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## Cost-effectiveness of cladribine tablets versus fingolimod in patients with highly active relapsing multiple sclerosis in Portugal

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### ABSTRACT

**Aims:** To assess the cost-utility of cladribine tablets *versus* fingolimod in patients with highly active relapsing-remitting multiple sclerosis (RRMS) in Portugal.

**Methods:** A 1-year cycle cohort-based Markov state transition model was developed to simulate disease progression, measured by Kurtzke Expanded Disability Status Scale (EDSS), relapses, and conversion to secondary-progressive MS (SPMS). Patients were assumed to remain on treatment until progression to EDSS level 7, conversion to SPMS, or complete loss of efficacy due to waning effect. Natural history was based on British Columbia Multiple Sclerosis registry, London Ontario database, UK MS Trust, and cladribine tablets clinical trial (CLARITY). Portuguese all-cause mortality was adjusted for the MS associated increased mortality. Clinical inputs for active treatments (disability progression and relapse rate) were estimated on a network meta-analysis. Utility weights were derived from UK-MS Survey and published literature. Resource consumption by EDSS and due to relapses was based on published literature, National DRG microdata and expert opinion. Unit costs were obtained from official sources. The analysis was conducted from payers' perspective, time horizon of 50 years and discount rate of 5%, for both costs and benefits. Uncertainty was assessed *via* probabilistic and deterministic sensitivity analyses.

**Results:** Compared to fingolimod, cladribine tablets were associated with a delay in progression, resulting in a gain of 0.85 quality adjusted life years (QALYs) and a cost decrease of 25,935 €. Probabilistic sensitivity analysis resulted in a mean ICER of –31,781 € per QALY and was dominant in 98.7% of the simulations. Cladribine tablets were dominant across the scenario analyses tested.

**Conclusions:** Treatment of highly active RRMS with cladribine tablets was less costly and more effective than treatment with fingolimod. Hence, it is a dominant strategy in the Portuguese setting. No conclusions can be drawn from the present study regarding other treatment options, in particular natalizumab and alemtuzumab.

### ARTICLE HISTORY

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### Introduction

Multiple sclerosis (MS) is an immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) with loss of motor and sensory functions<sup>1</sup>. The incidence and prevalence rates of MS vary substantially between geographic regions<sup>2</sup>. In Europe, the overall estimated incidence and prevalence rates are 5.5 and 108 per 100,000, respectively<sup>2</sup>. Lower estimations have been reported for Portugal (4.48 and 56.20 per 100,000 for incidence and prevalence rates, respectively)<sup>3,4</sup>. MS is twice as common in women as men, with an average age of onset of about 30 years. Disease progression is variable and influenced by both environmental and genetic factors<sup>5</sup>.

Different subtypes of MS have been identified, based on clinical presentation and disease course. The most common MS type is relapsing-remitting MS (RRMS; around 85% of MS cases), which is characterized by clearly defined relapses (attacks of new or increasing neurologic symptoms) followed

by remissions (periods of partial or complete recovery). By definition, in RRMS there is no apparent progression of the disease during remission. However, most RRMS cases will eventually transit to another MS type designated secondary progressive MS (SPMS), in which there is a progressive worsening of neurologic function (accumulation of disability) over time<sup>6,7</sup>. Patients with RRMS may be further classified as having or not a highly active disease characterized by frequent clinical relapses and/or magnetic resonance imaging (MRI) activity, either when untreated or on a disease-modifying drug (DMD)<sup>8</sup>. DMDs are indicated for most cases of RRMS, with the aim of modifying disease progression, either reducing the number of relapses or delaying the progression of disability<sup>9,10</sup>. In RRMS, the current treatment options include interferon- $\beta$ , glatiramer acetate, natalizumab, fingolimod, teriflunomide, alemtuzumab and dimethyl fumarate. Second-line treatment with natalizumab, fingolimod or alemtuzumab is recommended to patients with active disease and an insufficient response to at least one drug, as well as

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[www.tandfonline.com/ijme](http://www.tandfonline.com/ijme)

to patients with rapidly evolving severe RRMS<sup>11-14</sup>. In Portugal, these second-line treatments are used in the treatment of patients with highly active disease.

