# Cladribine for treating relapsing multiple sclerosis [ID6263]

Redacted – for screen

**Technology appraisal committee B, 13th November 2024**

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# Cladribine for treating relapsing multiple sclerosis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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# Cladribine appraisals recap

**Dec 2017**

- **TA493** Cladribine recommended for adults with *highly active* relapsing multiple sclerosis

**Nov 2019**

- **TA616** (Review of TA493 to accelerate uptake)
- Same population as TA493, but removed barriers to accessing cladribine, namely, the requirement for gadolinium-enhancing MRI before treatment

**May 2024**

- Recommendation 1.1 of **TA616** was updated to address concerns that definition of rapidly evolving severe (RES) multiple sclerosis was overly restrictive

**Nov 2024**

- ACM1 for **ID6263**
- Population addressed by company is ‘Adults with active relapsing-remitting multiple sclerosis’
- Won’t consider highly active relapsing multiple sclerosis as this is covered in TA616



Abbreviations: MRI, magnetic resonance imaging.

# Background on multiple sclerosis

Chronic, lifelong, neurological with no cure, resulting in progressive, irreversible disability

**Causes**

- Risk factors include age, female sex, common infections, smoking and vitamin D deficiency

**Epidemiology**

- 130,000 people with MS in the UK, 7,000 new diagnoses annually, onset typically 25-35yrs
- Disproportionately affects women (3 females:1 male)

**Diagnosis and classification**

- Diagnosis using the McDonald criteria, blood tests, lumbar puncture and MRI
- 3 main types of MS: relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS)

**Symptoms and prognosis**

- Pain, fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment
- Progression and prognosis can differ significantly between people
- Disability can accumulate gradually, either due to incomplete recovery from relapse or progression
- Symptoms managed by disease-modifying therapies; aim to reduce frequency of relapses & slow progression



Abbreviations: MRI, magnetic resonance imaging.

# Types of multiple sclerosis

**Primary progressive MS**
- 10-15% people at diagnosis
- Gradual disability progression from onset with no obvious relapses or remission

**Relapsing-remitting MS (RRMS)**
- 85% of people at diagnosis
- Treatment strategy: patient choice, number of relapses, MRI activity and response to previous treatment

50%-60% in 15-20 yrs

**Secondary progressive MS (SPMS)**
- Steady progression of neurological damage with or without relapses
- Comes after RRMS for many people

Active
- At least two clinically significant relapses occur within the last 2 years

Highly active
- 1 relapse in previous year and MRI evidence of disease activity despite treatment with DMT

Rapidly evolving severe (RES)
- 2 or more relapses in the previous year
- baseline MRI evidence of disease activity

TA616

Abbreviations: MRI, magnetic resonance imaging; DMT, disease-modifying therapy.

# Clinical perspectives

## Cladribine is effective, expands access and reduces NHS costs

**Submissions from Association of British Neurologists and clinical expert**

- Cladribine is an effective treatment with minimal appointment and monitoring burden
- Clinical trials indicate that cladribine is effective in those with active disease – current access for highly active or RES, RRMS is restrictive
- Cladribine's low appointment burden expands effective DMT access to travelling communities, those living further from neuroscience centres, those who can't afford time off work for appointments, and allows proactive pregnancy planning
- Could free up NHS resources from reduced appointments and has the possibility to reduce early relapses which saves future costs from earlier complications and worsening disability

*'Wider use of cladribine has the potential to save the NHS money in terms of **effective treatment**, **reduced monitoring costs**, and **reduced complications of long-term immunosuppression**, alongside **reduced longer term disability**'*



Abbreviations: RES, rapidly evolving severe; RRMS, relapsing-remitting multiple sclerosis; DMT, disease-modifying therapy.

# Patient perspectives

## Patients welcome the short-course dosing of cladribine as an additional option

**Submissions from Multiple Sclerosis Trust and patient expert**

- Living with MS is unpredictable and impacts individuals' lives differently
- QoL, from physical and psychosocial, to ability to work, deteriorates
- Diagnosis (commonly between 20 and 40) occurs when individuals are developing careers, starting families and taking on financial obligations
- Progression imposes heavy personal and family informal care burdens
- People with MS need multiple effective DMT options to suit personal needs at different stages of this lifelong condition and following relapses
- Cladribine meets unmet need because it doesn't entail continuous immunosuppression and frequent monitoring, as with other DMTs
- People with MS and neurologists find that access to cladribine has been restrictive and more people could benefit from its minimal administration
- Uncertainty around follow-on treatments leaves much to be understood about care following a four-year course of cladribine

*MS has a reoccurring 'grief cycle' and evidence on cladribine's efficacy "gave me more hope than I had had in many years"*

*'[Cladribine's short administration and long-acting effect] is an attractive feature especially for women of childbearing age'*

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Abbreviations: QoL, quality of life; DMT, disease-modifying therapy.

# Equality considerations

## Cladribine uniquely offers DMT access to groups that other treatments may not

- MS affects women at 2-3 times the rate of men
- Cladribine offers fewer restrictions than comparators for family planning, so a negative recommendation could disproportionately impact younger people
- Delivery burden of cladribine is comparatively insignificant, offering greater access to groups including homeless, travelling communities, disability groups, lower socioeconomic groups, others who find it hard to attend appointments.



Abbreviations: DMT, disease-modifying therapy.

