compared with Dimethyl fumarate to [redacted] compared with IFNβ-1b (Betaferon/Extavia). Note that the EAG could not generate cost-effectiveness estimates for the comparison with Ponesimod due to the lack of real-world evidence on treatment persistence for this medication. As a result, Ponesimod was not included in the EAG's analysis.

Table 40. EAG's deterministic base-case assumptions

	Total discounted		Incremental		
Intervention	Costs	QALYs	Costs	QALYs	ICER vs. Cladribine (QALY)
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod					
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.1.3 EAG: Probabilistic base-case

The EAG was unable to conduct a probabilistic sensitivity analysis based on its preferred assumptions without making significant modifications to the model due to the setup of the company's economic model. Implementing the probabilistic analysis would require sampling from the distribution of treatment discontinuation probabilities, which the EAG calculated from its survival analysis of treatment persistence using real-world evidence. Although the mean parameter estimates and standard errors were calculated from the EAG's analysis, the company's economic model did not sample from these probability distributions for treatment discontinuation. As a result, the EAG could not implement the probabilistic analysis according to its preferred assumptions.

6.1.3.1 EAG's Scenario Analyses

The EAG conducted several robustness checks on the EAG's base-case, testing alternative assumptions and data inputs. Given the EAG's primary concern about how the company modelled treatment discontinuation, as well as the uncertainties arising from the EAG's parametric survival extrapolation of the immature treatment discontinuation data for cladribine and comparator DMTs, the EAG performed a number of scenario analysis some of which are related to this specific issue.

Scenario Analysis1 (SA1): In the EAG's base-case, the exponential distribution was selected as the source of treatment discontinuation probabilities because this distribution generated probabilities that closely matched those observed in UK data for alemtuzumab, used as external reference data. The EAG then conducted a scenario analysis using the best-fit model to the observed data to generate treatment discontinuation probabilities (Section 3.2.5.5). The results are displayed in Table 41.

Table 41. EAG Scenario Analysis 1 results

	Total discounted		Incremental QALYs		ICER vs. Cladribine (QALY)
Intervention	Cost (£)	QALY	Cost (£)	QALY	
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponesimod	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario Analysis2 (SA2): This scenario used the Weibull distribution as the source of treatment discontinuation probabilities (Section 3.2.5.6). Results for SA2 presented in Table 42.

Table 42. EAG's scenario analysis using probability of treatment discontinuation generated by the Weibull distribution

	Total discounted		Incremental (cladribine vs.)		
Intervention	Cost (£)	QALY	Cost (£)	QALY	ICER vs. Cladribine (QALY)
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod					
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario Analysis3 (SA3): The EAG explored the possibility that modelling both treatment discontinuation and waning simultaneously might be inappropriate, as both factors likely have a similar impact on DMT efficacy over time. An alternative approach assumed that discontinuation probabilities account for treatment waning, thus assuming 100% efficacy for all DMTs, including cladribine, over the modelled time horizon. This perspective aligns with previous NICE appraisals, such as those for ocrelizumab (TA533) and ofatumumab (TA699), where treatment discontinuation was considered a proxy for waning.

Table 43. EAG SA3 results. Applied no waning assumption to EAG base-case

	Total discounted			Incremental (cladribine vs.)	
Intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod					

Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario SA4: Applied Differential waning assumption on EAG base-case

Table 44. SA4 Results. Differential waning assumption applied to EAG base case

	Total discounted				
Intervention	Cost (£)	QALY	Cost (£)	QALY	ICER vs. Cladribine (QALY)
Cladribine Tablets	[redacted]	[redacted]			
Dimethyl fumarate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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]	[redacted]
Teriflunomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ofatumumab	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
Ponesimod					
Diroximel fumarate	[redacted]	[redacted]	[redacted]	[redacted]	Cladribine dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2 *Conclusions of the cost effectiveness section*

The 11-state model structure adopted by the company is appropriate for modelling the impact, health effects, consequences, and costs of disease-modifying therapies (DMTs) on disease progression in people with relapsing-remitting multiple sclerosis (RRMS). The model effectively captures the effects of DMTs through metrics such as the annualized relapse rate

ratio for relapses, 6-month confirmed disability progression (CDP) for disease progression through EDSS states, and the side effects of treatment. However, a significant area of uncertainty lies in the modelling of treatment discontinuation, including the data sources used to inform the CS base-case, and the waning of treatment effects over time. Cladribine's unique posology complicates the typical concept of treatment discontinuation when patients stop taking a medication, leading to uncertainty about the long-term benefits of treatments like cladribine. The lack of evidence on its effectiveness beyond four years, as presented in the CS, adds to this uncertainty. Therefore, the EAG recommends a more conservative approach,

modelling both treatment discontinuation and waning of treatment effects equally across all DMTs to better address these uncertainties. Addressing these uncertainties considerably worsens the company's base-case ICER for cladribine compared with BSC and competitor DMTs.

7 SEVERITY MODIFIERS

Severity modifiers were not applied in this appraisal. According to the company's CS, absolute and proportional QALY shortfalls were estimated and used to inform a QALY shortfall analysis. This process generated a severity weighting of 1.0, indicating that a QALY shortfall was not applicable in the model.

8 REFERENCES

1. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA*, et al.* Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler* 2020;**26**(14):1816-21. http://dx.doi.org/10.1177/1352458520970841

2. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D*, et al.* ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018;**24**(2):96-120. http://dx.doi.org/10.1177/1352458517751049

3. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Epidemiology of multiple sclerosis: results from a large observational study in the UK. *J Neurol* 2015;**262**(9):2033-41. http://dx.doi.org/10.1007/s00415-015-7796-2

4. Marck CH, Neate SL, Taylor KL, Weiland TJ, Jelinek GA. Prevalence of Comorbidities, Overweight and Obesity in an International Sample of People with Multiple Sclerosis and Associations with Modifiable Lifestyle Factors. *PLoS One* 2016;**11**(2):e0148573. http://dx.doi.org/10.1371/journal.pone.0148573

5. Kowalec K, McKay KA, Patten SB, Fisk JD, Evans C, Tremlett H, Marrie RA. Comorbidity increases the risk of relapse in multiple sclerosis: A prospective study. *Neurology* 2017;**89**(24):2455-61. http://dx.doi.org/10.1212/wnl.0000000000004716

6. Salter A, Thomas N, Tyry T, Cutter G, Marrie RA. Employment and absenteeism in working-age persons with multiple sclerosis. *J Med Econ* 2017;**20**(5):493-502. http://dx.doi.org/10.1080/13696998.2016.1277229

7. Karampampa K, Gustavsson A, Miltenburger C, Eckert B. Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. *Mult Scler* 2012;**18**(2 Suppl):7-15. http://dx.doi.org/10.1177/1352458512441566

8. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. 2017;**23**(8):1123-36.

9. Jonker MF, Donkers B, Goossens LMA, Hoefman RJ, Jabbarian LJ, de Bekker-Grob EW*, et al.* Summarizing Patient Preferences for the Competitive Landscape of Multiple Sclerosis Treatment Options. *Med Decis Making* 2020;**40**(2):198-211. http://dx.doi.org/10.1177/0272989x19897944

10. Evans C, Tam J, Kingwell E, Oger J, Tremlett H. Long-term persistence with the immunomodulatory drugs for multiple sclerosis: a retrospective database study. *Clin Ther* 2012;**34**(2):341-50. http://dx.doi.org/10.1016/j.clinthera.2012.01.006

11. Croft A, Mynors G, Roberts M, Doncaster D, Bowen A, Trust M. MS Forward View: a consensus for the future of MS services. *Mult Scler Trust* 2016;**9**:S5-S48.

12. Mynors G, Bowen A, Doncaster D. MS Specialist Nursing in the UK 2016: Report on progress towards equitable provision. *Mult Scler Trust* 2016.

13. Costello K, Halper J. *Multiple Sclerosis: Key Issues in Nursing Management* International Association of Multiple Sclerosis Nurses (IOMSN); 2004. URL: https://iomsn.org/wp-content/uploads/2016/07/KeyIssues_2nd.pdf (Accessed 5 September 2024).

14. National Institute for Health and Care Excellence. *Cladribine tablets for treating relapsing–remitting multiple sclerosis (TA493)*. 2017. URL: https://www.nice.org.uk/guidance/ta493 (Accessed 5 September 2024).

15. National Institute for Health and Care Excellence. *Cladribine for treating relapsing–remitting multiple sclerosis (TA616) - Update Information (21 May 2024)*. 2024. URL: https://www.nice.org.uk/guidance/ta616/chapter/Update-Information (Accessed 5 September 2024).

16. Bar-Or A. The immunology of multiple sclerosis. *Semin Neurol* 2008;**28**(1):29-45. http://dx.doi.org/10.1055/s-2007-1019124

17. European Medicines Agency. *Cladribine tablets SmPC*. EMA; 2024. URL: https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf (Accessed 5 September 2024).

18. Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. *Clin Neuropharmacol* 2011;**34**(1):28-35. http://dx.doi.org/10.1097/WNF.0b013e318204cd90

19. Novakovic AT, A. Schindler, E. Jönsson, S. Munafo, A. Karlsson, MO. Pharmacometric analysis of the relationship between absolute lymphocyte count, and expanded disability status scale and relapse rate, efficacy endpoints, in multiple sclerosis trials. *J Clin Pharmacol* 2018;**58**(10):1284-94. http://dx.doi.org/10.1002/jcph.1136

20. Albor C, du ST, Kali VN, Turner BP, Boomla K, Schmierer K. Ethnicity and prevalence of multiple sclerosis in east London. *Mult Scler* 2017;**23**(1):36-42. http://dx.doi.org/10.1177/1352458516638746

21. He A, Merkel B, Brown JWL, Zhovits Ryerson L, Kister I, Malpas CB*, et al.* Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. *Lancet Neurol* 2020;**19**(4):307-16. http://dx.doi.org/10.1016/s1474-4422(20)30067-3

22. Casanova B, Quintanilla-Bordás C, Gascón F. Escalation vs. Early Intense Therapy in Multiple Sclerosis. *J Pers Med* 2022;**12**(1). http://dx.doi.org/10.3390/jpm12010119

23. Pipek LZ, Mahler JV, Nascimento RFV, Apóstolos-Pereira SL, Silva GD, Callegaro D. Cost, efficacy, and safety comparison between early intensive and escalating strategies for multiple sclerosis: A systematic review and meta-analysis. *Mult Scler Relat Disord* 2023;**71**:104581. http://dx.doi.org/10.1016/j.msard.2023.104581

24. Harding K, Williams O, Willis M, Hrastelj J, Rimmer A, Joseph F*, et al.* Clinical Outcomes of Escalation vs Early Intensive Disease-Modifying Therapy in Patients With Multiple Sclerosis. *JAMA Neurol* 2019;**76**(5):536-41. http://dx.doi.org/10.1001/jamaneurol.2018.4905

25. Prosperini L, Mancinelli CR, Solaro CM, Nociti V, Haggiag S, Cordioli C*, et al.* Induction Versus Escalation in Multiple Sclerosis: A 10-Year Real World Study. *Neurotherapeutics* 2020;**17**(3):994-1004. http://dx.doi.org/10.1007/s13311-020-00847-0

26. Giovannoni G. Disease-modifying treatments for early and advanced multiple sclerosis: a new treatment paradigm. *Curr Opin Neurol* 2018;**31**(3):233-43. http://dx.doi.org/10.1097/wco.0000000000000561

27. Ontaneda D, Tallantyre E, Kalincik T, Planchon SM, Evangelou N. Early highly effective versus escalation treatment approaches in relapsing multiple sclerosis. *Lancet Neurol* 2019;**18**(10):973-80. http://dx.doi.org/10.1016/s1474-4422(19)30151-6

28. Filippi M, Danesi R, Derfuss T, Duddy M, Gallo P, Gold R*, et al.* Early and unrestricted access to high-efficacy disease-modifying therapies: a consensus to optimize benefits for people living with multiple sclerosis. *J Neurol* 2022;**269**(3):1670-7. http://dx.doi.org/10.1007/s00415-021-10836-8

29. Scottish Intercollegiate Guidelines Network (SIGN). *Search filters*. Health Improvement Scotland. URL: https://www.sign.ac.uk/using-our-guidelines/methodology/search-filters/ (Accessed 4 September 2024).

30. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B*, et al.* ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol* 2016;**69**:225-34. http://dx.doi.org/10.1016/j.jclinepi.2015.06.005

31. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P*, et al.* A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;**362**(5):416-26. http://dx.doi.org/10.1056/NEJMoa0902533

32. Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan K, Rieckmann P, Comi G*, et al.* Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. *Mult Scler* 2018;**24**(12):1594-604. http://dx.doi.org/10.1177/1352458517727603

33. Leist TP, Comi G, Cree BA, Coyle PK, Freedman MS, Hartung HP*, et al.* Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. *Lancet Neurol* 2014;**13**(3):257-67. http://dx.doi.org/10.1016/s1474-4422(14)70005-5

34. Leist T, Cook S, Comi G, Montalban X, Giovannoni G, Nolting A*, et al.* Long-term safety data from the cladribine tablets clinical development program in multiple sclerosis. *Mult Scler Relat Disord* 2020;**46**:102572. http://dx.doi.org/10.1016/j.msard.2020.102572

35. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;**343**:d5928. http://dx.doi.org/10.1136/bmj.d5928

36. National Institute for Health and Care Excellence. *Cladribine tablets for treating relapsing-remitting multiple sclerosis - Committee Papers*. 2017. URL: https://www.nice.org.uk/guidance/ta616/evidence/committee-papers-for-ta493-pdf-7021081261 (Accessed 5 September 2024).