Cladribine tablets have recently been approved in Europe for the treatment of adult patients with highly active RRMS as defined by clinical or imaging features<sup>15</sup>. This decision was based on the positive results from a large randomized, double-blind, placebo-controlled clinical study (CLARITY)<sup>16,17</sup> and its extension phase (CLARITY EXT)<sup>18</sup>. The recommended dose of cladribine tablets is 3.50 mg/kg over 2 years, administered orally in one treatment course of 1.75 mg/kg per year (each treatment course comprises two treatment weeks during the first 2 months).

The objective of this study is to estimate the cost-utility of cladribine tablets compared to fingolimod in the treatment of highly active RRMS in Portugal from the payer's perspective.

## Methods

### Model structure

The analyses were conducted using an existing cohort-based Markov model that simulated the costs and effectiveness of RRMS treatment, following the structure used in previous economic models<sup>19,20</sup>.

Disease progression was modelled using the Kurtzke's Expanded Disability Status Scale (EDSS) and comprises 21 states: 10 EDSS states for RRMS, 10 EDSS states for SPMS and an all-cause death state (Figure 1). At each yearly cycle, patients are at risk of experiencing disability progression (moving to a higher EDSS state); improving in disability status (moving to a lower EDSS state); remaining at their current EDSS state; converting to SPMS with a simultaneous disability progression; or die. Patients are assumed to remain on treatment until progression to EDSS level 7, conversion to SPMS, treatment discontinuation, or complete loss of efficacy due to waning effect on disability progression and relapse rate. The analysis assumed a time horizon of 50 years and a discount

rate of 5%, for both costs and benefits, as specified by the Portuguese guidelines for the economic evaluation of pharmaceuticals<sup>21</sup>.

### Model inputs

The cohort considered in the model replicates the subgroup of patients included in the CLARITY trial with high disease activity (HDA), defined as: (a) at least one relapse in the previous year while on DMD and at least one T1 gadolinium-enhancing lesion or at least nine T2 lesions, or (b) two or more relapses in the previous year whether on DMD or not. As observed in CLARITY trial, the mean age is 37.1 years and the female to male ratio is 1.7. Table 1 shows the initial distribution amongst EDSS states.

Disease progression and relapse occurrence with either treatment were modelled by applying a relative treatment effect to the disease natural history. Assuming that the latter represents what would occur if patients were on placebo, this allows use of the results of a network meta-analysis that compares the treatment effect of each DMD and placebo.

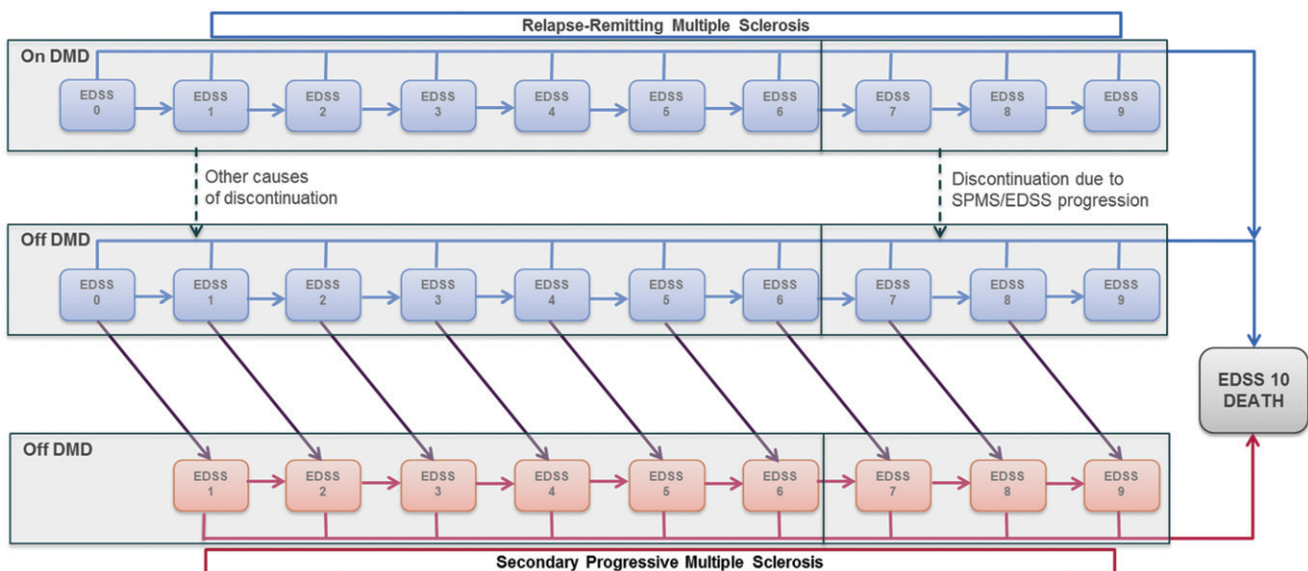
No prospective registry data for MS patients is available in Portugal. Therefore, the disease natural history was based on the British Columbia Multiple Sclerosis registry ([BCMS, Canada]<sup>16</sup>). This registry includes a large representative MS population, recording EDSS scores prospectively with a long-term follow-up (28 years). In this research, transition probabilities differ between those patients whose age at disease onset are equal or greater, or less than 28 years old. Given that the mean age at CLARITY baseline was 38 years old, the