# Treatment pathway for active RRMS

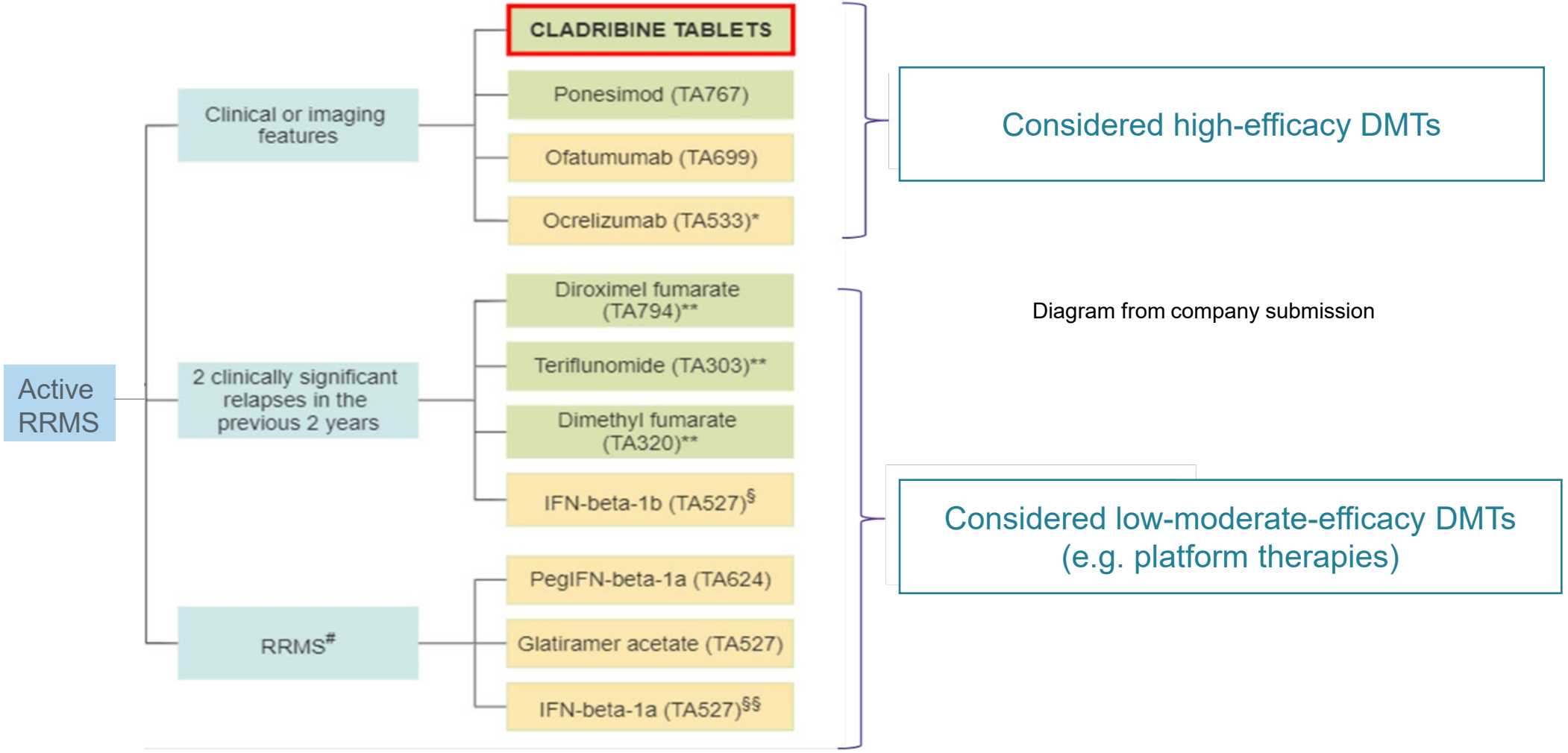


Diagram from company submission

What are the key comparators for cladribine? What is the preferred approach to treatment sequencing in clinical practice (i.e. offering high-efficacy DMTs at early stages of MS)?

#Active disease not specified. Recommendation for patients with RRMS Abbreviations: RRMS, relapsing-remitting multiple sclerosis; DMT, disease-modifying therapy.

See table of recent NICE appraisals in appendix

# Technology (Mavenclad, company)

| | |
|---|---|
| **Marketing authorisation** | Extended marketing authorisation approved by MHRA in March 2024:<br>• Treatment of adult patients with relapsing forms of multiple sclerosis with active disease as defined by clinical or imaging features |
| **Mechanism of action** | • Immune reconstitution therapy; temporarily depletes immune system, allowing it to regenerate<br>• Deaminase-resistant nucleoside analogue of deoxyadenosine<br>• Selectively reduces dividing and non-dividing T and B cells, which interrupts the cascade of immune events central to MS |
| **Administration** | • Tablets are administered orally<br>• Cumulative dose is 3.5 mg/kg body weight over 2yrs (1.75 mg/kg per year)<br>  ○ Two treatment weeks per year; beginning of the first month and beginning of second month (same for second year)<br>  ○ Each treatment week consists of 4 or 5 days on which a patient receives 10mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight<br>  ○ No further treatment is required in Years 3 and 4 (see dosing diagram in appendix) |
| **Price** | Confirmed list price for cladribine tablets:<br>• 10 mg x 1 tablet £2,047.24<br>• Annual cost: approximately £13,000 per annum, based on £52,000 (complete treatment cost spread over 4-yr period)<br>• No PAS agreed |

Abbreviations: PAS, patient access scheme.

# Key issues

| Issue | ICER impact | For discussion? |
|---|---|---|
| Company submission includes relapsing-remitting MS only, but not SPMS, while the NICE scope is for all relapsing forms of MS | N/A | No – submission did not include evidence on SPMS |
| Interpretation of NMA results due to statistical and clinical uncertainties | Unclear | Yes |
| Modelling of treatment discontinuation | Large | Yes |
| Mortality does not vary with disease progression in company base case | Small | Yes |
| Nurse costs to train patients on self-administration of injectable DMTs (comparators) | Small | Yes |
| Cladribine treatment monitoring (costs) beyond year 1 | Small | Yes |
| Routine practice monitoring (costs) for year 1 for patients on glatiramer acetate and beta interferons | Small | Yes |

= Largest ICER impact

NICE Abbreviations: EAG, external assessment group; NMA, network meta-analysis.

# Cladribine for treating relapsing multiple sclerosis

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# Key clinical trials

| | CLARITY | CLARITY-EXT |
|---|---|---|
| **Design** | Phase III double-blind, placebo-controlled, 96-week RCT | Phase IIIb double-blind, 96-week RCT; safety extension |
| **Population** | • RRMS with ≥1 relapses within 12 months Clinically stable and no relapses within 28 days prior to day 1 of study<br>• MRI lesions consistent with MS<br>• 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** | Cladribine 5.25 mg/kg<br>Cladribine 3.5 mg/kg | Patients randomised to receive either cladribine (5.25 mg/kg or 3.5 mg/kg) or placebo |
| **Comparator** | Placebo | N/A |
| **Outcomes** | • Qualifying ARR<br>• Disability progression (3-month CDP)<br>• Mortality<br>• Adverse effects of treatment<br>• HRQoL<br>• NEDA-3 (post-hoc)<br>• 6-month CDP (post-hoc) | • Safety and tolerability |

**3/6-month CDP** = sustained progression (for at least 3/6 months) as defined by a 1.0 point increase in EDSS score - or a 1.5 point increase when the baseline EDSS score was 0.

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Abbreviations: RCT, randomised controlled trial; RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status scale; ARR, annualised relapse rate; HRQoL, health-related quality of life; NEDA, no evidence of disease activity; CDP, confirmed disease progression.