37. Giovannoni G, Boyko A, Correale J, Edan G, Freedman MS, Montalban X*, et al.* Long-term follow-up of patients with relapsing multiple sclerosis from the CLARITY/CLARITY Extension cohort of CLASSIC-MS: An ambispective study. *Mult Scler* 2023;**29**(6):719-30. http://dx.doi.org/10.1177/13524585231161494

38. National Institute for Health and Care Excellence. *Cladribine for treating relapsing-remitting multiple sclerosis (TA616)*. 2019. URL: https://www.nice.org.uk/guidance/ta616/resources/cladribine-for-treating-relapsingremitting-multiple-sclerosis-pdf-82608960149701 (Accessed).

39. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J*, et al.* Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. 2014;**13**(7):657-65.

40. Saida T, Yamamura T, Kondo T, Yun J, Yang M, Li J*, et al.* A randomized placebo-controlled trial of delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis from East Asia and other countries. *BMC Neurol* 2019;**19**(1):5. http://dx.doi.org/10.1186/s12883-018-1220-3

41. Kira JI, Nakahara J, Sazonov DV, Kurosawa T, Tsumiyama I, Willi R*, et al.* Effect of ofatumumab versus placebo in relapsing multiple sclerosis patients from Japan and Russia: Phase 2 APOLITOS study. *Mult Scler* 2022;**28**(8):1229-38. http://dx.doi.org/10.1177/13524585211055934

42. Hauser SL, Bar-Or A, Cohen JA, Comi G, Correale J, Coyle PK*, et al.* Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med* 2020;**383**(6):546-57. http://dx.doi.org/10.1056/NEJMoa1917246

43. Cadavid D, Wolansky L, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K*, et al.* Efficacy of treatment of MS with IFNβ-1b or glatiramer acetate by monthly brain MRI in the BECOME study. 2009;**72**(23):1976-83.

44. O`Connor. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *The Lancet Neurology* 2009;**8**(10):889-97.

45. Bornstein MB, Miller, A., Slagle, S. A pilot trial of cop 1 in exacerbating-remitting multiple sclerosis. *New England Journal of Medicine* 1987;**317**(7):408-14.

46. Vollmer T, Sorensen P, Selmaj K, Zipp F, Havrdova E, Cohen J*, et al.* A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. 2014;**261**:773-83.

47. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F*, et al.* Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. *Mult Scler* 2012;**18**(4):418-24. http://dx.doi.org/10.1177/1352458510394702

48. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F*, et al.* Randomized study combining interferon and glatiramer acetate in multiple sclerosis. 2013;**73**(3):327-40.

49. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M*, et al.* Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. 2012;**367**(12):1087-97.

50. Johnson K, Brooks B, Cohen J, Ford C, Goldstein J, Lisak R*, et al.* Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. 1995;**45**(7):1268-76.

51. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K*, et al.* Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. 2012;**367**(12):1098-107.

52. Etemadifar M, Janghorbani, M., Shaygannejad, V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. *Acta Neurologica Scandinavica* 2006;**113**:283-7.

53. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Annals of neurology* 2001;**49**(3):290-7.

54. Naismith RT, Wundes A, Ziemssen T, Jasinska E, Freedman MS, Lembo AJ*, et al.* Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study. *CNS Drugs* 2020;**34**(2):185-96. http://dx.doi.org/10.1007/s40263-020-00700-0

55. Schwid SR, Panitch, H.S. Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: A multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon ÃŸ-1a for relapsi. *Clinical Therapeutics* 2007;**29**(9):2031-48.

56. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, neurology GSGJAo. Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis. 2013;**73**(6):705-13.

57. Cohen J, Belova A, Selmaj K, Wolf C, Sormani MP, Oberyé J*, et al.* Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. 2015;**72**(12):1433-41.

58. Duquette P, Girard, M., Despault, L., DuBois, R., Knobler, R.L., Lublin, F.D., Kelley, L., Francis, G.S., Lapierre, Y., Antel, J., Freedman, M., Hum, S., Greenstein, J.I., Mishra, B., Muldoon, J., Whitaker, J.N., Evans, B.K., Layton, B., Sibley, W.A. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo- controlled trial. *Neurology* 1993;**42**(4):655-61.

59. Stefano N, Sormani MP, Stubinski B, Blevins G, Drulovic JS, Issard D*, et al.* Efficacy and safety of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis: Further outcomes from the IMPROVE study. *Journal of the neurological sciences* 2012;**312**(24):97-101.

60. Durelli L, Verdun, E., Barbero, P., Bergui, M., Versino, E., Ghezzi, A., Montanari, E., Zaffaroni, M. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: Results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet* 2002;**359**(9316):1453-60.

61. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F*, et al.* Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet* 2011;**378**(9805):1779-87. http://dx.doi.org/10.1016/S0140-6736(11)61649-8

62. Knobler RL, Greenstein, J.I., Johnson, K.P., Lublin, F.D., Panitch, H.S., Conway, K., Grant-Gorsen, S.V., Muldoon, J., Marcus, S.G., Wallenberg, J.C., Williams, G.J., Yoshizawa, C.N. Systemic recombinant human interferon-ÃŸ treatment of relapsing-remitting multiple sclerosis: Pilot study analysis and six-year follow-up. *Journal of Interferon Research* 1993;**13**(5):333-40.

63. Mokhber N, Azarpazhooh, A., Orouji, E., Rao, S.M., Khorram, B., Sahraian, M.A., Foroghipoor, M., Gharavi, M.M., Kakhi, S., Nikkhah, K., Azarpazhooh, M.R. Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial. *Journal of the Neurological Sciences* 2014;**342**(42371):16-20.

64. Montalban X, Arnold DL, Weber MS, Staikov I, Piasecka-Stryczynska K, Willmer J*, et al.* Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis. *N Engl J Med* 2019;**380**(25):2406-17. http://dx.doi.org/10.1056/NEJMoa1901981

65. Jacobs LD CD. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). *Annals of neurology* 1996;**39**(3):285-94.

66. O`Connor PW, Li, D., Freedman, M.S., Bar-Or, A., Rice, G.P.A., Confavreux, C., Paty, D.W., Stewart, J.A., Scheyer, R. A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology* 2006;**66**(6):894-900.

67. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B*, et al.* Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med* 2017;**376**(3):221-34. http://dx.doi.org/10.1056/NEJMoa1601277

68. Kappos L, Fox RJ, Burcklen M, Freedman MS, Havrdová EK, Hennessy B*, et al.* Ponesimod Compared With Teriflunomide in Patients With Relapsing Multiple Sclerosis in the Active-Comparator Phase 3 OPTIMUM Study: A Randomized Clinical Trial. *JAMA Neurol* 2021;**78**(5):558-67. http://dx.doi.org/10.1001/jamaneurol.2021.0405

69. Ebers GC. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *The Lancet* 1998;**352**(9139):1498-504. http://dx.doi.org/10.1016/S0140-6736(98)03334-0

70. Singer B, Bandari D, Cascione M, LaGanke C, Huddlestone J, Bennett R*, et al.* Comparative injection-site pain and tolerability of subcutaneous serum-free formulation of interferonβ-1a versus subcutaneous interferonβ-1b: results of the randomized, multicenter, Phase IIIb REFORMS study. 2012;**12**:1-11.

71. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR*, et al.* Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients

with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. 2008;**7**(10):903-14.

72. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP*, et al.* Randomized trial of oral teriflunomide for relapsing multiple sclerosis. 2011;**365**(14):1293-303.

73. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L*, et al.* Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. 2014;**20**(6):705-16.

74. Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP*, et al.* Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. 2014;**13**(3):247-56.

75. De Stefano N et al. (Data on file) Early Onset of Action and Sustained Efficacy of MRI Outcomes during Cladribine Tablets Treatment in Highly Active Relapsing Multiple Sclerosis: Results of the 2-year MAGNIFY-MS Study. ECTRIMS. In; 2022.

76. Vartanian T. An examination of the results of the EVIDENCE, INCOMIN, and phase III studies of interferon beta products in the treatment of multiple sclerosis. *Clin Ther* 2003;**25**(1):105-18. http://dx.doi.org/10.1016/s0149-2918(03)90013-0

77. National Institute for Health and Care Excellence. *Ponesimod for treating relapsing–remitting multiple sclerosis (TA767)*. 2022. URL: https://www.nice.org.uk/guidance/ta767 (Accessed 5 September 2024).

78. National Institute for Health and Care Excellence. *Ofatumumab for treating relapsing multiple sclerosis (TA699)*. 2021. URL: https://www.nice.org.uk/guidance/ta699 (Accessed 5 September 2024).

79. Newsome SD, Kieseier BC, Liu S, You X, Kinter E, Hung S, Sperling B. Peginterferon beta-1a reduces disability worsening in relapsing-remitting multiple sclerosis: 2-year results from ADVANCE. *Ther Adv Neurol Disord* 2017;**10**(1):41-50. http://dx.doi.org/10.1177/1756285616676065

80. National Institute for Health and Care Excellence. *Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533)*. 2018. URL: https://www.nice.org.uk/guidance/ta533 (Accessed 5 September 2024).

81. Tallantyre EC, Dobson R, Froud JLJ, St John FA, Anderson VM, Arun T*, et al.* Real-world persistence of multiple sclerosis disease-modifying therapies. *European Journal of Neurology* 2024;**31**(7):e16289. http://dx.doi.org/10.1111/ene.16289

82. Spelman T, Ozakbas S, Alroughani R, Terzi M, Hodgkinson S, Laureys G*, et al.* Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry. *Mult Scler* 2023;**29**(2):221-35. http://dx.doi.org/10.1177/13524585221137502

83. Reder AT, Arndt N, Roman C, Geremakis C, Mendoza JP, Su R*, et al.* Real-world propensity score comparison of treatment effectiveness of peginterferon beta-1a vs. subcutaneous interferon beta-1a, glatiramer acetate, and teriflunomide in patients with relapsing-remitting multiple sclerosis. *Mult Scler Relat Disord* 2021;**51**:102935. http://dx.doi.org/10.1016/j.msard.2021.102935

84. Zhornitsky S, Greenfield J, Koch MW, Patten SB, Harris C, Wall W*, et al.* Long-term persistence with injectable therapy in relapsing-remitting multiple sclerosis: an 18-year observational cohort study. *PLoS One* 2015;**10**(4):e0123824. http://dx.doi.org/10.1371/journal.pone.0123824

85. Bucello S, Annovazzi P, Ragonese P, Altieri M, Barcella V, Bergamaschi R*, et al.* Real world experience with teriflunomide in multiple sclerosis: the TER-Italy study. *J Neurol* 2021;**268**(8):2922-32. http://dx.doi.org/10.1007/s00415-021-10455-3

86. Tai M-H, Shao Q, Brown B, Taiji R, Faucher A, Gadkari A. Real-World Persistence and Adherence to Ofatumumab vs Ocrelizumab in Patients With Multiple Sclerosis. Paper presented at: Consortium of Multiple Sclerosis Centers (CMSC) 38th Annual Meeting; Nashville, TN, US. URL: https://medcommshydhosting.com/USQR/CMSC/pdf/DMT38.pdf).

87. Elzhov TV, Mullen, K. M., Spiess, A.-N., & Bolker, B. . *minpack.lm: R Interface to the Levenberg-Marquardt Nonlinear Least-Squares Algorithm Found in MINPACK, Plus Support for Bounds. R package version 1.2-1*. The Comprehensive R Archive Network (CRAN); 2023. URL: https://CRAN.R-project.org/package=minpack.lm (Accessed 4 September 2024).

88. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2023. URL: https://www.R-project.org/ (Accessed 24 September 2024).

89. Lager B, Liseno J, Božin I, England SM, Shankar SL, Mendoza JP, Lewin JB. Real-World Analysis Affirms the High Persistence and Adherence Observed with Diroximel Fumarate in Patients with Multiple Sclerosis. *Neurol Ther* 2023;**12**(1):145-59. http://dx.doi.org/10.1007/s40120-022-00413-0

90. Palace J, Bregenzer T, Tremlett H, Oger J, Zhu F, Boggild M*, et al.* UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. *BMJ Open* 2014;**4**(1):e004073. http://dx.doi.org/10.1136/bmjopen-2013-004073

91. National Institute for Health and Care Excellence. *Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527)*. 2018. URL: https://www.nice.org.uk/guidance/ta527/resources/beta-interferons-and-glatiramer-acetate-for-treating-multiple-sclerosis-pdf-82606845513157 (Accessed 5 September 2024).

92. National Institute for Health and Care Excellence. *Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624)*. 2020. URL: https://www.nice.org.uk/guidance/ta624 (Accessed 5 September 2024).