**Table 1.** Initial HDA patient distribution, by EDSS state.

EDSS state	0	1	2	3	4	5	6	7	8	9
	2.8%	2.8%	32.5%	21.5%	23.4%	11.1%	5.9%	0%	0%	0%

Abbreviations. HDA, high-disease activity; EDSS, expanded disability status scale.

Source: EMD Serono, data on file.



**Figure 1.** Markov model.

**Table 2.** Annual transition probability matrix by EDSS state (MS age of onset  $\geq 28$  years), after adjustment for HDA-RRMS.

EDSS from/to	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)
0	60.5	26.3	9.4	2.8	0.5	0.2	0.2	0.0	0.0	0.0
1	5.8	61.8	20.7	8.0	2.2	0.6	0.8	0.1	0.0	0.0
2	1.6	12.1	52.9	22.0	5.8	2.4	2.8	0.2	0.1	0.0
3	0.6	5.0	12.0	45.9	11.9	7.6	15.2	1.3	0.5	0.0
4	0.2	2.2	6.7	11.5	39.9	13.5	21.8	3.3	0.9	0.1
5	0.1	0.5	2.9	5.9	8.7	39.2	35.2	5.0	2.4	0.1
6	0.0	0.1	0.4	2.5	3.1	4.1	68.8	14.6	5.9	0.6
7	0.0	0.0	0.1	0.2	0.7	0.4	11.7	69.3	16.1	1.6
8	0.0	0.0	0.0	0.0	0.1	0.1	1.9	5.6	90.3	2.1
9	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.6	17.4	81.8

Abbreviations. EDSS, expanded disability status scale; HDA-RRMS, high disease activity-relapsing remitting multiple sclerosis.

Source: Palace et al.<sup>22</sup> and CLARITY trial.

**Table 3.** SPMS conversion probabilities, by EDSS state.

EDSS state	Median time to SPMS conversion (years)	Transition probability (%)
0	0	0.0
1	15	4.5
2	11	6.1
3	7	9.4
4	6	10.9
5	4	15.9
6	3	20.6
7–9	2	29.3

Abbreviations. EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.

Source: Ebers<sup>23</sup>.

latter transition matrix was considered. Moreover, as the original BCMS analysis was performed on a cohort that covers a broad group, including patients with mild and less progressive forms of RRMS alongside people with highly active or rapidly evolving disease, an acceleration factor that accounts for a faster rate of progression on HDA population was included. A hazard ratio (HR) of 1.38 was estimated by comparing the proportion of progression-free at week 96, for the placebo arm, in the HDA-RRMS (71.7%) subgroup of CLARITY with its complement (non HDA-RRMS, 78.6%). Due to the lack of information by EDSS level, we assumed that the HR was constant across all EDSS levels. The resulting annual transition probabilities are shown in Table 2.

Besides EDSS transition, between RRMS health states, patients were at risk of converting from RRMS to SPMS. Annual transitions to SPMS, by EDSS RRMS state, were based on the median time to event estimated using the London Ontario registry<sup>23</sup>, as this registry allows estimation of a conversion rate dependent on EDSS state. The annualized conversion probabilities are shown in Table 3.

The transition progression matrix for SPMS based on data from London Ontario is presented in Table 4.

The annualized relapse rate was obtained from the UK MS Trust, which allows to estimate different relapse rates according to EDSS state for both RRMS and SPMS<sup>24</sup> (Table 5).