# CLARITY clinical trial results

Cladribine more effective than placebo in patients with active RRMS across a spectrum of outcomes

**Qualifying ARR at 96 weeks in CLARITY**

| | Cladribine (N=433) | Placebo (N=437) |
|---|---|---|
| Qualifying ARR (95% CI) | 0.14 (0.12, 0.17) | 0.34 (0.30, 0.38) |
| Relative reduction in ARR, % | 58.22 (p value <0.0001) | |
| Rate ratio (95% CI) | 0.42 (0.33, 0.52) | |
| **Time to first qualifying relapse** | | |
| % relapse-free, K-M estimate (95% CI) | 80.3 (76.1, 83.8) | 61.1 (56.2, 65.6) |
| HR (95% CI) | 0.45 (0.34, 0.58) (p value <0.0001) | |

**Qualifying relapse-free at 96 weeks, n (%)**

| | Cladribine (N=433) | Placebo (N=437) |
|---|---|---|
| Relapse | [redacted] | [redacted] |
| Relapse-free | [redacted] | [redacted] |
| Unknown* | [redacted] | [redacted] |
| **Time to 3-month CDP** | | |
| % progression-free, KM estimate (95% CI) | [redacted] | [redacted] |
| HR (95% CI) | [redacted] (p value = [redacted]) | |
| **Time to 6-month CDP** | | |
| % progression-free, KM estimate (95% CI) | [redacted] | [redacted] |
| HR (95% CI) | [redacted] (p value = [redacted]) | |

- Cladribine group had statistically significant 58% relative reduction in qualifying ARR vs placebo
- Cladribine associated with significant delay in the time to first qualifying relapse vs. placebo (HR: 0.45)
- % patients who were relapse-free at 96wks was higher in cladribine vs placebo group ([redacted] vs. [redacted])
- % patients who were 3M CDP-free at 96wks was significantly higher in cladribine vs placebo ([redacted] vs. [redacted])
- CLARITY-EXT extension study demonstrates sustained safety over 4-year follow-up

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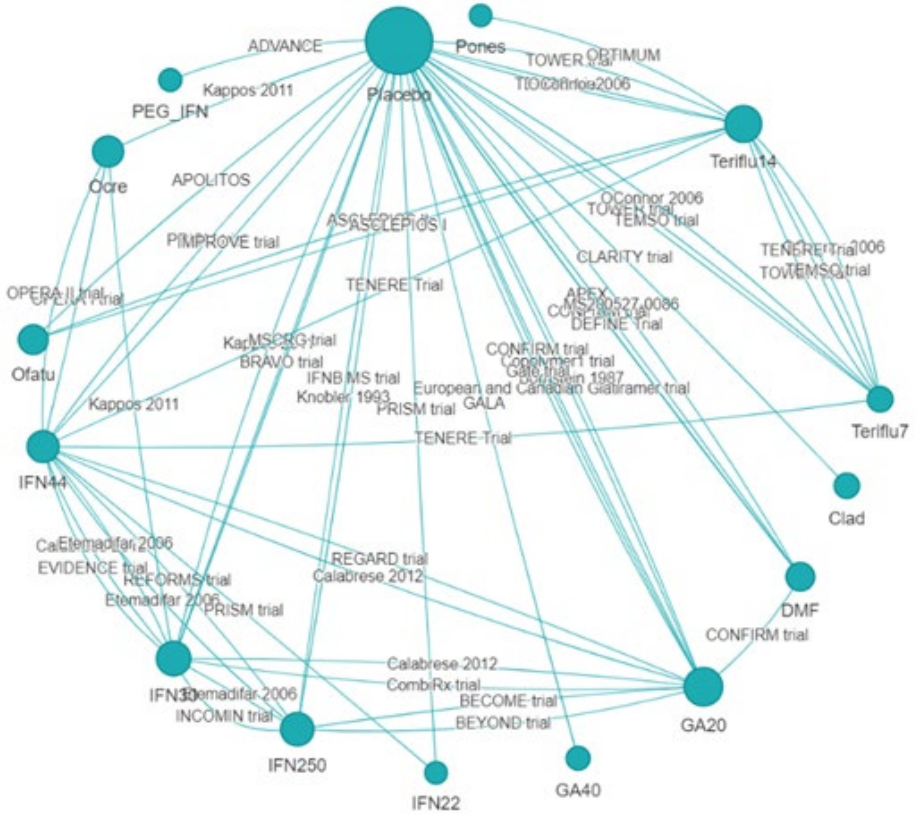
Abbreviations: ARR, annualised relapse rate; CDP, confirmed disability progression; KM = Kaplan-Meier, RRMS, relapsing-remitting multiple sclerosis;

# Network meta-analysis

## NMA conducted to assess effectiveness of cladribine vs comparators

- 61 studies identified in the SLR; 38 trials were included in the NMA
- CLARITY study was included in the NMA, however, the CLARITY-EXT study could not be considered due to the lack of a common treatment arm with competitor trials and heterogeneity of the study designs
- Outcomes were:
  - Annualised relapse rate (ARR)
  - 3-month confirmed disease progression (CDP)
  - 6-month confirmed disease progression (CDP)
  - Treatment discontinuations

**Network diagram for the base case NMA of ARR**




From company submission

Abbreviations: SLR, systematic literature review.

# NMA results – Cladribine vs. DMTs in active RRMS

**Change in ARR vs DMTs**

- Cladribine showed statistically significant benefit compared to teriflunomide, glatiramer acetate, beta interferon, peginterferon beta-1a
- No statistically significant difference vs ofatumumab, ocrelizumab, ponesimod and dimethyl fumarate

**Change in CDP vs DMTs**

- Inconclusive results given statistically non-significant estimates, wide and overlapping credible intervals

**Results vs placebo**

- Cladribine significantly improved ARR, 3 & 6 month CDP vs placebo, but not treatment discontinuations

**EAG:** NMA are consistent to those in the previous NICE submission of cladribine in RRMS, but should be interpreted with caution due to statistical and clinical uncertainties

See forest plot of NMA results in the appendix



Abbreviations: NMA, network meta-analysis; DMT, disease-modifying therapy; ARR, annualised relapse rate; CDP, confirmed disability progression; EAG, external assessment group.

# NMA results – Summary of efficacy outcomes

## Cladribine has significant benefit over most comparators for ARR, other results mixed

| 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 | ↑ | ↔ | - | - | ↑ |

▮= statistically significant results in favour of cladribine.

↑ favours cladribine;
↓ favours comparator;
"↔" equivalent efficacy;
"-" analyses not feasible

There were no significant results in favour of comparators.

- * Direction of numerical benefit at 6-month CDP not consistent with 3-month CDP
- The ranking of treatment effects in the NMA may differ from the ranking in the model due to differences in discontinuation rate

Table from company submission. Abbreviations: ARR, annualised relapse rate; bid, twice a day; CDP, confirmed disability progression; DMF, dimethyl fumarate; eod, every other day; GA, glatiramer acetate; IFN, interferon; ITT, intention to treat; qd, once a day; q1w, once a week; q2W, every 2 weeks; q4w, every 4 weeks; RF, relapse-free; tiw, three times a week.