93. National Institute for Health and Care Excellence. *Cladribine for treating relapsing multiple sclerosis: Final scope*. 2024. URL: https://www.nice.org.uk/guidance/gid-ta11293/documents/final-scope (Accessed 5 September 2024).

94. European Medicines Agency. *Teriflunomide tablets SmPC*. 2023. URL: https://www.ema.europa.eu/en/documents/product-information/aubagio-epar-product-information_en.pdf (Accessed 5 September 2024).

95. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013, NICE process and methods [PMG9]*. 2013. URL:

https://www.nice.org.uk/process/pmg9/chapter/foreword (Accessed 5 September 2024).

96. Gorrod HB, Latimer NR, Damian D, Hettle R, Harty GT, Wong SL. Impact of Nonrandomized Dropout on Treatment Switching Adjustment in the Relapsing-Remitting Multiple Sclerosis CLARITY Trial and the CLARITY Extension Study. *Value Health* 2019;**22**(7):772-6. http://dx.doi.org/10.1016/j.jval.2018.11.015

97. Armoiry X, Wang-Steverding X, Connock M, Grove A, Clarke A, Arun T*, et al.* Is the assumption of waning of treatment effect applied consistently across NICE technology appraisals? A case-study focusing on disease-modifying therapies for treatment of multiple sclerosis. *Int J Technol Assess Health Care* 2022;**38**(1):e83. http://dx.doi.org/10.1017/s0266462322003269

98. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. *J Neurol* 2014;**261**(8):1508-17. http://dx.doi.org/10.1007/s00415-014-7370-3

99. Sadovnick AD, Ebers GC, Wilson RW, Paty DW. Life expectancy in patients attending multiple sclerosis clinics. *Neurology* 1992;**42**(5):991-4. http://dx.doi.org/10.1212/wnl.42.5.991

100. Pokorski RJ. Long-term survival experience of patients with multiple sclerosis. *J Insur Med* 1997;**29**(2):101-6.

101. Hawton A, Green C. Health Utilities for Multiple Sclerosis. *Value Health* 2016;**19**(4):460-8. http://dx.doi.org/10.1016/j.jval.2016.01.002

102. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. *Value Health* 2007;**10**(1):54-60. http://dx.doi.org/10.1111/j.1524-4733.2006.00144.x

103. Heather A, Goodwin E, Green C, Morrish N, Ukoumunne OC, Middleton RM, Hawton A. Multiple sclerosis health-related quality of life utility values from the UK MS register. *Mult Scler J Exp Transl Clin* 2023;**9**(2):20552173231178441. http://dx.doi.org/10.1177/20552173231178441

104. Acaster S, Perard R, Chauhan D, Lloyd AJ. A forgotten aspect of the NICE reference case: an observational study of the health related quality of life impact on caregivers of people with multiple sclerosis. *BMC Health Serv Res* 2013;**13**:346. http://dx.doi.org/10.1186/1472-6963-13-346

105. Ruutiainen J, Viita AM, Hahl J, Sundell J, Nissinen H. Burden of illness in multiple sclerosis (DEFENSE) study: the costs and quality-of-life of Finnish patients with multiple sclerosis. *J Med Econ* 2016;**19**(1):21-33. http://dx.doi.org/10.3111/13696998.2015.1086362

106. Hawton AJ, Green C. Multiple sclerosis: relapses, resource use, and costs. *The European Journal of Health Economics* 2016;**17**(7):875-84. http://dx.doi.org/10.1007/s10198-015-0728-3

107. Tyas D, Kerrigan J, Russell N, Nixon R. The distribution of the cost of multiple sclerosis in the UK: how do costs vary by illness severity? *Value Health* 2007;**10**(5):386-9. http://dx.doi.org/10.1111/j.1524-4733.2007.00192.x

Appendix 1
CLARITY RoB Assessment- Using Cochrane RoB [35]

	Domain	Support for judgement	Risk of bias EAG assessment

Selection bias	Random sequence generation	"Briefly, CLARITY is the pivotal Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week trial that supports the marketing authorisation for cladribine tablets"- Doc B 2.3.2 (page 38) and Table 5 Clarification document A7 (page7]: CLARTY EXT followed same procedure of CLARITY and reported 'the use of a central system and a computer-generated treatment randomisation code'	Low RoB
	Allocation concealment	Briefly, CLARITY is the pivotal Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week trial that supports the marketing authorisation for cladribine tablets"- Doc B 2.3.2 (page 38) Overall, treatment allocation over the first 96 weeks of the CLARITY-EXT trial depended on the initial treatment randomisation in the CLARITY trial [Clarification document A7, page 7]	Low RoB
Performance bias	Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	"Double-blinding was also conducted using the same procedures used in the CLARITY study" [Clarification document A7, page 8]	Moderate RoB Not explicitly reported in details for CLARITY

Detection bias	Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	No supporting information provided	High RoB
Attrition bias	Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	No supporting statement provided	High RoB Doc B 2.3.1 (Page 38) mentioned that "Upon completion of CLARITY, patients were then eligible for entry into CLARITY-EXT. Overall, 806 patients eligible for inclusion in the CLARITY-EXT trial were re-randomised (2:1) to receive either 3.5 mg/kg cladribine tablets or placebo. " whereas the CLARITY included 870 [433 low dose and 437 placebo]
Reporting bias	Selective reporting	The analysis was done based on ITT population	Low RoB
Other bias	Other sources of bias	Baseline patient characteristics were not comparable [Table 9, B 2.3.5, Pge 44]	Moderate RoB

CLARITY-EXT RoB Assessment- Using Cochrane RoB [35]

	Domain	Support for judgement	Review authors' judgement
Selection bias	Random sequence generation	"CLARITY-EXT was a Phase IIIb double-blind, parallel group, multicentre, 96-week extension trial of CLARITY that provides supportive evidence for sustained efficacy (i.e., 2 years of treatment and no further treatment required	Low RoB

		in years 3 and 4)"- Doc B 2.3.2, (page 38) and Table 5. CLARTY EXT followed same procedure of CLARITY and reported 'the use of a central system and a computer-generated treatment randomisation code'	
	Allocation concealment	"Patients were assigned a unique 12-digit identification number, with the first five digits comprising the trial number, the next three digits the site number, and the final four digits the sequential subject number. For the purposes of this trial, patients retained the same last seven digits that had been assigned to them in CLARITY, and only the five-digit trial number prefix was changed. In addition to obtaining the patient identification number from the electronic case report form, the trial personnel had to register the patient in the central randomisation system by completing a screening form" [Clarification document A7 page 7]	Low RoB
Performance bias	Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	"The double-blinded nature of CLARITY-EXT was as follows: a treating physician, blinded to treatment, was responsible for supervision of study medication administration, monitoring of safety assessments, and the recording and treatment of adverse events (AEs) and	Low RoB

		relapses." [Clarification document A7 , page 7-8]	
Detection bias	Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	"The double-blinded nature of CLARITY-EXT was as follows: a treating physician, blinded to treatment, was responsible for supervision of study medication administration, monitoring of safety assessments, and the recording and treatment of adverse events (AEs) and relapses." [Clarification document A7 , page 7-8]	Low RoB
Attrition bias	Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	No supporting statement provided	Unclear RoB
Reporting bias	Selective reporting	The analysis was done based on ITT population	Low RoB
Other bias	Other sources of bias	"The two patients in the placebo arm required a delay in the treatment administration due to relapses, for which they both received rescue treatment (steroids). One patient received no further courses of treatment because of disease progression and was placed on rescue medication but remained in the study for follow-up and completed all of the study assessments through Week 96. The other patient receiving	Moderate RoB

		placebo reported for two follow-up visits after completing the initial four courses and then was withdrawn from the study because of a protocol violation, i.e., the patient was not attending study visits" [Clarification document A 2, Page 3]	

Single Technology Appraisal

Cladribine for treating relapsing multiple sclerosis [ID6263]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 19 September 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 The population include RRMS

Description of problem	Description of proposed amendment	Justification for amendment
N/A	N/A	N/A

Issue 2 The NMA results should be interpreted with caution

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 73: The uncertainties in terms of statistical variability could be a result of a smaller number of RCTs that contributed data to NMAs for 3-month CDP, 6-month CDP, and all-cause treatment discontinuations (15, 17, and 25 RCTs, respectively) compared to ARR NMA that was based on 37 RCTs. Moreover, a relatively rare occurrence of CDP event (3- or 6-month) compared to ARR might have additionally contributed to this uncertainty if the length of follow-up of these trials was not long enough. Moreover, not all trials were designed to have had a power sufficient for	The company propose to amend the wording to the below: The challenge of limited RCT evidence to support 3-month CDP, 6-month and all-cause treatment discontinuations is universal across all NICE evaluations of treatments for RRMS. The approach to account for the uncertainty in the results of NMA was handled through the usage of random effects model.	For outcomes CDP3M and CDP6M where there is a smaller number of studies for NMA, the minimum follow-up is 24 months. The number of patients in each trial is sufficiently powered (range N:123 - 897) except for one trial (BEYOND) where only 25 patients in each arm were trialled.	Not a factual inaccuracy. However, the clarification was added.

detecting the outcomes of disability progression.			
Page 76: According to the company and EAG, placebo arms varied across the NMA in terms of mode, frequency, and blinding methods which may have influenced the comparability and treatment connectivity in the NMA. This may have violated the transitivity assumption. However, the company analysis (Merck_Meta-Regression-Meta Analysis and Inconsistency", sheet named: "Beta_result_metaregression") showed that the rates for ARR, CDP, and treatment discontinuations were similar in the placebo arms across the trials. The EAG could not locate this analysis in order to verify or refute this claim.	The company propose that the issue pertaining to transitivity due to differences in mode and frequency of placebo should be removed.	The mode and frequency of the placebo arm depends on the intervention arm to assure the blinding. To assess the potential effect of variability in the efficacy of the placebo arm, the company carried out the baseline risk-adjusted NMA. The results were consistent with the random effect results, and beta coefficients were not statistically significant. The results of this analysis were shared with the EAG in the file named "Merck_Meta-Regression-Meta Analysis and Inconsistency", sheet named "Beta_result_metaregression". If the EAG is not able to access the file the company can reshare it.	The text has been revised accordingly
Page 76: The company checked the inconsistency assumption with results comparing indirect and direct evidence for the mixed treatment	The company propose the below amendment to the wording of this issue: Company carried out the inconsistency check using the	The company carried out the inconsistency check using the node-split method and provided the forest plots to compare the direct and indirect evidence.	EAG agrees partially, i.e., mostly there was some consistency except for few cases of

estimates presented in the forest plots. The company stated that the test for inconsistency between multiple closed loops were suggestive of low likelihood of inconsistency. In contrast, the EAG noted several inconsistencies in HR magnitude and 95% CrIs from the visual inspection of the forest plots of closed loops in regards to direct, indirect, and mixed (pooled) HR estimates of treatment effects for all four NMA outcomes. The company did not provide inconsistency factor (IF statistic), as EAG requested.	node-split method and forest plot for the direct and indirect evidence was provided. The direct and indirect estimations for all the four outcomes were overlapping suggest absence of inconsistency.	95%CrIs for direct and indirect evidence were overlapping suggesting the absence of inconsistency for all four outcomes. If required, the company can provide the p-values for each comparison to demonstrate the absence of inconsistencies.	inconsistency (examples below here). Overlapping 95% CIs is not necessarily indication of consistency. If the intervals are wide because of small sample size, they will likely overlap even in the presence of inconsistency. The point estimates for some interventions are numerically different regardless of the overlapping CIs. Examples: <u>CDP-3 mo</u> GA 20 mg vs. IFN-β1b 250 µg; direct HR=0.69, 95% CI; 0.51, 0.94 vs.

			indirect HR=1.25, 95% CI: 0.68, 2.32 Treatment discontinuation (DMF 240 mg vs. PL; direct HR=0.80, 95% CI: 0.55, 1.15) vs. Indirect HR=5.42, 95% CI: 1.18, 24.88) IFN-β 1a 22 µg vs. PL; direct HR=1.44, 95% CI: 0.48, 4.27 vs. indirect HR=0.79, 95% CI: 0.14, 4.47 ARR PI vs. Teriflunomide 7 mg; direct HR=1.38, 95% CI: 1.18, 1.60 vs. indirect HR=0.74, 95% CI: 0.47, 1.17