All-cause mortality rate, averaged by gender and age, was derived from general population mortality reported in national life tables<sup>25</sup>, and inflated by the authors of the model<sup>20</sup> to account for the excess mortality associated with MS. The standardized mortality ratio by EDSS state was

**Table 4.** Annual transition probability matrix by EDSS state for SPMS.

EDSS from/to	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)	7 (%)	8 (%)	9 (%)
2	74.4	18.7	2.1	2.8	1.8	0.1	0.1	0.0
3	0.0	70.4	15.9	3.1	9.6	0.5	0.4	0.0
4	0.0	0.0	66.4	13.8	18.1	0.9	0.9	0.0
5	0.0	0.0	0.0	57.4	37.4	2.6	2.6	0.0
6	0.0	0.0	0.0	0.0	87.4	4.8	7.7	0.0
7	0.0	0.0	0.0	0.0	0.0	76.1	23.5	0.4
8	0.0	0.0	0.0	0.0	0.0	0.0	99.6	0.4
9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	100.0

Abbreviations. EDSS, expanded disability status scale; SPMS, secondary progressive multiple sclerosis.

Source: Ebers<sup>23</sup>.

**Table 5.** Annualized relapse rate by EDSS state and MS classification.

EDSS state	RRMS	SPMS
0	0.890	0.000
1	0.789	0.000
2	0.648	0.605
3	0.616	0.515
4	0.553	0.487
5	0.525	0.423
6	0.515	0.360
7	0.448	0.303
8	0.367	0.251
9	0.296	0.217

Abbreviations. EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Source: UK MS Trust<sup>30</sup>.

**Table 6.** MS standardised mortality ratios by EDSS state.

EDSS state	Mortality multiplier
0	1.000
1	1.430
2	1.600
3	1.637
4	1.674
5	1.842
6	2.273
7	3.097
8	4.447
9	6.454

Abbreviation. EDSS, expanded disability status scale.

Source: Sadovnick et al.<sup>26</sup>.

modelled using data from a prospective survey of MS people reported in Sadovnick et al.<sup>26</sup> and Pokorski<sup>27</sup>. The mortality multiplier applied to both populations, RRMS and SPMS, is showed in Table 6. The original study by Sadovnick et al.<sup>26</sup> did not differentiate between MS subtypes. Therefore, we assumed the same multiplier for both populations.

Comparative efficacy of cladribine tablets was obtained from a systematic review and network meta-analysis (NMA)<sup>28</sup>, which included aggregated data from 44 clinical trials assessing 12 DMDs, and provided data for the subgroup of patients with HDA. The clinical efficacy of DMDs in the subgroup with HAD was modelled for the relative reduction in annualized relapse rate (ARR) and a reduction in the hazard rate for EDSS progression, defined as 3-month confirmed disability progression. Although the original publication from Siddiqui et al.<sup>28</sup> presents only the results for the overall ITT population and for confirmed disability progression at 6 months, the technical report of the NMA (not published)

and the model used provided data specifically for the HDA subgroup and for the 3-month period. Table 7 shows the results for the interventions assessed in the present study (cladribine tablets and fingolimod).

The risk of treatment-related adverse events was based in the systematic review and NMA<sup>28</sup> and published literature<sup>29–31</sup>.

Waning effect assumptions were based on CLARITY and the CLARITY extension study (CLARITY EXT) for cladribine tablets, and NICE submissions for fingolimod<sup>32,33</sup>. According to CLARITY EXT, treatment with cladribine tablets for two years resulted in a durable clinical response for at least two additional treatment-free years, with no significant differences in ARR or relapse-free proportion compared to the response achieved at the end of CLARITY. Therefore it was assumed that the full effect of cladribine tablets was

sustained through the first four years, waning from 66.7% (fifth year) to 33.3% (sixth year) of drug effect, with no effect assumed beyond year 6. For fingolimod, it was assumed 100% effect on the first 2 years, 75% from second year until fifth year and 50% thereafter.

Annual probability of treatment withdrawal was estimated based on CLARITY trial data for cladribine tablets (4.9%, applied until 2 years of treatment) and based in the NMA<sup>28</sup> for fingolimod (10.3%, applied while on treatment).