# Key issue: Interpretation of NMA results due to uncertainties

EAG says NMA results should be interpreted with caution

**Background**

- Trials included in the NMA differed in terms of:
  - 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
  - Difference in definition and time of measurement for outcomes (e.g. variations in definition of 3 and 6-month CDP)
- Trials included in the NMA were conducted over a period of 35 years (1987 to 2022)

**Company**

- Methodology aligned with NMAs accepted in recent NICE submissions in RRMS (TA533, TA699, TA767)
- Company identified many of the above variations/limitations between trials
- Company tested inconsistency assumption which was suggestive of low likelihood of inconsistency

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; CDP, confirmed disease progression; RRMS, relapsing-remitting multiple sclerosis.

# Key issue: Interpretation of NMA results due to uncertainties

## EAG says NMA results should be interpreted with caution

**EAG**

- Due to statistical and clinical uncertainties, NMA results should be interpreted with caution
- Statistical uncertainty: 37 of 38 trials informed ARR, but other outcomes relied on fewer (underpowered) trials; 3-month CDP (15), 6-month CDP (17), treatment discontinuations (25)
- Heterogeneity with respect to these trial/design-specific features across the trials' networks may have introduced some bias in the NMA, and therefore threatens the transitivity assumption*
  - Missing data on ethnicity and prior treatment history across studies potentially treatment modifiers
  - Lack of understanding of placebo frequency/mode of administration could bias placebo as common comparator
- Violating transitivity assumption compromises the credibility of treatment effect estimates in NMA
  - Considering direct, indirect, and mixed (pooled) HRs for all four NMA outcomes, most of the time there was consistency between the direct and indirect evidence
  - But some inconsistencies between the direct and indirect evidence were identified, despite wide CIs.

***Transitivity:** If A > B and B > C, then A > C
Letters refer to efficacy estimates for treatments

Is the NMA to acceptable for decision making? What are committee considerations on the NMA results?

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; ARR, annualised relapse rate; CDP, confirmed disease progression; CI, confidence intervals; HR, hazard ratio.

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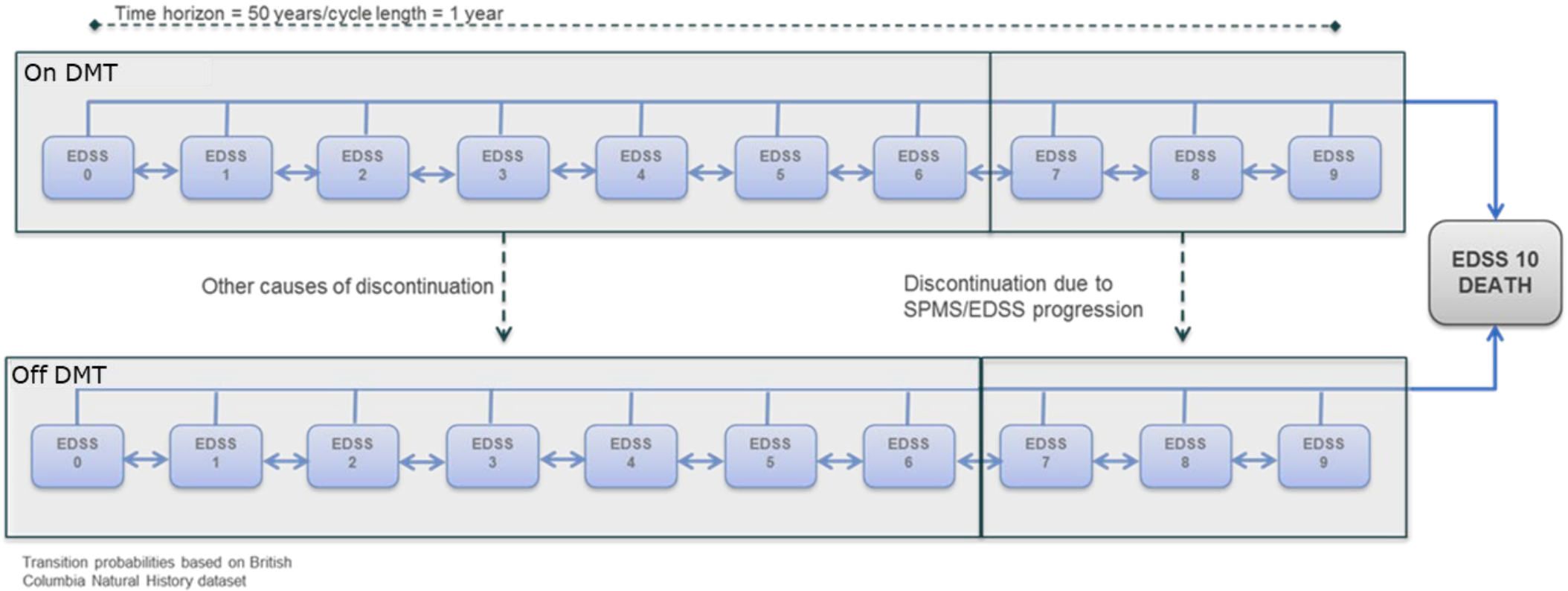
# Model structure

## 11 health state model, based on EDSS scores

- Markov state cohort simulation model
- EAG agrees the model structure is appropriate for decision making




**EDSS** measures your current level of disability
EDSS 0 = no disability; higher states indicate worsened/progressed disability

Abbreviations: EDSS, Expanded Disability Status Scale.

See model inputs for current & previous MS appraisals in appendix

# Impact of treatment on QALYs and costs

## Treatments impact QALYs by:

- Reducing annualised relapses (hospitalisations)
- Prolonging transitions (lowering probability) to higher EDSS (disease progression)
- Having a different adverse event profile
- Reducing caregiver QALY decrement through slower progression*

* Caregiver disutility worsens from EDSS 3, peaks at EDSS 6, and worsens from EDSS 7 to 9

## Treatments impact costs by:

- Reducing annualised relapse (hospitalisations and rescue therapy)
- Prolonging transitions (lowering probability) to higher EDSS (disease progression)
- Having different acquisition, administration and monitoring costs
- Having different adverse event profile

## Model features:

**Time horizon:** 50 years (lifetime)

**Cycle length:** 1 year

**Sequencing**: No treatment sequencing. If people discontinue treatment, they move to BSC arm.

**Waning**: Efficacy wanes across DMTs to 75% after yr4 and to 50% after yr5 onwards

Abbreviations: DMT, disease-modifying therapy; QALY, quality-adjust life year; EDSS, expanded disability status score; RMSS, relapsing-remitting multiple sclerosis; BSC, best supportive care.