Page 77: For example, the NMA results comparing effects of cladribine tablets to DMT regimens for reducing risk of 3-month CDP were not available for 24 (61.5%) of the 38 trials. Similarly, the outcome data for 6-month CDP were not available for 22 trials (56%). The outcome data for treatment discontinuations were not available for 14 (36%) of the trials included in the NMA.	The company have several corrections below (in bold): For example, the NMA results comparing effects of cladribine tablets to DMT regimens for reducing risk of 3-month CDP were not available for **23** (**60.5%)** of the 38 trials. Similarly, the outcome data for 6-month CDP were not available for **21** trials (**55.3%).** The outcome data for treatment discontinuations were not available for **13** (**34.2%)** of the trials included in the NMA.	The number of studies providing the inputs for CDP3M, CDP6M and treatment discontinuation were incorrect in the EAG report, and are 15, 17 and 25 respectively. So (38-15)/38 = 60.5%, (38-17)/38 = 55.3% and (38-25)/38 = 34.2%.	Text revised.
Page 77-78: Consistency of hazard ratio proportionality: Since the individual trials included in the NMA reported Cox regression-based HRs for CDP and treatment discontinuations, it was important to ensure that the assumption of hazard ratio proportionality was not violated. In the CS, the company did not report if the	The company propose the below amendment to the wording of this issue: Consistency of hazard ratio proportionality: Proportionality assumption validation was not required since both CDP and treatment discontinuation were provided in the form of a dichotomous data i.e. number	The wording of this issue is misleading as it wrongly implies the assessment of hazard ratio proportionality is appropriate yet was omitted by the company. CDP and treatment discontinuation were not provided as KM curves in any of the DMT trials, instead they are provided as binomial data. Given these	Text revised.

primary study reports provided any information whether or not this assumption was assessed. In the clarification letter (Q: A17), the EAG requested that the company provide their assessment of the hazard ratio proportionality assumption from the reports of individual trials. The company's response to EAG clarification letter indicated that there are no time-to-event data or KM curves available in the primary study reports to check the proportionality assumption. Therefore, EAG believe there is uncertainty in this regard.	of patients with CDP or number of patients discontinued the treatment. The hazard ratio was calculated in the NMA because a binomial clog-log model was used with the timepoint at which these data were measured.	outcomes are presented as binomial data rather than time-to-event data, assessment of the hazard ratio proportionality assumption is not required nor appropriate.	
Page 88: The company did not assess the validity of underlying assumptions, such as the consistency assumption, and the EAG was unable to implement these assessments due to time constraints and the extensive volume of data and analyses in the company's submission.	The company propose the below amendment to the wording of this issue: The company provided the inconsistency forest plots for each comparison in the loops. The direct and indirect evidence was overlapping suggest the absence of the inconsistency.	The company carried out the inconsistency check using the node-split method and provided the forest plots to compare the direct and indirect evidence. 95% CrIs for direct and indirect evidence were overlapping suggest the absence of inconsistency for all the four outcomes. If required, the company can provide the p-values for each comparison to	Not a factual inaccuracy.

		show the absence of inconsistencies.	

Issue 3 Treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16: "The EAG considers real-world evidence to be more reflective of the experiences of RRMS patients regarding the discontinuation of DMTs." Page 92: "The EAG considers real-world evidence to be more reflective of the actual experiences of RRMS patients regarding the discontinuation of DMTs"	The company proposes that all mention of the use of the Tallantyre study as the source of data for DMT discontinuation is removed (see justification in the next column) or that it is clearly stated that "The EAG analysis of the discontinuation of DMTs, which leveraged real-world evidence from the Tallantyre (2024) study was purely exploratory as it is not in line the NICE reference case and NICE precedent in MS appraisals.	The company considers that the use of the Tallantyre (2024) study in the base case analysis suggested by the EAG is inappropriate due to the following reasons: • The company's approach of using trial data sourced from an NMA as a source of discontinuation is in line previous NICE evaluations of other RRMS treatments including Ocrelizumab (TA533), Peginterferon (TA624), Ponesimod (TA767), Ofatumumab (TA699) (as summarised in the CS for cladribine, Document B, Table 28).	Not factual error. No changes made.
Page 83: The EAG selected the Tallantyre (2024) study as the most relevant source of data on DMT persistence.			No factual error, no changes made. The company cites precedent from previous appraisals of RRMS treatments as

		The use of the Tallantyre (2024) study would be incongruent with NICE precedent. • The company's approach is aligned with the previous NICE appraisal of Cladribine tablets (TA493/TA616). Where possible, the company has followed a similar methodological approach, as this has been previously accepted by the NICE committee. • Identification of studies relevant to the NICE decision problem is outlined in the NICE guidelines manual (PMG6), clearly stating that 'A systematic review process should be used that is explicit and transparent'. This process was not followed by the EAG for the	justification for continued use of trial data to inform treatment discontinuation probabilities in the current appraisal of cladribine. Despite this precedent, the EAG takes the view that real-world evidence and for that matter the Tallantyre (2024) data better reflects the experience of DMTs use in practice than RCT data, including discontinuation from treatment.
Page 87: "For cladribine, only two years of follow-up data are reported and available from Tallantyre (2024), with the best fit model to the observed persistence probabilities being the log-normal model. The data are immature, and the median survival (in this case, persistence) has not been			Not factual error. The issues cited by the company under "Justification for amendment," aside from those related to precedent, highlight potential limitations in the EAG's literature searches regarding treatment

reached, so caution is warranted when extrapolating beyond the observed data” “When faced with uncertainties in long-term extrapolation of survival data, one approach to addressing this uncertainty is to compare the predictions to external reference data. The survival curve that generates predictions closest to the external reference data could be preferred on this basis. One potential external data source is the Tallantyre (2024) study, which also reported up to 10 years of treatment persistence data for alemtuzumab, an older immune-reconstituting DMT with a short-course administration similar to that of cladribine […] Given this information, and if it is reasonable to use the alemtuzumab data as an external reference to guide the selection of a long-term extrapolation model for cladribine, the exponential curve (Figure 13) would appear to generate predicted probabilities for		identification of the Tallantyre (2024) study. • The Tallantyre (2024) study was published in July 2024 and outside the search date for the clinical evidence. Even if this study was identified via a systematic approach: • The Tallantyre (2024) study does not have data for all comparators relevant to the NICE decision problem (i.e., ofatumumab, ponesimod, and diroximel fumarate). • The Tallantyre (2024) study used inconsistent definitions of persistence for cladribine (i.e., time to first DMT switch or time to last known follow-up if no subsequent DMT had been prescribed) and other DMTs (i.e., length of time a patient	discontinuation and the limitations of the Tallantyre (2024) data. The EAG did not have the resources or time to conduct a systematic literature review for real-world evidence on the persistence of DMTs in RRMS. Instead, it conducted a rapid review of the literature and identified the Tallantyre (2024) study, which reported real-world evidence on the use of DMTs among UK patients. The EAG believes that the Tallantyre data represents the best available published evidence it identified regarding persistence to DMT treatment for the current appraisal of cladribine. In light of these points, the EAG acknowledges the company's concerns

cladribine that most closely match the alemtuzumab data” Page 104: “Secondly, the data source used to inform the discontinuation probabilities in the economic model raises concerns. The company derived these probabilities from an NMA of RCT data, which the EAG believes may not accurately reflect the real-world experiences of MS patients using DMTs”		remained on a single DMT). • Any attempt to compare extrapolated immature cladribine data supported by an external validation using alemtuzumab data (a DMT with a different safety profile and not indicated for the population in scope, i.e., active RRMS) will be associated with high uncertainty and not consistent with the approach validated by the company. • There is no randomisation or stratification in the analysis. Only three baseline characteristics (gender ratio, mean age at start of DMT and mean disease duration) were compared. This is equivalent to a naïve comparison which is not as robust as an NMA	and has updated the EAG report to reflect the limitations of the EAG’s searches and the Tallantyre (2024) data. The EAG report has been revised at the end of section 3.5.1.2 to include the following paragraphs: "The EAG’s work on estimating the probability of treatment discontinuation has several limitations. Due to time and resource constraints, the EAG could not conduct a comprehensive systematic literature review for real-world evidence on the persistence of DMTs in RRMS. Instead, it performed a rapid review, identifying the Tallantyre (2024) study, which offers real-world

		performed systematically using RCT evidence (as per the company base case).	evidence on the use of DMTs among UK patients. However, the Tallantyre (2024) study does not cover all comparators relevant to the NICE decision problem, such as ofatumumab, ponesimod, and diroximel fumarate. Like the company's NMA data, the definitions of treatment discontinuation or persistence in the Tallantyre study are inconsistent for cladribine and other DMTs. For example, cladribine's persistence is defined as the time to the first DMT switch or the time to the last known follow-up if no subsequent DMT was prescribed, while other DMTs use the duration

			a patient remained on a single DMT. Additionally, the EAG recognises challenges in using alemtuzumab data as an external reference when choosing its preferred model for extrapolating cladribine's treatment persistence. This approach introduces significant uncertainty due to the immature cladribine data and the differences in safety profiles between the two treatments. Furthermore, the analysis did not involve randomization or stratification, and only three baseline characteristics—gender ratio, mean age at the start of DMT, and mean disease duration—were compared, making this a naïve comparison.

			Despite these challenges, the EAG considers the Tallantyre data to be the best currently available real-world evidence on the persistence of DMTs among UK patients with RRMS. It remains valuable in exploring uncertainties regarding the long-term persistence of DMTs in RRMS.”
Page 81: For the NMA of treatment discontinuation, the EAG’s replication of the CS analyses was only partially successful. While the EAG was able to generate hazard ratios for treatment discontinuation that align with those provided in the CS documents, some discrepancies remain. Table 14 compares the hazard ratios using cladribine as baseline treatment, in line with how the company	The company propose that these statements should be removed.	If hazard ratios are matching, the absolute treatment effect should also match. The only reason that the absolute effect is not matching is due to an incorrect placebo effect. In the WinBUGS code, the company have included the code for calculating the absolute treatment effect i.e. annualised	No change. The EAG has thoroughly reviewed the NMA model used to generate the treatment discontinuation probabilities and confirms that the method was correctly implemented. An R script, adapted from the appendix of the CS, was used by the EAG to replicate the model,

presented its results (Table 17 of appendix accompanying CS). There is high level of agreement between the CS and EAG estimates of the treatment discontinuation hazard ratio.		treatment discontinuation which is as follows:
		
		A ~ dnorm(meanA,precA)
		
		for (k in 1:nt) { cloglog(T[k]) <- log(timeA) + A + d[k].
		
		Here meanA and precA have to be calculated for the placebo arm. Since the model is using cloglog as the link function, the effect should also be calculated in cloglog format before calculating the mean and precision. Another way to calculate the mean effect for placebo is through the baseline model as outlined in NICE guidelines. If required, the company can prepare the WinBUGS code for the baseline model and provide it for recalculating the annualised treatment discontinuation.
			and the corresponding WinBUGS code is also provided.
			
			Regarding the estimation of the parameter "A" in the formula:
			
			for (k in 1:nt) { cloglog(T[k]) <- log(timeA) + A + d[k]
			
			}
			
			Since "A" is a hyperparameter within the model, it can be automatically included in the calculation of the discontinuation probability on the scale of the link function. Any uncertainty in "A" is automatically propagated to the posterior estimates of T. A separate line of

			code embedded in the company's NMA model provided in the CS appendix performs the appropriate calculations in WinBUGS (See EAG R Script).
Page 95 “Notably, it appears that the model does not allow for discontinuation due to a lack of efficacy of a DMT, which would typically necessitate switching to another DMT. “	The company propose that the whole sentence is removed.	Discontinuation due to a lack of efficacy is captured in the cost-effectiveness model through the all-cause discontinuation estimates (which comprise treatment discontinuation due to adverse events, lack of efficacy, and other clinical trials withdrawal causes) used in the economic analysis.	Not factual error. The EAG maintains that the model does not allow for treatment discontinuation due to lack of efficacy for the following reasons: 1. For cladribine, the probability of treatment discontinuation beyond the first two years after treatment initiation is set to zero. This implies that the model does not permit patients to discontinue cladribine beyond year two for any reason including no benefit from the treatment. Note that the model allows patients

			to discontinue treatment if they progressed to EDSS states >7.0 2. The definition of all-cause treatment discontinuation is not explicitly stated in the company's submission documents. During clarification, the EAG asked the company to define how treatment discontinuation was defined in the trials included in the NMA for treatment discontinuation (Clarification question A18). In response, the company provided a list of outcomes included in the counts for treatment discontinuation. These outcomes varied across studies, with most reporting all-cause treatment discontinuation, but it

			was unclear what exactly was included in the definition of all-cause treatment discontinuation in the data provided (company response to question A18). Given the above concerns, the EAG believes the probability of treatment discontinuation used in the company's base-case is highly uncertain, particularly with regard to capturing discontinuation due to loss of efficacy beyond year 2 for cladribine.