Adverse events were assumed to occur at the start of the simulation. The list of adverse events was defined following revision of the summary of product characteristics for each drug. This information was validated by experts' opinion. Model inputs related to adverse events are presented on Table 10.

**Table 7.** Relative clinical efficacy of cladribine tablets and fingolimod, vs. placebo.

Treatment related inputs	Cladribine tablets	Fingolimod
EDSS state progression (HR vs. placebo)	0.281 (0.148–0.532)	0.620 (0.416–1.018)
Annualized relapse rate (RR vs. placebo)	0.356 (0.242–0.506)	0.375 (0.269–0.507)

Abbreviations. EDSS, expanded disability status scale; HR, hazard ratio; RR, rate ratio. 95% credible interval in parenthesis.

**Table 8.** Mean utility scores.

Event	Patients		Caregivers
	RRMS	SPMS	RRMS/SPMS
EDSS 0	0.870	−0.045	−0.002
EDSS 1	0.799		−0.002
EDSS 2	0.705		−0.002
EDSS 3	0.574		−0.045
EDSS 4	0.610		−0.142
EDSS 5	0.518		−0.160
EDSS 6	0.460		−0.173
EDSS 7	0.297		−0.030
EDSS 8	−0.049		−0.095
EDSS 9	−0.195		−0.095
Relapse	−0.071		0

Abbreviations. EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

**Table 9.** Estimated annual costs, by EDSS.

EDSS state	Disease management (€)	Relapse (€)
0–3	1,185	1,567
4	5,004	2,347
5	6,781	2,178
6	8,557	2,009
7–9	12,677	1,706

Abbreviation. EDSS, expanded disability status scale.

**Table 10.** Model inputs related to adverse events.

Event	Probability of event		Desutility per event <sup>27</sup>	One-off costs (€)	Source of probabilities
	Cladribine tablets (%)	Fingolimod (%)			
Progressive multifocal leukoencephalopathy	0.0	0.001	−0.200	3,233	MS Trust (2016) e EMA <sup>24</sup>
Serious infection	2.8	2.2	−0.190	1,917	NMA
Macular oedema	0.0	0.4	−0.400	95	Pooled data
Gastrointestinal disorder	24.5	30.4	−0.240	906	NMA
Thyroid related event	5.1	1.2	−0.110	1,034	NMA
Influenza-like symptoms	1.3	0.5	−0.210	16	NMA
Malignancy	0.6	0.6	−0.116	5,290	Pakpoor et al. (2015)

Abbreviation. NMA, network meta-analysis.

### Utility scores

Utility weights for patients and caregivers, as well as the disutility due to relapses, were derived from the UK MS Survey and published literature<sup>34</sup>. The scores used in the model are presented in Table 8. Adverse event disutility (ranging between 0.110 and 0.400) and duration were obtained from published literature<sup>35</sup>.

### Resource utilization and costs

Resource consumption estimates were based on relevant national published literature<sup>36</sup>. The estimates reported were revised by clinical experts from the National MS society. Hospital resource utilization and costs were directly sourced from the Portuguese 2015 diagnostic related group (DRG) microdata. Multiple sclerosis inpatient episodes were identified through International Classification of Diseases, 9th Revision (ICD9: 340).

Resources were valued according to Portuguese official sources: Portaria 234/2015<sup>37</sup> Catalogue for Public Health Procurement (SPMS, 2016) and Infomed<sup>38</sup>. Only direct costs were computed.

Table 9 presents the estimated annual costs by EDSS state. In contrast with most previous cost-effectiveness analyses on MS, the base-case scenario considered different costs for relapse, according to EDSS state. The reason being because the Portuguese experts consistently identified different relapse resource consumption according to EDSS state (including differences on the number of hospitalizations, on rehabilitation and technical aids).

Cladribine tablets price was made available by the market authorization holder. The dose depends on body weight

(3.5 mg/Kg), so drug costs were estimated according to the weight distribution published in the Portuguese National Health Survey 2014<sup>25,39</sup>. Both cladribine tablets and fingolimod are oral treatments, therefore no administration costs were considered.

Costs associated with rescue therapy among cladribine-treated patients were considered in the model as one-off cost. A logistic-regression model with fixed effects for trial group and region was adjusted to estimate the probability of receiving rescue therapy for cladribine tablets *versus* placebo (OR = 0.40 [0.19–0.81]). It was estimated that rescue therapy with interferon beta-1a was given to 2.6% of patients in cladribine arm.