# Key issue: Modelling of treatment discontinuation

## EAG has broader definition of treatment discontinuation/non-persistence vs. company

### Background

- Company base case uses treatment discontinuation probabilities from NMA of RCTs
- Discontinuation probability for cladribine applied to 1st cycle only in company base case (discontinuation between the 1st & 2nd courses). No active treatment after 2nd course, so no discontinuation
- EAG uses parametric survival modelling of treatment persistence based on observational RWE from UK
- EAG has broader definition of discontinuation than company, considering overall treatment persistence.
- Company models the cessation of active treatment, but EAG also assumes discontinuation occurs if patient takes a different DMT. So, if someone had 2 years of cladribine, then started taking a different DMT, this would count as discontinuation of cladribine in EAG model, but not in company model.
- In both company and EAG models, people who discontinue treatment are moved to the BSC arm, losing the benefits of their initial treatment.
- EAG approach results in large, significant increase to cladribine ICERs vs BSC and comparators

| Reasons for treatment discontinuation used in EAG base case (from Tallantyre 2024) | % |
|---|---|
| Adverse events, | 34.8% |
| Disease Progression | 5.8% |
| Drug holiday | 2.7% |
| Increased risk of adverse event | 6.8% |
| Lack of efficacy | 30.1% |
| Patient choice | 7.2% |
| Pregnancy | 7.7% |
| Other | 0.7% |
| Unknown | 4.1% |

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; RCT, randomised controlled trial; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; DMT, disease-modifying therapy; RRMS, relapsing-remitting multiple sclerosis; RWE, Real World Evidence

# Key issue: Modelling of treatment discontinuation

## Company and EAG have different approaches for modelling discontinuation

**EAG**

- Unable to replicate discontinuation probabilities used in company base-case from NMA data. E.g. the 1yr probability of treatment discontinuation in the placebo group is [redacted]% in company model and [redacted] from the EAG re-analysis of the company's data. Similar discrepancies between the EAG's extrapolated estimates and CS estimates are evident across all DMTs
- NMA of RCTs may not accurately reflect the real-world experiences of RRMS patients using DMTs
- Data and reasons for stopping treatment reported by Tallantyre et al. (2024) more accurately reflect clinical practice with cladribine.
- Tallantyre et al. (2024) data did not include ponesimod, ofatumumab and diroximel fumurate. EAG assumed similar treatment discontinuation probabilities for ofatumumab as ocrelizumab, used Lager et al. (2023) for diroximel fumurate and did not estimate probabilities for ponesimod for lack of data.

**Company**

- Discontinuation based on NMA of trial data have been used in previous NICE TAs for RRMS and cladribine
- Probabilities are aligned with previous NMAs reported in TA533 (ocrelizumab) and TA767 (ponesimod)
- Discontinuation due to lack of efficacy is captured in discontinuation rates used in the model

What is committees preferred approach to modelling treatment discontinuation?

See EAG-modelled treatment discontinuation in appendix

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Abbreviations: EAG, external assessment group; NMA, network meta-analysis; RCT, randomised controlled trial; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; DMT, disease-modifying therapy; RRMS, relapsing-remitting multiple sclerosis.

# Treatment discontinuation assumptions

## Comparison of company and EAG discontinuation probabilities

Predicted values highlighted in **bold**

| DMT | Treatment discontinuation probabilities (company preferred) | | | Treatment discontinuation probabilities (EAG preferred) | | | |
|---|---|---|---|---|---|---|---|
| | Year: 0-2 | Year: 2-10 | Year: 10+ | Year: 0-2 | Year:2-10 | Year: 10+ | Source |
| Cladribine Tablets | 4.9% | 0.0% | 0.0% | 4.5% | **10.0%** | **19.1%** | Tallantyre (2024) |
| Dimethyl fumarate | [redacted] | [redacted] | [redacted] | 28.4% | 48.6% | **66.1%** | 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%** | Tallantyre (2024) |
| Ocrelizumab | [redacted] | [redacted] | [redacted] | 5.8% | **13.5%** | **25.3%** | Tallantyre (2024) |
| Ofatumumab | [redacted] | [redacted] | [redacted] | 5.8% | **13.5%** | **25.3%** | Assumed same as ocrelizumab |
| Ponesimod | [redacted] | [redacted] | [redacted] | Not included due to lack of data availability | | | |
| Diroximel fumarate | [redacted] | [redacted] | [redacted] | **21.9%** | **34.4%** | **46.8%** | Lager (2023) |

EAG probabilities include broader classification of discontinuation

Abbreviations: EAG, external assessment group; DMT, disease-modifying therapy.

# Key Issue: Mortality doesn't vary with disease progression in company base case

Company and EAG have different approaches for modelling mortality

## Background

- Company base case uses standardised mortality ratios from a UK MS study (Jick et al. 2014); applies same SMR to all people with MS, regardless of EDSS status (disease progression)
- EAG uses mortality multiplier which adjusts for disability progression (using EDSS)

## Company

- Mortality rates by EDSS state derived from Pokorski et al. (1997), which is historical data and may not accurately reflect mortality risk in contemporary populations
- Limited evidence to show DMTs indirectly reduce mortality risk by delaying EDSS progression
- Explored variable mortality ratios in scenario analyses; insignificant impact on ICERs

## EAG comments

- Fixed mortality assumption, where mortality does not vary with EDSS progression, is oversimplification
- Mortality rate which differs by EDSS state is more realistic; higher EDSS state likely has higher mortality risk
- Not allowing mortality to vary with EDSS and form of MS implies there is no survival advantage from slowing disease progression from using DMTs
- Variable SMR leads to a difference in survival of about [redacted] for cladribine vs BSC; minimal ↑ of ICER vs BSC

How should mortality rates be included in the model? Preference to vary by EDSS status (EAG) or fixed SMR (company)? Would survival be expected to improve if treatments delay EDSS progression?

Abbreviations: EAG, external assessment group; SMR, standardised mortality rate; EDSS, expanded disability status scale; DMT, disease-modifying therapy; ICER, incremental cost effectiveness ratio; RMSS, relapsing-remitting multiple sclerosis; BSC, best supportive care.

# Key issue: Cladribine treatment monitoring (costs) for year 2

Company and EAG prefer different monitoring resources for 2nd year of treatment

**Background**

- Company expects fewer monitoring resources in year 2 vs year 1 (No MRI scan, 1 neurology visit)
- EAG prefers the same monitoring costs in years 1 & 2 (1 MRI scan, 2 neurology visits)

**Company**

- Additional year 2 monitoring is only relevant for treating highly active MS with IRTs (TA312)

**EAG comments**

- EAG's clinical advice suggests that *regular monitoring* – understood as the various tests, 1x MRI scan and 2x neurology visits annually – is necessary for detecting MRI activity or relapse
- Applying regular monitoring in both years 1 and 2 has a small impact on ICERs
- EAG grants that ABN guidelines do not mandate annual MRI scans or neurology visit for MS
- EAG welcomes additional evidence to clarify each year's monitoring resource requirements for cladribine

- In the NHS, how closely would people with active RRMS taking cladribine be monitored after their first year of treatment? Would they have an MRI scan, and would they have 1 or 2 neurology visits?
- What is committee's preferred approach to modelling monitoring of cladribine treatment?