Issue 4 Treatment waning

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17: "The company applied a uniform treatment waning assumption, where the effects of cladribine and competitor DMTs on relapses and disability progression waned over time. Specifically, cladribine was assumed to have 0% waning during the first four years of treatment (compared to 0% in 0-2 years followed by 25% in year 2 to 4 for competitor DMTs)." "The net effect would be to worsen the ICER for cladribine compared to competitor DMTs, while the ICER relative to BSC will remain unchanged. However, the EAG is unable	The company propose that this section is corrected to state that the company applied the same treatment waning effect estimates across cladribine and all comparators DMTs in the base case analysis.	The company disagree with EAG statements regarding how treatment waning effect implementation was applied in the base case and would like to highlight the following points: • As described in the original submission (Section 3.3.3.3), the same treatment waning effect estimates applied for cladribine were also conservatively applied to all comparators (in the absence of treatment waning data for other DMTs) in the base case analysis. Therefore, 0% waning during the 0-4 year period was applied for all DMTs and not only for cladribine as	Key issue 4 has been removed from the EAG report and Sections 4.2.5.8 and 4.2.5.8 have been revised accordingly.

to provide an ICER based on this assumption because the company's model does not allow for the implementation of 0% waning during the 0-4 year period for competitor DMTs." "The company should consider the feasibility of updating its economic model to allow for 0% waning during the 0-4 year period for competitor DMTs, particularly for high-efficacy treatments."		described by EAG in this report. • The use of the same treatment waning between cladribine and comparators is also evident in the base case waning selection in the model, where "Same waning" is actively selected at cell *K14* in the "*Settings*" worksheet; in the "*Treatment waning effect (proportion of trial benefit)*" section at the "*Clinical - treatment effect*" worksheet, where 100% (1.0) of treatment effect is attributed to all DMTs during the 0-4 year period; and in all waning-related calculations in each DMT transition sheet (i.e., in each transition sheet the treatment waning effect is applied based on the same	
Page 110: "The EAG has concerns regarding the company's application of its 'same waning' assumption, which only applies from year 5 onward. In the first four years, the company applied different waning rates for cladribine and competitor			

DMTs. Specifically, cladribine was assigned a 0% waning rate throughout the first four years after treatment initiation, while competitor DMTs were assigned 0% waning in years 0-2 and 25% waning in years 2-4." "The EAG believes the company's base-case assumption about waning should be revised to be equally applied to cladribine and competitor DMTs, particularly high-efficacy treatments such as ocrelizumab, ofatumumab, and ponesimod"		values as observed at cell range *O10:P18*). • Besides the three options already available for selection in the cost-effectiveness model (i.e., "*Same waning*" as base case, "*Different waning*" and "*No waning*" as scenarios), the model does provide further flexibility to explore any other treatment waning effect estimates for cladribine and all other DMTs. These can be done by adding any value from 0.0 to 1.0 (which can be applied for each DMT considering different periods of time: 0 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6, 6 to 8, 8 to 10, 10 + years) in the User inputs cells in "*Clinical-treatment effect*" worksheet.	
Page 111: "Therefore, the EAG recommends applying a consistent waning assumption across all DMTs, with 0% waning assumed for years 0-4, 25% for years 4-5, and 50% thereafter for both cladribine			Please see earlier response. Text have been revised to align with application of the same waning assumption described in the CS.

and its competitors. Implementing this change would likely worsen the ICER for cladribine compared to competitor DMTs, although the ICER relative to best supportive care (BSC) would remain unaffected. However, the model in its current form does not allow for the implementation of 0% waning during the 0-4 year period for competitor DMTs.”			

Issue 5 Constant mortality in RRMS

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 18:	The company propose the wording is edited to read:	As highlighted in the proposed amendment, the model submitted by the	Amended. The “What alternative approach has the EAG suggested?”

“The company used a fixed standardised mortality rate (SMR) in its base-case model, which implies that mortality rates for patients with RRMS do not vary with changes in disability progression as indicated by EDSS scores or the form of MS. The EAG considers that a variable SMR is more realistic and aligns better with the natural history of RRMS, where mortality increasing with disease progression.”	“The company used a fixed standardised mortality rate (SMR) in its base-case model, which implies that mortality rates for patients with RRMS do not vary with changes in disability progression as indicated by EDSS scores or the form of MS. The EAG considers that a variable SMR is more realistic and aligns better with the natural history of RRMS, where mortality increasing with disease progression. The model submitted by the Company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b).”	company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b). The company would like this to be reflected in the report for completeness. Please note, the company do not consider this a key issue as the impact on cost-effectiveness is not considered to be significant.	the EAG report has been updated to include the following text: “The model submitted by the Company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b).”
Page 113: “However, the EAG believes that the fixed mortality assumption, where mortality in RRMS does not vary with EDSS progression, oversimplifies reality, as patients in higher EDSS	The company propose the wording is edited to read: “However, the EAG believes that the fixed mortality assumption, where mortality in RRMS does not vary with EDSS progression, oversimplifies reality, as patients in higher EDSS states are likely to have a higher		Amended by adding the following text “The model submitted by the company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and

states are likely to have a higher mortality risk than those in lower EDSS states. That's because, in the course of RRMS, as patients experience greater levels of disability, their overall health often deteriorates, leading to a higher risk of mortality. This aligns with an assumption that a variable standard mortality rate (SMR), which adjusts for levels of disability, provides a more realistic and nuanced depiction of mortality compared to a fixed SMR."	mortality risk than those in lower EDSS states. That's because, in the course of RRMS, as patients experience greater levels of disability, their overall health often deteriorates, leading to a higher risk of mortality. This aligns with an assumption that a variable standard mortality rate (SMR), which adjusts for levels of disability, provides a more realistic and nuanced depiction of mortality compared to a fixed SMR. The model submitted by the company includes a functionality to change the mortality inputs from the fixed mortality assumption to mortality varying by EDSS and form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b)."		form. The company also explored the varying mortality ratios in their scenario analyses (scenarios S4a and S4b)."

Issue 6 Cost of cladribine tablets

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19: "Truncating the weight distribution at the extreme	The company propose to change the wording so that this is not described as an error.	The acquisition costs of cladribine tablets were calculated based	No factual error. No change

ends (either very high or very low weights) has led to minor errors in calculating the cost of cladribine.”		omonitoringn the actual CLARITY trial proportion of patients in each weight range (i.e., proportion of patients within 40 to <50 kg, 50 to <60 kg, 60 to <70 kg, 70 to <80 kg, 80 to <90 kg, 90 to <100 kg, 100 to <110 kg, and 110 kg and above) and the distribution of the total dose recommended by the MHRA Summary of Product Characteristics for each weight range above (and not the midpoint value for each range as described by EAG). Please note, the company do not consider this a key issue as the impact on cost-effectiveness is not considered to be significant.	
Page 117: “The weights are grouped into bands, and the CS calculations use the midpoint value for each band. This method was applied to all weight bands except for the >110kg group, where no midpoint was available. In the company’s base case, a weight of 110kg was assumed for this group, leading to an estimated per-patient total acquisition cost of approximately £25,986 (£25,953 according to the company’s calculations).			No factual error. As it is not obvious from the CS document B that the weights were calculated based on actual CLARITY trial population weights, the EAG update the text on page 117 of the report to include the word: “it seems that”

However, the EAG believes this calculation is flawed because it assumes that the central estimate for patients with a body weight >110kg is 110kg. When a more conservative central estimate of 115kg is used for this group, the total annual acquisition cost of cladribine tablets increases to £26,017 (Table 31)".			
Page 118: "Since the acquisition costs of the tablets are sensitive to patient weight in the model, the EAG would prefer to use individual patient data from the CLARITY trial to estimate the exact weight distribution observed at study entry for this appraisal of cladribine's cost-effectiveness." "Changing the total acquisition cost per patient			No factual error. No change.

of cladribine from £25,986 (CS base-case) [redacted] (EAG's estimate) increased the base-case deterministic ICER slightly [redacted] to [redacted] per QALY gained compared with BSC. Cladribine remained dominant in comparison with teriflunomide, ocrelizumab, ofatumumab, ponesimod, and diroximel fumarate"			
Page 116: "The patient weight distribution taken from 3.5mg cladribine arm of CLARITY (mean weight [redacted]kg). Based on the mean body weight, each patient would thus require a total of 50 of the 10mg cladribine tablets (25 tablets per year) to complete the course of treatment."	The company propose the wording on page 116 is edited to read: "The patient weight distribution taken from 3.5 mg**/kg** cladribine arm of CLARITY (mean weight [redacted]**kg**). Based on the mean body weight, each patient would thus require a total of **24** of the 10mg cladribine tablets (**12** tablets per year) to complete the course of treatment."	The mean weight from CLARITY of the patients in the 3.5mg/kg cladribine treatment arm (n=433) is 68.1kg as reported in Giovannoni (2010). However, the model uses a more conservative calculation of the pooled mean weight of the patients in the 3.5 mg/kg and the placebo arm (n= 870) from the CLARITY trial (i.e., a mean weight of [redacted] kg).	No factual error. No change

Page 117: “Alternatively, total acquisition costs for cladribine could be calculated using an average weight derived from the distribution of patient weights in the CLARITY 3.5mg/kg cladribine arm. This approach results in a total annual acquisition cost of £26,619.06 for cladribine tablets, whether using the company’s estimated mean weight of [redacted]kg or the EAG’s mean weight of [redacted]kg.”	The company propose the removal of this sentence unless the EAG meant to explore the use of the mean weight of the CLARITY patients in the cladribine 3.5 mg/kg treatment arm (n=433) in contrast with the mean weight from both placebo and cladribine 3.5 mg/kg treatment arm (n=870) as estimated and used by the company. In this case, calculations should be performed with the reported mean weight for the cladribine 3.5 mg/kg treatment arm only (i.e., 68.1kg)	Considering the recommended cumulative dose of 3.5 mg/kg body weight over 2 years, a patient weighing [redacted] kg would require approximately 12 tablets per year to achieve the target dose (i.e., 3.5 mg x [redacted] → [redacted] mg over 2 years, requiring 24 x 10 mg tablets).	Amended.
Page 117: "In the company’s base case, a weight of 110kg was assumed for this group, leading to an estimated per-patient total acquisition cost	The company propose the wording on page 117 is edited to read: "In the company’s base case, a weight of 110kg was assumed for this group, leading to an estimated per-patient total acquisition cost of approximately	The company’s and EAG’s estimates differ because the latter uses rounded proportion values for calculations. This should be clarified so as not to lead to misinterpretation of a	Amended.

of approximately £25,986 (£25,953 according to the company's calculations)."	£25,986 (£25,953 when not using rounded values as calculated by the company)."	potential error in the company's calculation.	

Issue 7 Nurse time to train patients in self-administration of injectable DMTs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20: "The company estimated that 3 hours of nurse time is required for a one-time training of patients on how to self-inject. This was applied to DMTs that require injection, including glatiramer acetate, interferon betas, teriflunomide, and ofatumumab. EAG's clinical advice indicates that training patients to self-inject DMTs is conducted by company-sponsored nurses, meaning it does not represent an opportunity cost for the NHS. Therefore, EAG adjusted the	The company propose that the EAG report is amended to reflect that even though some companies sponsor nurses to support training for patient, it is not appropriate to include this in the cost-effectiveness model as the model analyses should reflect NHS and PSS costs, as per the NICE reference case.	The company considers it is inappropriate for the EAG to assume that the one-time training provided to patients treated with self-inject DMTs is conducted by company-sponsored nurses. While this may be true in some cases, it is inappropriate to assume this service applies to all patients or that it will continue to be provided by companies indefinitely into the future. Importantly, the NICE reference case states that cost-effectiveness analyses should reflect a NHS and PSS cost perspective, which	No change. Not factual error.

model to set the nurse training visits in the first year after treatment initiation to zero for patients on injectable DMTs requiring self-administration." Page 124: "Instead, injection techniques are taught by company-led nurses, not neurologists. Since this training is provided by company-led nurses, the associated costs should not represent an opportunity cost for the NHS and, therefore, should not be included in the modelling"		does not include cases of company-sponsored nursing.	

Issue 8 Treatment monitoring (neurology consultations and MRI scans) beyond the first-year of treatment initiation.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 118: "Based on this advice, the EAG interpreted that MRI scans and regular neurology visits are necessary for monitoring disease activity in cladribine-treated patients. However, the company's model included one MRI scan and two neurology visits in the first year of treatment only. The EAG believes that these monitoring practices (1 MRI and 2 neurology visits per year) should extend beyond the first year of treatment, covering the entire period during which the patient remains on cladribine."	The company propose that this interpretation of monitoring requirements for cladribine are removed.	The company disagree with the EAG's interpretation regarding the necessity for annual MRI scans and neurology visits for patients treated with cladribine beyond the first year of treatment. The ABN (Association of British Neurologists) guidelines for prescribing disease-modifying treatments in multiple sclerosis (2015) do not explicitly recommend annual MRI scans and neurological monitoring for patients on DMTs. The ABN indicates that while MRI monitoring is becoming more common, it is not a mandated annual	No change. Not factual error.

		requirement for DMT monitoring: "In Europe and the USA, it is common practice to use MRI to monitor disease activity in patients on disease-modifying treatments. This is increasingly part of regular practice in the UK and may help in decisions concerning either the escalation or the stopping of treatments." The guidelines further acknowledge: "There is limited direct evidence upon which to base the frequency of imaging, and we require more research on this topic." The company believe that extending the requirement for annual MRI scans and neurology visits is not supported by current clinical guidelines or evidence. Please note, the company do not consider this a key issue	

		as the impact on cost-effectiveness is not considered to be significant.	
Page 21: "The EAG's clinical advice suggests that cladribine, as an immune reconstitution therapy (IRT) similar to alemtuzumab (another IRT used for RRMS), necessitates regular monitoring with clinical and MRI assessments to detect MRI activity or relapse"	The company propose the wording is edited to read: The EAG's clinical advice suggests that cladribine, as an immune reconstitution therapy (IRT) similar to alemtuzumab (IRT used for **highly-active** RRMS), necessitates regular monitoring with clinical and MRI assessments to detect MRI activity or relapse	The comparison with alemtuzumab is not fully accurate, as its population i.e. highly active RRMS, is more restricted than the population for cladribine tablets.	Amended.