Costs associated with treatment-related adverse events are presented in Table 10.

### Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were performed. One-way deterministic sensitivity analyses were undertaken on the following parameters: transition probabilities, mortality risk, discontinuation, treatment waning effect, utility weights, discount rate, time horizon and costs (EDSS disability, relapse and adverse events). For costs and utility weights parameters, the deterministic sensitivity analyses considered the estimates for Portugal<sup>40</sup> from the recent cross-sectional study<sup>41</sup>, conducted in 16 European countries. A total of 535 Portuguese patients (54% with RRMS) were included in the European cross-sectional study.

Probabilistic sensitivity analysis (PSA) was performed to account for uncertainty in the estimate of the parameters. The simulation included 10,000 iterations. The parameters considered in the PSA and the corresponding distributions are described in Table 11.

## Results

### Base-case scenario

Treatment with cladribine tablets was associated with a delay in disease progression, resulting in a gain of 0.85 quality adjusted life years (QALYs). From an economic viewpoint, this delay allowed for a decrease in total follow-up costs that amount to 25,935 € (time-horizon of 50 years). Paradoxically, as the relative relapse risk was higher in lower EDSS states, it implies an increase in relapse costs. These results showed that cladribine tablets was dominant when compared to fingolimod (Table 12).

### Sensitivity analysis

The sensitive analysis performed (Table 13) showed that base-case results were robust, with cladribine tablets remaining a dominant strategy compared to fingolimod.

All the assumptions regarding costs had a minor impact on results. Considering an 11-state model, without distinction between RRMS and SPMS, resulted in higher cost savings. Although CLARITY EXT trial supports the durability of

**Table 11.** Parameters and distributions used in probabilistic sensitivity analysis.

Parameters	Distribution
Mean initial age	Lognormal
Number of relapses on previous year	Lognormal
Weight distribution	Dirichlet
EDSS initial distribution	Dirichlet
Mortality rate	Lognormal
Annualized relapse rate	Lognormal
Proportion of patients with rescue therapy	Beta
Transition probabilities for SPMS	Dirichlet
Transition probabilities for RRMS	Dirichlet
HDA adjustment factor	Lognormal
Progression risk (HR vs. placebo)	Lognormal
Relapse rate (RR vs. placebo)	Lognormal
Rescue therapy risk (OR vs. placebo)	Lognormal
Withdraw risk	Beta
Adverse events risk	Beta
RRMS utility decrements	Lognormal
SPMS utility decrement	Lognormal
Utility decrement for caregivers RRMS/SPMS	Lognormal
Utility decrement by relapse/adverse events	Lognormal
Adverse events costs	Lognormal
Costs by EDSS state/relapse	Gamma
Salvage therapy duration	Normal

Abbreviations. EDSS, expanded disability status scale; HDA, high-disease activity; HR, hazard ratio; RR, rate ratio; OR, odds ratio; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

**Table 12.** Results for estimated costs and consequences (base-case scenario).

	Cladribine tablets	Fingolimod	Incremental
Total costs (€)	190,076€	216,012€	–25,935€
Treatment	49,779€	65,985€	–16,206€
Administration	0€	20€	–20€
Monitoring	244€	478€	–234€
EDSS	129,207€	139,445€	–10,238€
Relapse	9,947€	9,720€	227€
Rescue therapy	536€	0€	536€
Adverse events	363€	364€	0€
QALY	3.42	2.58	0.85
ICUR (€/QALY)			–30,651€/QALY

Abbreviations. QALY, Quality adjusted life years; ICUR, incremental cost-utility ratio.

cladribine tablets effect, if we assume that treatment effect doesn't sustain after the third year (worst case scenario), the dominance was maintained.

Probabilistic sensitivity analysis resulted in a mean ICER of –31,781 € per QALY. These results confirmed the dominant profile of cladribine tablets compared to fingolimod. Cladribine tablets was dominant in 98.7% of the 10,000 simulations (Figure 2).