Abbreviations: EAG, external assessment group; MRI, magnetic resonance imaging; IRT, immune reconstitution therapy; ICER, incremental cost effectiveness ratio; ABN, Association of British Neurologists.

See full breakdown of costs in appendix

# Key issue: Routine practice monitoring (costs) for year 1 for patients on glatiramer acetate and beta interferons

**Background**

- Company base case includes neurology visits for glatiramer acetate and beta interferons
- EAG's clinical advice indicates that neurology appointments in year 1 are not routine practice for these

**Company**

- Company finds it very unlikely that people taking these DMTs will be unsupervised in year 1
- Company sourced the number of neurology visits for glatiramer acetate and beta interferons from TA312 (alemtuzumab) which explicitly uses 2 visits in year 1 and in subsequent years
- These values were, in turn, sourced from TA254 (fingolimod)

**EAG comments**

- Clinical advice suggests neurology appointments in yr 1 are not routine practice for these comparators
- Reducing these appointments to 0 increased ICERs of cladribine versus glatiramer acetate and beta interferons, but only slightly
- EAG welcomes additional evidence regarding routine yr-1 neurology appointments for these comparators

- Is it routine practice for people with active RRMS taking glatiramer acetate or beta interferons to have 2 neurology appointments in yr 1? If not, how many would they have?
- What is committee's preferred approach to modelling monitoring costs for comparators?

NICE



Abbreviations: EAG, external assessment group; DMT, disease-modifying therapy; ICER, incremental cost-effectiveness ratio.

# Key issue: Nurse costs to train patients in self-administration

## Company and EAG disagree about whether to include nurse time to train patients

**Background**

- Company model includes 3 hours of nurse time (£216) to train patients to self-administer injectable DMTs
- Clinical advice to EAG says training is done by company-sponsored nurses, so would not cost the NHS

**Company**

- The cost is applied uniformly to injectable DMTs, including: glatiramer acetate, interferon betas, teriflunomide and ofatumumab
- Although some companies provide training for patients, it is inappropriate to assume this service applies to all patients or that it will continue to be provided indefinitely. Model should reflect NHS and PSS costs

**EAG comments**

- EAG seeks clarity on whether administration training is provided by NHS or industry
- If company-sponsored, EAG recommends zero hours of nurse training visits for patients on injectable DMTs requiring self-administration
- Has minimal impact on cost effectiveness results (small increase to cladribine ICERs vs injectable DMTs)

Should nurse time to train patients to self-administer injectable DMTs be included in the model?

NICE

Abbreviations: EAG, external assessment group; DMT, disease-modifying therapy; PSS, personal social services; ICER, incremental cost effectiveness ratio.

# Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

# Summary of company and EAG base case assumptions

| Assumption | Company base case | EAG base case | Impact on ICERs vs BSC/comparators |
|---|---|---|---|
| Treatment discontinuation | NMA RCT data | Published UK RWE (exponential distribution) | Large |
| Treatment waning | • 0% in the first 0-4 years<br>• 25% in Years 4-5<br>• 50% beyond year 5. | Same as company; conservative to apply both treatment discontinuation and waning | N/A |
| Mortality rate | Fixed standardised mortality rate (SMR); mortality does not vary with disease progression | Variable SMR; mortality varies with disease progression. | Very small |
| Injection device training for patients* | • 3 hours | • 0 hours | Very small |
| Treatment monitoring costs for cladribine *(in year 2)* | • No MRI scan<br>• 1 neurology visit | • 1 MRI scan<br>• 2 neurology visits | No change/ very small |
| First-year monitoring costs for glatiramer acetate and beta interferons | • 2 neurology appointments | • 0 neurology appointments | No change/ very small |

NICE

* Applies to glatiramer acetate, interferon betas, teriflunomide, and ofatumumab; Abbreviations: EAG, external assessment group; NMA, network meta-analysis; RWE, real-world evidence; SMR, standardised mortality rate; MRI, magnetic resonance imaging.

# Cladribine for treating relapsing multiple sclerosis

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

# Committee preferred assumptions

| | |
|---|---|
| Decision problem | • Is the population used in CS acceptable? |
| Clinical effectiveness data | • Does the transivity assumption hold for the NMA?<br>• Is the NMA acceptable for decision making? |
| Cost-effectiveness data | • Does the committee prefer the EAG (parametric survival modelling of treatment persistence based on observational real-world evidence on UK RRMS ) or company approach (NMA of RCT data) to modelling treatment discontinuation?<br>• Should mortality vary with disease progression? Does committee prefer the variable mortality rate (EAG) or the fixed SMR (company)?<br>• What is committees preferred approach to modelling monitoring costs for cladribine in year 2?<br>• What is committees preferred approach to modelling monitoring costs for comparators?<br>• Should nurse time to train patients to self-administer injectable DMTs be included in the model? |
| ICER | What is the committee's preferred ICER threshold? |
| Uncertainties | What are the remaining uncertainties? |

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Abbreviations: CS, company submission; NMA, network meta-analysis; EAG, external assessment group; RRMS, relapsing-remitting multiple sclerosis; RCT, randomised controlled trial; SMR, standardised mortality rate; DMT, disease-modifying therapy; ICER, incremental cost-effectiveness threshold.

# Supplementary appendix

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# Dosing regimen and treatment effect for cladribine tablets

Cladribine is administered over a 2yr period, but treatment effect persists beyond this


*Re-initiation of therapy after Year 4 has not been studied*

Treatment effect waning begins to occur

- 25% in Years 4-5
- 50% beyond year 5
- Same assumptions for all DMTs

Image from company submission

Abbreviations: DMT, disease-modifying therapy.

# Recent NICE appraisals for multiple sclerosis

| Technology appraisal | Drug | Recommendation |
|---|---|---|
| TA493/TA616 (2024) | Cladribine | Highly active MS if RRMS with inadequate response to treatment, or RES |
| TA312 (2024) | Alemtuzumab | Highly active RRMS with inadequate response from 1+ DMT or RES MS |
| TA794 (2022) | Diroximel fumarate | Active RRMS – but not for highly active, or RES MS |
| TA767 (2022) | Ponesimod | Active RRMS |
| TA699 (2021) | Ofatumumab | Active RRMS |
| TA624 (2020) | Peginterferon beta-1a | Active RRMS – but not for highly active, or RES MS |
| TA533 (2018) | Ocrelizumab | Active RRMS if alemtuzumab is contraindicated |
| TA527 (2018) | Beta interferons and glatiramer acetate | Interferon beta-1a for RRMS<br>Interferon beta-1b (Extavia but not Betaferon) for active RRMS or SPMS with continuing relapses<br>Glatiramer acetate for RRMS |
| TA320 (2014) | Dimethyl fumarate | Active RRMS – but not for highly active, or RES MS |
| TA303 (2014) | Teriflunomide | Active RRMS – but not for highly active, or RES MS |

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; RES, rapidly evolving severe; SPMS, secondary progressive multiple sclerosis.