Issue 9 EAG06: First-year monitoring costs (neurology appointments) for patients on glatiramer acetate and the beta interferons.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 124: "Further clinical advice (Table 33) suggests that standard practice for patients on glatiramer	N/A	Although clinical practice may vary across the UK, the company believe that is very unlikely that patients on glatiramer acetate, beta interferon, and teriflunomide	No change

acetate, beta interferon, and teriflunomide does not typically include two neurology visits in the first year of treatment”		will not be supervised by a neurologist or a physician experienced in the treatment of MS during the first year of receiving these DMTs. Please note, the company do not consider this a key issue as the impact on cost-effectiveness is not considered to be significant.	

Issue 10 Factual inaccuracies in EAG report not related to the key 9 issues summarised in Section 1.3. of the report (1.3. The decision problem: summary of the EAG’s key issues)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13: “Overall, the technology is modelled to affect costs by: • One-off drug acquisition, administration and monitoring costs”	The company propose the wording is edited to read: “Overall, the technology is modelled to affect costs by: • One-off drug acquisition and monitoring costs”	This is inaccurate. There are no administration costs for cladribine.	No change. Not factual error.

Page 32: "Appendix D, section 1.1.1.2, and Table 7 (pages 27-30, Document B) in the CS reported the full list of included and excluded studies. The EAG team counted 22 excluded (Red) and 39 included (Green) studies, which do not correspond to the numbers reported in the PRISMA diagram (Figure 1, page 25, Document B)."	The company propose the wording on is edited to read: "Appendix D, section 1.1.1.2, and Table 7 (pages 27-30, Document B) in the CS reported the full list of included and excluded studies. The EAG team counted 22 excluded (Red) and 39 included (Green) studies, which do not correspond to the numbers reported in the PRISMA diagram (Figure 1, page 25, Document B). However, at clarification stage, the company explained that in the original submission, one study (Mokhber 2014) study was mistakenly included in the list of studies included in the NMA. The number of studies in the NMA is 38 (not 39 as initially stated). The company corrected this across the submission documents."	This is inaccurate. At clarification stage, in response to question A4, the company explained that: *"…one study (Mokhber 2014) study was mistakenly included in the list of studies included in the NMA. This has been corrected, therefore, the number of studies in the NMA is 38 (not 39 as initially stated). All necessary changes were introduced in the CS documents."*	The full list of studies (according to SR method) should include all included and excluded studies. Additionally, the table titled 'List of studies included in the SLR', and expecting the report of 61 included studies.

Page 32: "Additionally, Table 7 does not include the CLARITY-EXT trial, and no justification for its exclusion was provided."	The company propose that the whole sentence is removed.	This is inaccurate. At clarification stage, in response to question A8, the company explained that: *"…The CLARITY-EXT trial is a secondary publication of the CLARITY trial. (…) since both studies are linked and share the same methodology, the critical appraisal is performed for only the primary study (which in this case is CLARITY trial)."* As such, CLARITY-EXT is not included in Table 7 nor in other Tables/Figures focusing only on trials identified in the SLR.	This is a reporting style issue and not a factual inaccuracy. Usually in SLR, all studies with same author and population are clearly mentioned and assessed. Text removed.

Page 32: “However, the items of the data extraction template (such as population characteristics, intervention details, and outcome details) were not clearly reported”	The company propose that the whole sentence is removed.	This is inaccurate. The company shared the extraction grid with all the study details provided as a separate document (“Merck_Clinical_Data Extraction Grid_inception-2024”).	It was extremely challenging to follow the file template. It remains unclear. t

Page 50: "Amongst 61 RCTs identified by the SLR searches, there were only two CLARITY (n=1,326)[31] (Merck Group. CLARITY GEVD Re-Analysis. Data on file.; 2017.) and CLARITY-EXT (n=806) (Merck Group. CLARITY-EXT GEVD Re-Analysis. Data on file.; 2017.) trials which evaluated cladribine tablets (3.5 mg/kg) as a monotherapy for the treatment of patients with active RRMS."	The company propose the wording is edited to read: Amongst 61 RCTs identified by the SLR searches, one study, CLARITY (n=1,326)[31] (Merck Group. CLARITY GEVD Re-Analysis. Data on file.; 2017), evaluated cladribine tablets (3.5 mg/kg) as a monotherapy for the treatment of patients with active RRMS. Upon completion of CLARITY, patients were then eligible for entry into extension trial, CLARITY-EXT (n=806) (Merck Group. CLARITY-EXT GEVD Re-Analysis. Data on file.; 2017.), in which they were rerandomised to receive cladribine tablets 3.5 mg/kg or placebo.	This is inaccurate. CLARITY-EXT is a secondary publication of CLARITY and is not among the 61 RCTs identified the SLR.	Amended.

Page 51: "The summary of 39 trials included in the NMA by their contribution to each NMA outcome, are presented in Table 9 of the EAG report."	The company propose the wording is edited to read: "The summary of **38** trials included in the NMA by their contribution to each NMA outcome, are presented in Table 9 of the EAG report."	This is inaccurate. The number of studies included in the NMA was 38 (this was corrected at clarification stage). Mokhber 2014 study was not included in the NMA. The updated study list was included in the re-submitted CS (2 August 2024).	Amended.
Page 51, Table 9: The table includes Mokhber 2014 study.	The company propose to remove the row with Mokhber 2014 study from the Table 9.		Amended.
Page 57: "The patient mean age across the 39 studies included in the review did not notably differ."	The company propose the wording is edited to read: "The patient mean age across the **38** studies included in the review did not notably differ."		Amended.
Page 32: "The company mentioned that the included studies were critically appraised using the NICE manufacturer template (Appendix D, section 1.1.2). However, a complete analysis of quality assessment (QA) and its implications on the final	The company propose the wording is edited to read: "The company mentioned that the included studies were critically appraised using the NICE manufacturer template (Appendix D, section 1.1.2). However, a complete analysis of quality assessment (QA) and its implications on the final synthesis was not reported. When the	This is inaccurate. At clarification stage, in response to question A5, the Quality Assessment was performed for the 61 clinical studies (presented in Table 18, Appendix D.1.3). However, there were 802 publications referring to these studies (multiple publications	The quality assessment was conducted for all 61 trials identified in the SLR. However, the total number of publications was 802. The supplementary Excel file named: *Merck_Clinical_NICE quality assessment."*— section from the clarification response

synthesis was not reported. When the EAG sought clarification, the company replied that the Excel file : Merck_Clinical_NICE quality assessment evaluated 61 trials from 802 publications. However, QA details were not provided for the 801 publications included in the SLR.”	EAG sought clarification, the company replied that the Excel file : Merck_Clinical_NICE quality assessment evaluated 61 trials from 802 publications and explained that there were multiple publications supporting the same study and that QA was performed only for the primary publications for the clinical trials.”	supporting the same study) and as such it was not deemed necessary to conduct a quality assessment on all 802 studies.	was considered. It remains unclear that this was carried out for the primary study.
Page 38: “The clarification document noted that both studies were conducted by Merck and contribute to the evidence base for oral cladribine tablets, providing supplementary safety data. However, the full methodology, including the dosage regimen, was not described.”	The company propose to remove or amend this comment as it implies the company did not share requested data.	The company would like to highlight that the full methodology, including the dosage regimen, was not requested in the clarification document. Clarification Question A6 only asked: “A6. Document B, page 35: Could you clarify how the safety evidence trials were identified, such as ORACLE MS, PREMIERE?”	Amended.
Page 98: “The company's base case analysis is conducted in accordance with NICE	The company propose the wording is edited to read: “The company's base case analysis is conducted in accordance with NICE	As stated in the CS, Document B, Table 28 (and throughout the CS) the time horizon	Not factual inaccuracy

methods guidelines for technology appraisals [95]. It adopts the following perspective: the National Health Service (NHS) and Personal Social Services (PSS) for cost considerations, and the patient and caregiver for quality-adjusted life years (QALYs). The analysis uses a lifetime horizon of 60 years, assuming a starting age of 38. Both costs and QALYs are discounted at an annual rate of 3.5%. The EAG notes that about 20% of patients remain alive in the model after 50 years."	methods guidelines for technology appraisals [95]. It adopts the following perspective: the National Health Service (NHS) and Personal Social Services (PSS) for cost considerations, and the patient and caregiver for quality-adjusted life years (QALYs). The analysis uses a lifetime horizon of **50 years**, assuming a starting age of 38. Both costs and QALYs are discounted at an annual rate of 3.5%. The EAG notes that about 20% of patients remain alive in the model after 50 years."	chosen for this appraisal is 50 years.	
Page 98: "Therefore, the EAG recommends extending the time horizon to 60 years, by which point less than 1% of patients would be alive under the company's base-case assumptions. While this change is unlikely to significantly impact cost-effectiveness, it ensures that	N/A	The company would like to highlight the following points: • As noted by the EAG, the company followed the NICE methods guidelines for technology appraisals [95] • The 50 year time horizon is in line with NICE precedent, i.e.,	NA

all costs and benefits of DMTs are fully captured by the model.”		time horizon of 50 years was used in NICE appraisals of other RRMS treatments including Interferon-beta and glatiramer acetate (TA527), Ocrelizumab (TA533), Peginterferon (TA624), Ponesimod (TA767) (as summarised in the CS, Document B, Table 28) • A 50 year time horizon is in line with the previous NICE appraisal of Cladribine tablets (TA493/ TA616). Where possible, the company decided to follow a similar approach, as it was previously accepted by NICE committee. • Moreover, although approximately 18% of patients remain alive at a time horizon of 50 years, less than 1% of	

		these patients are still on a DMT, meaning that only a very small proportion of patients are incurring DMT-related costs and treatment effects at a time horizon of 50 years As such, the impact on cost-effectiveness is not considered to be significant.	
Page 100: "At first, the EAG is concerned with the cladribine's superior performance compared to other DMTs predicted by the modelling. EAG thinks this inconsistent with the risk ratios for DMTs versus placebo generated from the company's NMAs (Table 22). Ofatumumab (RR=0.30) and Ocrelizumab (RR=0.36) are, on average, better were at reducing relapses than Cladribine (RR=0.42)	N/A	The company would like to highlight the following points: • As noted by the EAG, the long-term cumulative clinical benefit of reducing relapses and disease progression varies from cladribine and other DMTs based on the treatment effect estimates from the NMA and discontinuation rates (i.e., how long the patient is being treated	NA

compared with placebo. However, this is not reflected in the model as shown in graphs displayed in Figure 20, where Cladribine appears to perform better on average in reducing relapses. Although the credible intervals suggest that the rate ratios for Cladribine versus Ocrelizumab or Ofatumumab are not statistically significant (see Table 33, CS document B, page 114), the discrepancies between the relapse rates for different comparators indicate that efficacy alone may not be the sole driver of treatment benefit in the company's economic modelling."		still benefiting from the DMT treatment effect). • Although it is correct that long-term clinical efficacy from highly effective therapies (and any other DMTs in the model) is directly related to when the patient discontinues the treatment, it is worth mentioning that total DMT-related costs are also linked to discontinuation estimates, directly impacting the model results. As explored in scenario S5b, when discontinuation is halved for high efficacy therapies after the two initial treatment years, cladribine still remains dominant versus these therapies with lower positive incremental QALYs (i.e., more effective) and higher	
Page 102: The company's model base-case assumptions predicts that cladribine will perform better on average in reducing relapses and disease progression compared to all the comparator DMTs.			NA

However, this is not consistent with the clinical efficacy data generated by the company's NMA. Based on the NMA results for ARR and 6-month CDP outcomes alone, the EAG would expect high-efficacy comparator DMTs such as ocrelizumab and ofatumumab to perform better on average than cladribine in reducing relapses and disease progression. Where this is not the case, then the only other factor that might influence treatment efficacy is treatment discontinuation. In the model, patients automatically move to BSC after discontinuing DMT. Highly effective therapies could have their long-term clinical efficacy compromised if a significant number of patients discontinue treatment.		negative incremental costs (i.e., less costly) than the base-case estimates.	
Page 131			NA

“For example, despite cladribine having a numerically worse annualised relapse rate ratio and 6m-CDP compared to ocrelizumab, the model predicted that cladribine was more effective in preventing relapses and slowing disease progression over the 50-year modelled time horizon. The EAG’s investigation suggested that this discrepancy was due to the assumptions and data used to inform treatment discontinuation in the model”			

Page 131: "However, the EAG prefers to use probabilities of treatment discontinuation based on published UK data that provide real-world evidence on the persistence of DMTs among people with multiple sclerosis."	Please see response to 'Issue 3 Treatment discontinuation' in this document	Please see response to 'Issue 3 Treatment discontinuation' in this document	
Page 134: "In the EAG's base-case, the exponential distribution was selected as the source of treatment discontinuation probabilities because this distribution generated probabilities that closely matched those observed in UK data for alemtuzumab, used as external reference data."			NA