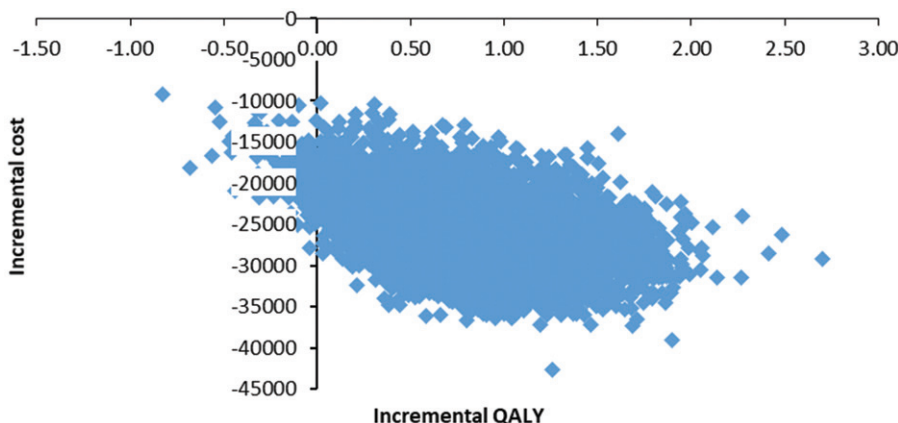
## Discussion and conclusion

In spite of the low incidence and prevalence rates, MS is one of the leading causes of non-traumatic disability in young adults (World Health Organization [WHO] 2013). Interestingly, the global MS burden of disease, assessed by disability-adjusted life years (DALY), has been recently reported to have a global downward trend<sup>43</sup>. This trend was found for both developed and developing countries, although MS DALY rates are about 25 higher in developed countries compared to developing ones. According to the authors, the reason for this decline, especially in European countries, was that by increasing level of health care (and budget) for MS

**Table 13.** One-way deterministic sensitivity analyses results.

	Incremental values	
	Costs (€)	QALY
Base-case	-25,935	0.85
Costs		
EDSS state		
+20%	-27,983	0.85
-20%	-23,888	0.85
Sá et al. <sup>40</sup>	-28,274	0.85
Relapse		
+20%	-25,890	0.85
-20%	-25,981	0.85
Sá et al. <sup>40</sup>	-25,742	0.85
Unique cost (equal to 1,845 €)	-25,898	0.85
EDSS and relapse		
+20%	-27,938	0.85
-20%	-23,933	0.85
Sá et al. <sup>40</sup>	-28,081	0.85
Health-related quality of life		
Hawton et al. <sup>42</sup>	-25,935	0.79
Sá et al. <sup>40</sup> – Portuguese tariffs	-25,935	0.81
Without disutility by adverse events	-25,935	0.85
Without caregivers' disutility	-25,935	0.80
No adverse events		
11-state model structure	-55,006	0.84
Progression based on London Ontario data	-22,343	0.62
Without HDA subgroup adjustment	-28,603	0.74
RRMS transition by disease duration	-47,786	0.85
Relapse rate by disease duration	-26,464	0.85
Fixed mortality (HR =1.68)	-27,303	0.88
Discontinuation		
No discontinuation	-36,075	0.81
Same probability of treatment withdrawal for both arms (4.9%)	-31,288	0.79
Waning effect		
No cladribine tablets effect after third year	-20,920	0.44
No cladribine tablets effect after second year	-17,485	0.17
Assume the same waning effect of fingolimod for cladribine tablets	-29,079	1.12
Assume the same waning effect of cladribine tablets for fingolimod (full efficacy for 4 years)	-25,749	0.80
No waning effect for both cladribine tablets and fingolimod	-40,966	2.04
Discount rate		
7%	-22,065	0.72
3%	-30,361	1.01
0%	-37,973	1.38
Time horizon (years)		
30	-26,249	0.84
40	-26,014	0.85

Abbreviations. QALY, Quality adjusted life years; EDSS, expanded disability status scale; HDA, high-disease activity; HR, hazard ratio.



**Figure 2.** Cost-effectiveness scatter plot.

patients, the age of death had risen significantly in recent years. Overall, this positive effect outweighs the negative impact on the number of years that MS patients live with disability.

Our study showed that cladribine tablets was a dominant strategy in patients with HDA-RRMS, being a less costly and

more effective treatment than fingolimod. Cladribine tablets demonstrated to have an incremental benefit on disease progression when compared to fingolimod. However, this benefit was not observed when relapse rate was considered, possibly due to the fact that estimated relapse rates were lower in higher EDSS states.