# Decision problem

Population, intervention, comparators and outcomes from the scope

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Population** | Adults with relapsing forms of multiple sclerosis (RMS) | Adults with active RRMS (did not present evidence on SPMS) | RRMS, a subset of RMS, excludes SPMS.<br>SPMS was also not considered in TA493/TA616<br>50% RRMS > SPMS over 20y |
| **Intervention** | Cladribine tablets | As per scope | As per scope |
| **Comparators (for active RMSS)** | Optimised standard care with no DMT<br>Beta interferon<br>Peginterferon beta-1a<br>Dimethyl fumarate<br>Diroximel fumarate<br>Glatiramer acetate<br>Teriflunomide<br>Ocrelizumab (if alemtuzumab contraindicated)<br>Ofatumumab<br>Ponesimod | As per scope | As per scope |

Abbreviations: EAG, external assessment group; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

# Decision problem

| | Final scope | Company | EAG comments |
|---|---|---|---|
| **Comparators (for SPMS)** | Siponimod<br>Beta interferon | Evidence for SPMS not included in CS | N/A |
| **Comparators (for progression after previous treatment)** | Autologous haematopoietic stem cell transplantation | Comparator excluded:<br>Not MHRA-authorised for RRMS<br>Not used in routine practice<br>No NICE rec in RMSS<br>For severe or progressed cases as per expert opinion | N/A |
| **Outcomes** | Relapse rate<br>Relapse severity<br>Disability (e.g. EDSS)<br>Disease progression<br>Multiple sclerosis symptoms<br>Freedom from disease activity<br>Mortality<br>Adverse effects of treatment<br>Health-related quality of life | As per scope | As per scope |

Abbreviations: EAG, external assessment group; SPMS, secondary progressive multiple sclerosis; CS, company submission; MHRA, Medicines and Healthcare products Regulatory Agency; EDSS, expanded disability status scale.

# NMA Results

NMA plot for 3-month CDP

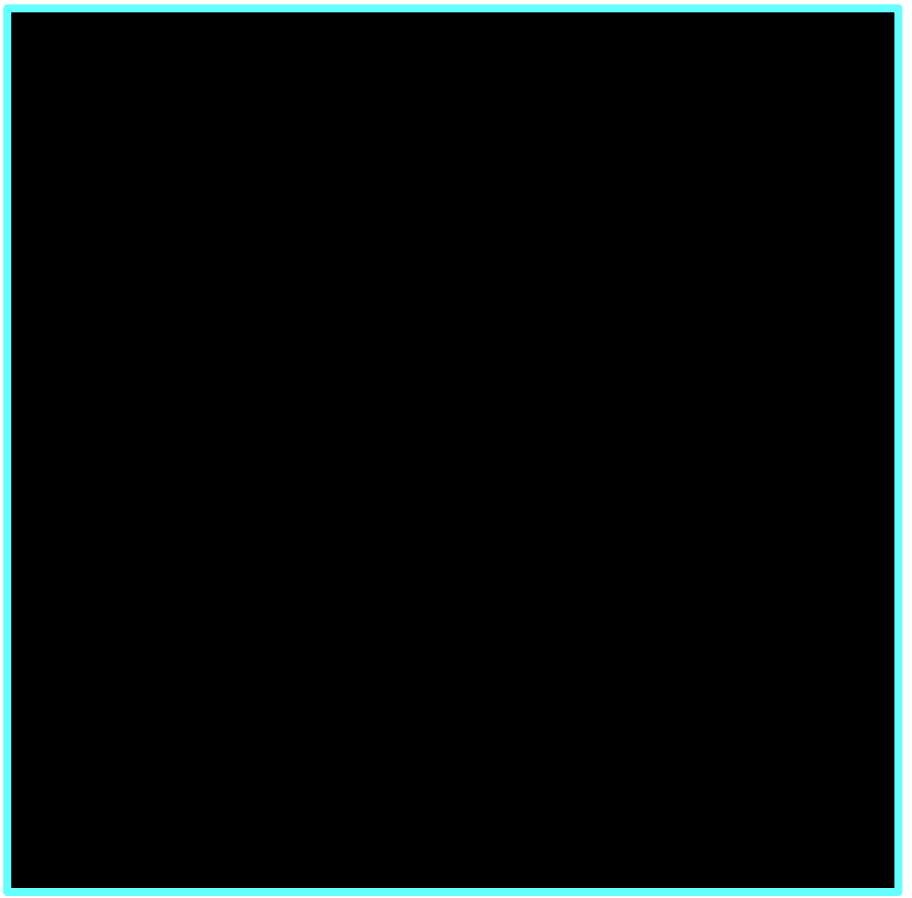
NMA plot for 6-month CDP (INCOMIN results excluded)

Abbreviations: NMA, network meta-analysis; ARR, annualised relapse rate; CDP, confirmed disease progression.

# NMA Results

NMA plot for ARR

NMA plot for treatment discontinuation



Abbreviations: ARR, annualised relapse rate NMA, network meta-analysis; CDP, confirmed disease progression.

# EAG treatment discontinuation extrapolation

Proportion of cohort alive and on DMTs based on data generated from EAG modelling of DMT discontinuation