Issue 11 Typographical errors, formatting errors and minor text alterations

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAG</th></tr>
<tr>
<td>Table 1 (page 12) provides a different numbering of issues versus the overview of issues listed in Executive Summary (starting from page 14):
<table>
<tr><th>ID 16263</th><th>Summary of issue</th><th>Report sections</th></tr>
<tr><td>Issue 1</td><td>The NMA results should be interpreted with caution</td><td>3.4.3</td></tr>
<tr><td>Issue 2</td><td>Potential error in the company’s method for deriving treatment discontinuation probabilities from the NMA of RCT data, particularly when real-world evidence on DMT persistence is available.</td><td>3.5.1.1</td></tr>
<tr><td>Issue 3</td><td>Estimating treatment discontinuation based solely on RCT data may not reflect real-world conditions.</td><td>3.5.1.2, 4.2.5.3, 4.2.5.4, 4.2.5.5, 4.2.5.6 & 4.2.5.7</td></tr>
<tr><td>Issue 4</td><td>The model does not allow for cladribine discontinuation after year 2 if patients switch to another DMT after completing the cladribine course.</td><td>3.5.1.2, 4.2.5.3</td></tr>
<tr><td>Issue 5</td><td>Inconsistent application of treatment waning assumptions between cladribine and competitor DMTs.</td><td>4.2.5.8 & 4.2.5.9</td></tr>
<tr><td>Issue 6</td><td>A fixed standardised mortality assumption does not align with the natural history of RRMS.</td><td>4.2.5.9.1 & 4.2.5.10</td></tr>
<tr><td>Issue 7</td><td>Miscalculation in the acquisition costs of cladribine tablets.</td><td>4.2.7.1 & 4.2.7.2</td></tr>
<tr><td>Issue 8</td><td>Incomplete consideration of monitoring costs for cladribine</td><td>4.2.7.3 & 4.2.7.4</td></tr>
</table>
</td>
<td>The company propose the following summary table with corrected issues numbering:
<table>
<tr><th>ID 16263</th><th>Summary of issue</th><th>Report sections</th></tr>
<tr><td>Issue 1</td><td>The population include RRMS</td><td>2.3</td></tr>
<tr><td>Issue 2</td><td>The NMA results should be interpreted with caution</td><td>3.4.3</td></tr>
<tr><td>Issue 3</td><td>Estimating treatment discontinuation based solely on RCT data may not reflect real-world conditions.</td><td>3.5.1.2, 4.2.5.3, 4.2.5.4, 4.2.5.5, 4.2.5.6 & 4.2.5.7</td></tr>
<tr><td>Issue 4</td><td>Inconsistent application of treatment waning assumptions between cladribine and competitor DMTs.</td><td>4.2.5.8 & 4.2.5.9</td></tr>
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<tr><td>Issue 7</td><td>Nurse time to train patients in self-administration of injectable DMTs</td><td>4.2.7.1 & 4.2.7.2</td></tr>
<tr><td>Issue 8</td><td>Incomplete consideration of monitoring costs for cladribine beyond the first year of treatment.</td><td>4.2.7.2</td></tr>
</table>
</td>
<td>Inconsistent numbering of issues in the document</td>
<td>Updated.</td>
</tr>
</table>

	beyond the first year of treatment.		Issue 9	First-year monitoring costs (neurology appointments) for patients on glatiramer acetate and the beta interferons.	4.2.7.2
Issue 9	Resources for ongoing monitoring competitor DMTs are not aligned with UK/NHS clinical practice	4.2.7.3 & 4.2.7.4			
Page 49: Only 9.2% od LLPP patient required rescue treatment.			Proposed change: Only 9.2% **of** LLPP patient required rescue treatment.		Typographical error	Done
Page 61: Moreover, the NMA results numerically favoured cladribine tablets over dimethyl fumarate (RR=1.26, 95% CrI: 0.93, 1.75) and ponesimod (RR=1.14, 95% CrI: 0.76, 1.71).			Proposed change: Moreover, the NMA results numerically favoured cladribine tablets over dimethyl fumarate (RR=**1.28**, 95% CrI: 0.93, 1.75) and ponesimod (RR=1.14, 95% CrI: 0.76, 1.71).		Wrong RR value provided for dimethyl fumarate	Done
Page 64: The cladribine tablets were numerically favoured in terms of reduced risk of 3-month CDP compared to teriflunomide 14 mg (HR=[redacted])			Proposed change: The cladribine tablets were numerically favoured in terms of reduced risk of 3-month CDP compared to teriflunomide 14 mg (HR=[redacted])		Wrong HR value provided for teriflunomide 14 mg	Done

Page 92, Table 18: The EAG comment on company's submission is missing in the row "Source of data for measurement of health-related quality of life"	The company propose to add the missing EAG comment	Missing value in the table	Added
Page 95: This includes a sample size of 870, with a mean age of 37.7 years,	Proposed change: This includes a sample size of 870, with a mean age of 38.7 years,	Wrong value provided for mean age at treatment	Done
Page 96: "The weight distribution appears approximately normal with a mean weight of around [redacted] kg (Figure 16)."	Proposed change: "The weight distribution appears approximately normal with a mean weight of around [redacted] kg (Figure 16)."	Wrong value provided for mean weight	Done
Page 101: Ocrelizimab (HR versus placebo =[redacted]), IFNβ-1a (HR=[redacted]), IFNβ-1b (HR=[redacted]) and ofatumumab (HR=[redacted]).	Proposed change: **Ocrelizumab** (HR versus placebo =[redacted]), IFNβ-1a (HR=[redacted]), IFNβ-1b (HR=[redacted]) and ofatumumab (HR=[redacted])	Typographical error	Done
Page 111: Cladribrine remained dominant over the remaining competitor DMTs.	Proposed change: **Cladribine** remained dominant over the remaining competitor DMTs.	Typographical error	Section ame

Page 110-112 Section “4.2.5.9 EAG critique: Treatment waning” duplicates almost all content/sentences from “section 4.2.5.8 Treatment waning”	Proposed change: Review and update these sections if needed	Duplicate error	Section revis
Page 115: “In the company’s base-case, SPMS disutility is set at [redacted] and is estimated from the Orme et al 2006 study [102] (Section H.1.3.4 of Appendix H of CS) as the regression coefficient associated with SPMS compared with RRMS. Table 35 displays the utility values derived for SPMS health states stratified by EDSS score. **Table 1. Quality of life values used in the company’s base-case”**	Proposed change: “In the company’s **21-health state model structure scenarios,** SPMS disutility is set at [redacted] and is estimated from the Orme et al 2006 study [102] (Section H.1.3.4 of Appendix H of CS) as the regression coefficient associated with SPMS compared with RRMS. Table 35 displays the utility values derived for SPMS health states stratified by EDSS score. **Table 2. Quality of life values used in the company’s 21-health state model structure scenarios”**	SPMS disutility is not used in the base case analysis as there is no distinction between RRMS and SPMS in the 11-health state model structure. SPMS disutility was only used in the scenarios (S1a and S1b) with a 21-health state model structure.	Revised
Page 115:	Proposed change: Review and update these sections if needed	Incomplete sentence error	Removed

“The impact of combining patient quality of life and caregiver disutility to provide an overall quality of life score, stratified by EDSS health state and form of MS (RRMS versus SPMS).”			
Page 118: “Monitoring are estimated based on resources consume and include Monitoring costs comprise biochemistry tests, complete blood counts, human papilloma virus (HPV) tests, MRI scans, thyroid function tests, tuberculin skin tests, urinalysis, hepatitis B and C virus testing, John Cunningham’s (JC) virus testing, and visits to health care practitioners to support the monitoring of DMT”	Proposed change: “Monitoring **costs** are estimated based on resources **consumed** and include biochemistry tests, complete blood counts, human papilloma virus (HPV) tests, MRI scans, thyroid function tests, tuberculin skin tests, urinalysis, hepatitis B and C virus testing, John Cunningham’s (JC) virus testing, and visits to health care practitioners to support the monitoring of DMT”	Typographical error	Revised
Page: 126 “The company's deterministic base case estimates the discounted costs presented presented in Table 35.”	Proposed change: “The company's deterministic base case estimates the discounted costs presented in Table 35”	Duplicate error	Done

Page 126: “Overall, cladribine is estimated to increase the average cost per patient by [redacted] compared with BSC (Table 36).”	Proposed change: “Overall, cladribine is estimated to increase the average cost per patient by [redacted] compared with BSC (Table 36).”	Wrong value	Done
Page 127: “At list prices, the deterministic ICER is [redacted] per QALY gained when compared with BSC, and it ranges from [redacted] to [redacted] per QALY gained when compared with the interferon group of DMTs.”	Proposed change: “At list prices, the deterministic ICER is [redacted] per QALY gained when compared with BSC, and it ranges from [redacted] to [redacted] per QALY gained when compared with the interferon group of DMTs.”	Wrong value	Done
Page 127: The probabilistic modelling yields a similar central cost-effectiveness estimate of [redacted] per QALY compared with BSC, with cladribine having a [redacted] probability of being cost-effective at a £20,000/QALY threshold and a [redacted] probability at a £30,000/QALY threshold (Figure 24 and Figure 25).	Proposed change: The probabilistic modelling yields a similar central cost-effectiveness estimate of [redacted] per QALY compared with BSC, with cladribine having a [redacted] probability of being cost-effective at a £20,000/QALY threshold and a [redacted] probability at a £30,000/QALY threshold (Figure 24 and Figure 25).	Wrong value	Done

Page 128: “In contrast, the probability that ponesimod, ofatumumab, or ocrelizumab are the optimal cost-effective strategies in this population ranges from [redacted] to [redacted] at the same thresholds.”	Proposed change: “In contrast, the probability that ponesimod, ofatumumab, or ocrelizumab are the optimal cost-effective strategies in this population ranges from [redacted] to [redacted] at the same thresholds.”	Wrong value	Done
Page 130: “The company also presents a range of scenarios in Table 61 of CS Document B, focusing on the comparison with high-efficacy DMTs (Ponesimode, ofatumumab and ocrelizumab). For completeness, the results of the company’s scenario analyses are reproduced below in Table 38.”	Proposed change: “The company also presents a range of scenarios in Table 61 of CS Document B, focusing on the comparison with high-efficacy DMTs (**ponesimod**, ofatumumab and ocrelizumab). For completeness, the results of the company’s scenario analyses are reproduced below in Table 38.”	Typographical error	Done
Page 133: Table 40. EAG’s deterministic base-case assumptions Cladribine Tables (Total discounted / Costs) [redacted]	Proposed change: Table 40. EAG’s deterministic base-case assumptions Cladribine Tables (Total discounted / Costs) [redacted]	Typographical error	Done

BSC (Total discounted / Costs) [redacted]	BSC (Total discounted / Costs) [redacted]		
Page 133: "For all other DMTs, the ICER ranged from [redacted] for compared with Dimethyl fumarate to [redacted] compared with IFNβ-1a (Peginterferon beta-1a)"	Proposed change: For all other DMTs, the ICER ranged from [redacted] for compared with Dimethyl fumarate to [redacted] compared with **IFNβ-1b (Betaferon/Extavia)**"	Reporting error	Done

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
Page 43, Section 3.2.2	The CIC marking currently provided is insufficient: "Similar to CLARITY, the CLARITY-EXT has 68.4% of female patients"	Please update the CIC marking to this text as provided: "Similar to CLARITY, the CLARITY-EXT has [redacted] of female patients"	Done

Page 47, Section 3.2.5.5	The CIC marking currently provided is insufficient: "It was found that in the LLPP group, patients who received a cumulative dose of 3.5 mg/kg cladribine tablets over 4 years, including data from the CLARITY trial, had an ARR of 0.15 (95% CI: 0.11, 0.21). During the CLARITY-EXT trial, the ARR was numerically higher in the LLPP treatment group compared to the CLARITY group, although this difference was not statistically significant (p=0.4526)."	Please update the CIC marking to this text as provided: "It was found that in the LLPP group, patients who received a cumulative dose of 3.5 mg/kg cladribine tablets over 4 years, including data from the CLARITY trial, had an ARR of [redacted] During the CLARITY-EXT trial, the ARR was numerically higher in the LLPP treatment group compared to the CLARITY group, although this difference was not statistically significant (p=[redacted])."	Lena

Page 48, Section 3.2.5.7	The CIC marking currently provided is insufficient: “By week 48, [redacted] of patients had no CU lesions, but this proportion decreased to 34.7% by week 96”	Please update the CIC marking to this text as provided: “By week 48, [redacted] of patients had no CU lesions, but this proportion decreased to [redacted] by week 96”	Done
Page 48, Section 3.2.5.7	The CIC marking currently provided is insufficient: “This reduction continued at week 96, with a further decrease of [redacted] mm³. For active T2 lesions, a substantial reduction was observed: a decrease of 1,068.9 mm³ at week 48 and an additional reduction of [redacted] mm³ at week 96.”	Please update the CIC marking to this text as provided: “This reduction continued at week 96, with a further decrease of [redacted] mm³. For active T2 lesions, a substantial reduction was observed: a decrease of [redacted] mm³ at week 48 and an additional reduction of [redacted] mm³ at week 96.”	Done

Page 48, Section 3.2.5.8	The CIC marking currently provided is insufficient: "CS reported that, in the CLARITY EXT trial, 38.8% of patients in the LLPP group achieved NEDA-3 at Year 1, while 23.5% reached this milestone by Year 2"	Please update the CIC marking to this text as provided: "CS reported that, in the CLARITY EXT trial, [redacted] of patients in the LLPP group achieved NEDA-3 at Year 1, while [redacted] reached this milestone by Year 2."	Done
Page 49, Section 3.2.5.9	The CIC marking currently provided is insufficient: "Only 9.2% of LLPP patient required rescue treatment."	Please update the CIC marking to this text as provided: "Only [redacted] of LLPP patient required rescue treatment."	Done
Page 61, Section 3.3.7.1	The CIC marking currently provided is insufficient: "According to Figure 7 (DMT comparator vs. cladribine), treatment with cladribine tablets	Please update the CIC marking to this text as provided: "According to Figure 7 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with a significantly greater reduction in ARR compared with placebo (RR=[redacted]), teriflunomide 14 mg (RR=[redacted]), teriflunomide 7 mg (RR=[redacted]), glatiramer acetate 20 mg (RR=[redacted]), glatiramer acetate 40 mg (RR=[redacted]), peginterferon (RR=[redacted]), interferon beta-1a 22 µg (RR=[redacted]), interferon beta-1a 44 µg (RR=[redacted]), interferon beta-1a 30 µg (RR=[redacted]) and interferon beta-1b 250 µg (RR=[redacted]). Moreover, the NMA results numerically favoured cladribine	done

	was associated with a significantly greater reduction in ARR compared with placebo (RR=[redacted]), teriflunomide 14 mg (RR=[redacted]), teriflunomide 7 mg (RR=[redacted]), glatiramer acetate 20 mg (RR=[redacted]), glatiramer acetate 40 mg (RR=[redacted]), peginterferon (RR=[redacted]), interferon beta-1a 22 µg (RR=[redacted]), interferon beta-1a 44 µg (RR=[redacted]), interferon beta-1a 30 µg (RR=[redacted]) and interferon beta-1b 250 µg (RR=[redacted]). Moreover, the NMA results numerically favoured cladribine tablets over dimethyl fumarate (RR=[redacted], 95% CrI: [redacted], [redacted]) and ponesimod	tablets over dimethyl fumarate (RR=[redacted]) and ponesimod (RR=[redacted]). According to this network results for ARR, cladribine tablets ranked [redacted] following [redacted] and [redacted].”	

	(RR=[redacted], 95% CrI: [redacted], [redacted]). According to this network results for ARR, cladribine tablets ranked [redacted] following [redacted] (RR=[redacted], 95% CrI: [redacted], [redacted]) and [redacted] (RR=[redacted], 95% CrI: [redacted], [redacted]).”		
Page 64, Section 3.3.7.2	The CIC marking currently provided is insufficient: “According to Figure 9 (DMT comparator vs. cladribine), the risk for 3-month CDP was not statistically significantly different between treatment with cladribine tablets vs. all DMTs, but it was significantly lower for cladribine tablets vs. placebo (HR=[redacted],	Please update the CIC marking to this text as provided: “According to Figure 9 (DMT comparator vs. cladribine), the risk for 3-month CDP was not statistically significantly different between treatment with cladribine tablets vs. all DMTs, but it was significantly lower for cladribine tablets vs. placebo (HR=[redacted]). The cladribine tablets were numerically favoured in terms of reduced risk of 3-month CDP compared to teriflunomide 14 mg [redacted]), teriflunomide 7 mg [redacted] interferon beta-1b 250 µg [redacted] interferon beta-1a 30 µg ([redacted] glatiramer acetate 20 mg ([redacted] interferon beta-1a 22 µg (HR=1.08), interferon beta-1a 44 µg ([redacted]), and dimethyl fumarate ([redacted]). Compared to cladribine tablets, treatment with three DMTs: ocrelizumab ([redacted] ofatumumab ([redacted]), and ponesimod ([redacted]) were associated with numerically lower risk of 3-month CDP”	Done

	95% CrI: [redacted], [redacted]). The cladribine tablets were numerically favoured in terms of reduced risk of 3-month CDP compared to teriflunomide 14 mg (HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), interferon beta-1b 250 µg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), interferon beta-1a 22 µg (HR=[redacted]), interferon beta-1a 44 µg (HR=[redacted]), and dimethyl fumarate (HR=[redacted]). Compared to cladribine tablets, treatment with three DMTs: ocrelizumab (HR=[redacted]), ofatumumab (HR=[redacted]), and		

	ponesimod (HR=[redacted]) were associated with numerically lower risk of 3-month CDP”		
Page 65, Section 3.3.7.3	The CIC marking currently provided is insufficient: “According to Figure 11 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with numerically (although not statistically significantly different) lower risk of 6-month CDP compared to dimethyl fumarate (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), interferon	Please update the CIC marking to this text as provided: “According to Figure 11 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with numerically (although not statistically significantly different) lower risk of 6-month CDP compared to dimethyl fumarate ([redacted]), glatiramer acetate 20 mg ([redacted] interferon beta-1a 30 µg ([redacted] interferon beta-1a 44 µg [redacted]), teriflunomide 14 mg [redacted]), teriflunomide 7 mg [redacted]), and ponesimod [redacted] Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for 6-month CDP following [redacted]	Done

	beta-1a 44 µg (HR=[redacted]), teriflunomide 14 mg (HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), and ponesimod (HR=[redacted]). Overall, cladribine tablets ranked [redacted] when evaluated in the NMA for 6-month CDP following [redacted] (HR=[redacted]), [redacted] (HR=[redacted]), [redacted] (HR=[redacted]) and [redacted] (HR=[redacted]).”		
Page 69, Section 3.3.7.4	The CIC marking currently provided is insufficient: “According to Figure 13 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with	Please update the CIC marking to this text as provided: “According to Figure 13 (DMT comparator vs. cladribine), treatment with cladribine tablets was associated with a significantly lower risk of treatment discontinuation than interferon beta-1a 44 µg (HR=[redacted]). Moreover, treatment with cladribine tablets was associated with numerically (although not statistically significantly) lower risk of treatment discontinuation compared to dimethyl fumarate (HR=[redacted]), ofatumumab (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), glatiramer acetate 40 mg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]_teriflunomide 14 mg (HR=[redacted]), interferon beta-1b 250 µg	Done

	a significantly lower risk of treatment discontinuation than interferon beta-1a 44 µg (HR=[redacted], 95% CrI: [redacted], [redacted]). Moreover, treatment with cladribine tablets was associated with numerically (although not statistically significantly) lower risk of treatment discontinuation compared to dimethyl fumarate (HR=[redacted]), ofatumumab (HR=[redacted]), glatiramer acetate 20 mg (HR=[redacted]), glatiramer acetate 40 mg (HR=[redacted]), interferon beta-1a 30 µg (HR=[redacted]), teriflunomide 14 mg (HR=[redacted]), interferon beta-1b 250 µg	(HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), ocrelizumab (HR=[redacted]), placebo (HR=[redacted] diroximel fumerate (HR=[redacted]), and ponesimod (HR=[redacted]).”	

	(HR=[redacted]), teriflunomide 7 mg (HR=[redacted]), ocrelizumab (HR=[redacted]), placebo (HR=[redacted]), diroximel fumerate (HR=[redacted]), and ponesimod (HR=[redacted]).”		
Page 95, Section 4.2.2	The CIC marking currently provided is insufficient: “This includes a sample size of 870, with a mean age of 37.7 years, a female to male ratio of 1.933 (equivalent to 70% female), and a mean of [redacted] relapses in the prior 12 months.”	Please update the CIC marking to this text as provided: “This includes a sample size of 870, with a mean age of 37.7 years, a female to male ratio of 1.933 (equivalent to 70% female), and a mean of [redacted] relapses in the prior 12 months.”	Done
Page 96, Section 4.2.2	The CIC marking currently provided is insufficient: “The weight distribution appears	Please update the CIC marking to this text as provided: “The weight distribution appears approximately normal with a mean weight of around [redacted] (Figure 16).”	Done

	approximately normal with a mean weight of around [redacted] kg (Figure 16)."		
Page 98, Section 4.2.5	The CIC marking currently provided is insufficient: The number of relapses in the first year is based on the observed annualised relapse rate in the placebo arm of the CLARITY study (mean [redacted], 95% CI: [redacted] to [redacted]).	Please update the CIC marking to this text as provided: The number of relapses in the first year is based on the observed annualised relapse rate in the placebo arm of the CLARITY study [redacted]	Done
Page 100, Section 4.2.5.2	The CIC marking currently provided is insufficient: "Ofatumumab (RR=[redacted]) and Ocrelizumab (RR=[redacted]) are, on average, better were at reducing relapses than Cladribine	Please update the CIC marking to this text as provided: "Ofatumumab (RR=[redacted]) and Ocrelizumab (RR=[redacted]) are, on average, better were at reducing relapses than Cladribine (RR=[redacted]) compared with placebo."	Done

	(RR=[redacted]) compared with placebo.”		
Page 101, Section 4.2.5.2	The CIC marking currently provided is insufficient: “Ocrelizumab (HR versus placebo =[redacted]), IFNβ-1a (HR=[redacted]), IFNβ-1b (HR=[redacted]) and ofatumumab (HR=[redacted]) all appear more effective on average than cladribine tablets (HR=[redacted]) at reducing disability progression”	Please update the CIC marking to this text as provided: “Ocrelizumab (HR versus placebo =[redacted], IFNβ-1a (HR=[redacted]), IFNβ-1b (HR=[redacted]) and ofatumumab (HR=[redacted]) all appear more effective on average than cladribine tablets (HR=[redacted]) at reducing disability progression”	Done
Page 102, Section 4.2.5.3	The CIC marking currently provided is insufficient: “The predicted probability of discontinuation for cladribine from the NMA was [redacted]%. However, for	Please update the CIC marking to this text as provided: “The predicted probability of discontinuation for cladribine from the NMA was [redacted]%. However, for patients on cladribine, the company chose not to use the probability of treatment discontinuation predicted by the NMA. The company stated this was to avoid overestimating discontinuation for this therapy, as in the model, tolerability events are only assumed to occur between the first and second courses of treatment. Instead, the company used an estimated probability of 4.85% which is much lower than [redacted]% value generated by the NMA, based on data from the CLARITY study, and applied it in the first two years of the model	Done

	patients on cladribine, the company chose not to use the probability of treatment discontinuation predicted by the NMA. The company stated this was to avoid overestimating discontinuation for this therapy, as in the model, tolerability events are only assumed to occur between the first and second courses of treatment. Instead, the company used an estimated probability of 4.85% which is much lower than [redacted]% value generated by the NMA, based on data from the CLARITY study, and applied it in the first two years of the model time	time horizon. For the other DMTs, the annual probability of treatment discontinuation applied in the model ranged from [redacted]% for ofatumumab to [redacted]% for interferon beta-1a 44 µg (Table 24)."	

	horizon. For the other DMTs, the annual probability of treatment discontinuation applied in the model ranged from [redacted]% for ofatumumab to [redacted]% for interferon beta-1a 44 µg (Table 24)."		
Page 113, Section 4.2.5.9.1	The CIC marking currently provided is insufficient for the **Figure 1. Assumptions about mortality rate used in the economic model. Survival gain from moving from fixed to variable mortality**	Please redact the Figure 23	Done
Page 117, Section 4.2.7.1	The CIC marking currently provided is insufficient for the **Table 3. Annual acquisition costs**	Please redact the Table 31	Done

	of cladribine tablets based on assumptions about then weight distribution in the CLARITY trial		
Page 126, Section 5.1	The CIC marking currently provided is insufficient: "The model predicts that cladribine will result in the fewest relapses, averaging [redacted] per patient, and will accumulate the highest number of QALYs ([redacted]) discounted over a 50-year model time horizon, compared to BSC and other DMTs, including high-efficacy DMTs like ocrelizumab and ofatumumab."	Please update the CIC marking to this text as provided: "The model predicts that cladribine will result in the fewest relapses, averaging [redacted] per patient, and will accumulate the highest number of QALYs ([redacted]) discounted over a 50-year model time horizon, compared to BSC and other DMTs, including high-efficacy DMTs like ocrelizumab and ofatumumab."	Done

Page 127, Section 5.1	The CIC marking currently provided is insufficient for the **Figure 2. Cost-effectiveness acceptability curves cladribine versus BSC at list price**	Please redact the Figure 24	Done
Page 128, Section 5.1	The CIC marking currently provided is insufficient for the **Figure 3. Cost-effectiveness plane: Cladribine versus BSC**	Please redact the Figure 25	Done
Page 129, Section 5.2	The CIC marking currently provided is insufficient for the following item: [redacted] (first row in Table 37)	Please redact the following value: [redacted] (first row in Table 37)	Done
Throughout the document	There are several instances where EAG redact values (especially model	The company is not going to challenge this, as the impact on the submission in minimal.	NA

	results) that were not originally redacted in company's submission.		