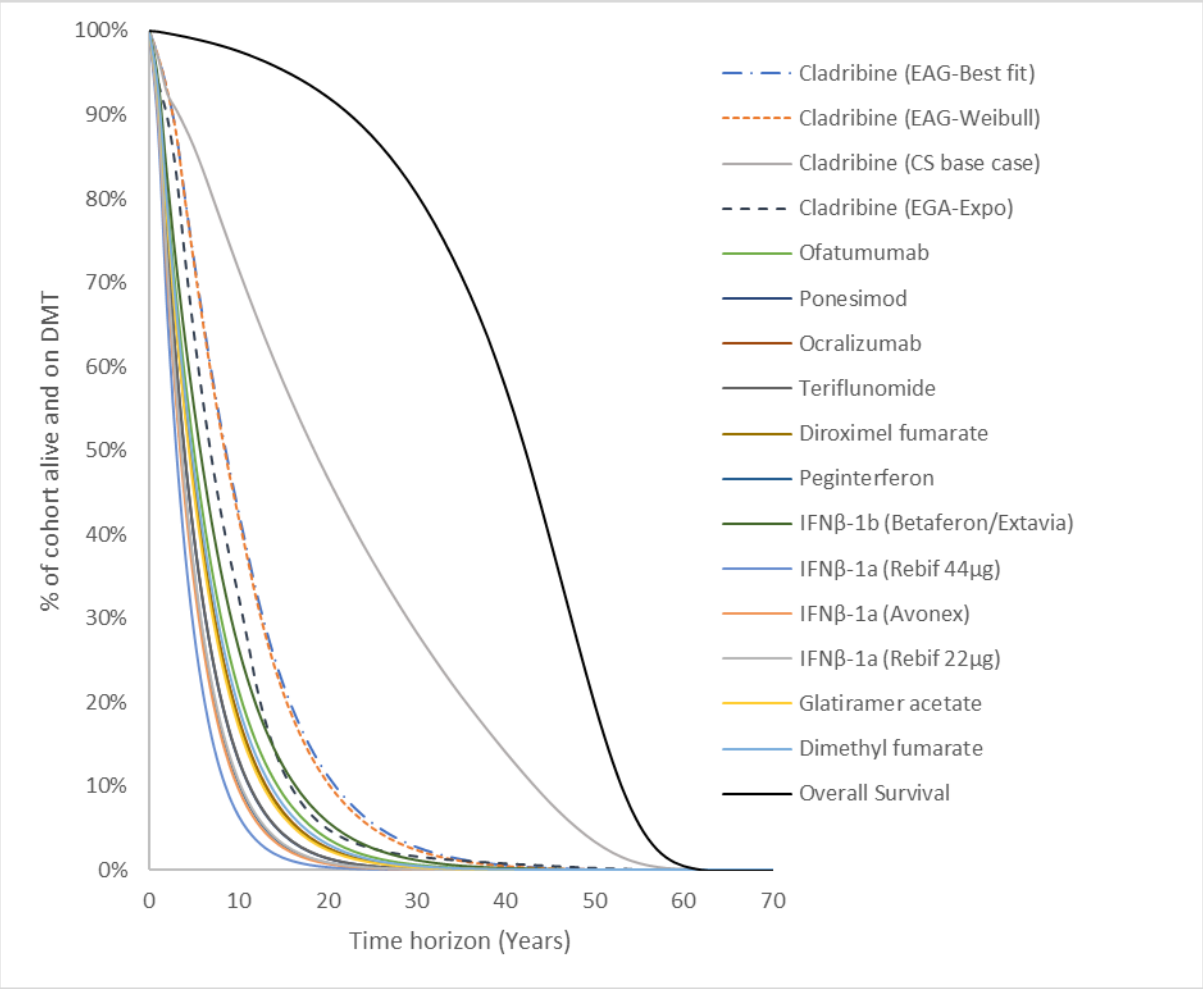



Figure from EAG report

Abbreviations: EAG, external assessment group; DMT, disease-modifying therapy.

# Cladribine monitoring costs

CS applies the following monitoring costs in each year

| | Company units | | | EAG units | | |
|---|---|---|---|---|---|---|
| Monitoring resource | Y1 | Y2 | Y3 & Y4 | Y1 | Y2 | Y3 & Y4 |
| MRI scan | 1 | 0 | 0 | 1 | 1 | 0 |
| Neurology visit | 2 | 1 | 0 | 2 | 2 | 0 |
| Complete blood count | 3 | 3 | 0 | 3 | 3 | 0 |
| Tuberculin skin test | 1 | 1 | 0 | 1 | 1 | 0 |
| Hepatitis C test | 1 | 1 | 0 | 1 | 1 | 0 |
| Hepatitis B test | 1 | 1 | 0 | 1 | 1 | 0 |
| Total cost | £829 | £332 | £0 | £829 | £829 | £0 |

EAG prefers the same monitoring resource units in year 1 and year 2

This takes the total discounted monitoring costs of cladribine from £1,128 to £1,578 over the model horizon

Abbreviations: CS, company submission; EAG, external assessment group; MRI, magnetic resonance imaging.

# Model inputs compared with previous TAs

| Factor | Ponesimod (TA767) | Ofatumumab (TA699) | Cladribine (TA493/TA616) | Chosen value for this appraisal | Justification |
|---|---|---|---|---|---|
| **Health state structure** | 20 health states | 21 health states | 11 health states | 11 health states | Simplification of 21 state model that combines RR and SP. |
| **Source of natural history EDSS** | BCMS for EDSS transitions (RRMS). London Ontario for transitions from RRMS to SPMS | BCMS for EDSS transitions (RRMS). London Ontario and EXPAND for 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** | 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 |
| **Source of MS mortality** | Pokorski (1997) extrapolated for EDSS states | Pokorski (1997) extrapolated for EDSS states | Jick et al. (2014) | Jick et al. (2014) | Largest UK MS sample |
| **Application of treatment effect** | • ARR<br>• CDP-3M | • ARR<br>• CDP-6M | • ARR<br>• CDP-6M | • ARR<br>• CDP-6M | |

Abbreviations: RR/RRMS, relapsing-remitting multiple sclerosis; SP/SPMS, secondary progressive multiple sclerosis; EDSS, expanded disability status scale; BCMS, British Columbia Multiple Sclerosis (registry); ARR, annualised relapse rate; CDP, confirmed disease progression.

# Model inputs compared with previous TAs

| Factor | Ponesimod (TA767) | Ofatumumab (TA699) | Cladribine (TA493/TA616) | Chosen value for this appraisal | Justification |
|---|---|---|---|---|---|
| **Treatment effect waning** | 25% after 2 years and 50% after 5 years | Not applied; all-cause treatment discontinuation acts as a proxy for waning | Cladribine:<br>• 100% for Yrs 0-4.<br>• 25% in Yr 4-5<br>• 50% Yr5+<br>Comparators:<br>• 100% in Yrs 0-2,<br>• 25% in Yrs 2-5<br>• 50% Yr 5+ | Cladribine and comparators:<br>• 100% for Yrs 0-4<br>• 25% in Yr 4-5<br>• 50% Yr 5+ | Cladribine waning based on CLARITY/ CLARITY EXT.<br>Same is modelled for comparators as a conservative assumption due to lack of evidence. |
| **Treatment discontinuation** | 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 previous RRMS appraisals |
| **Stopping rule** | EDSS ≥7.0<br>SPMS transition | EDSS ≥7.0<br>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) | 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 | Preference for trial data supplemented by literature estimates. |

Abbreviations: NMA, network meta-analysis; RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis; EQ-5D, EuroQoL five dimension (questionnaire).

# Model inputs compared with previous TAs

| Factor | Ponesimod (TA767) | Ofatumumab (TA699) | Cladribine (TA493/TA616) | Chosen value for this appraisal | Justification |
|---|---|---|---|---|---|
| **Source of relapse disutility** | 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 |
| **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) | In line with majority of previous RRMS appraisals |
| **Source of EDSS cost** | 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 utility values. |
| **Source of relapse cost** | Tyas et al. (2007), inflated to 2019 | Hawton et al. (2016) | Hawton et al. (2016) | Hawton et al. (2016) | In line with TA493/TA616 |

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; EDSS, expanded disability status score.