Our study had several limitations. First, this study does not include other current treatment options for MS patients with HAD, in particular natalizumab and alemtuzumab. The reasons for not having included these comparators are: (1) Fingolimod is the first treatment option in Portugal for MS patients with HAD, representing about 2/3 of the overall second-line treatments; (2) Alemtuzumab was not an option at the time of the study (Q1, 2018) because it was not reimbursed for use in Portuguese NHS hospitals; (3) When fingolimod was evaluated by the national HTA Authority, the selected comparator was natalizumab because natalizumab was, at that time (Q1, 2012), the only treatment option for patients with HAD and an insufficient response to first-line treatments, as well as for patients with rapidly evolving severe RRMS. The national HTA Authority considered that, for this population, fingolimod had an added therapeutic value in comparison to natalizumab due to safety and convenience aspects. Fingolimod proved cost-effectiveness in a minimization cost analysis due to the lower treatment costs; and (4) Both fingolimod and cladribine tablets are oral treatments, and mode of administration is considered a relevant factor associated with patient preferences.

Second, the 21-health state model structure is commonly used in multiple sclerosis assessments but it should be stressed that the RRMS matrix was based on BCMS data which also includes patients with SPMS (16%). Although this was not expected to influence results, it should be addressed as a limitation. Third, after discontinuation, patients were assumed to switch to Best Supportive Care, with progression and relapse rates based on disease natural history. Although treatment switching may occur in clinical practice, this was not considered in our study, once no clinical data after switch was available.

Moreover, according to the perspective followed, only direct costs were included. Although it could be argued that the inclusion of indirect costs would have provided a more comprehensive analysis, our approach can be potentially viewed as a conservative one, as it could be assumed that the inclusion of indirect costs may demonstrate a stronger dominance of cladribine tablets.

The results from the sensitivity analyses showed that the cost-effectiveness estimates on cladribine tablets were robust. The major source of uncertainty was the efficacy of DMDs beyond clinical trial duration. In line with previous studies<sup>32,33</sup>, we considered a reduced effect of DMD beyond year 2 through the waning effect. Although CLARITY-EXT justifies the waning effect assumed for cladribine tablets over 4 years, there was no data to support the assumptions beyond the fourth year. Considering no cladribine tablets effect after the fourth year impacted the estimated QALYs (reduced from 0.85 to 0.44).

Recently, Hettle *et al.*<sup>20</sup> published a cost-effectiveness analysis comparing cladribine tablets with alemtuzumab and natalizumab in the treatment of relapsing-remitting multiple sclerosis with HDA in England. The authors found that cladribine tablets was a dominant alternative. However, no comparison regarding fingolimod was done. Of note, in this study the authors used an 11-health state structure that tracks the disability status of a combined cohort of people

with RRMS and SPMS, instead of the 21-health state model used in the present case.

NICE appraised the cost-effectiveness of cladribine tablets, compared to alemtuzumab, daclizumab, fingolimod and natalizumab, for two separate subgroups of HDA-RRMS (patients with rapidly evolving severe and sub-optimally treated), not providing data for the overall HDA-RRMS population. Despite the uncertainty in the available data, NICE concluded that cladribine tablets could be considered a cost-effective use of National Health Service (NHS) resources in both subgroups of HDA-RRMS<sup>44</sup>.

To the best of our knowledge, our study was the first to assess the cost-effectiveness of cladribine tablets versus fingolimod in patients with HDA-RRMS. The results showed that cladribine tablets were a cost-effective alternative to fingolimod in the treatment of HDA-RRMS from the portuguese payers' perspective.

## Transparency

### Declaration of funding

The study was funded by Merck S.A. Funding was independent of the study outcome. The sponsor did not participate in the design, analysis or interpretation of the data. The drafting and final version of the paper is the solely responsibility of the authors.

### Declaration of financial/other relationships

All authors are members of the Evidence Based Medicine (EBM) Center at Lisbon School of Medicine, Portugal. This research centre is devoted to pre- and postgraduate medical education. Since 2002, the Lisbon EBM Center has undertaken several clinical, epidemiological and pharmaco-economic research projects, which had unrestricted funding from over 20 different pharmaceutical companies. One of those was Merck S.A., which developed cladribine tablets. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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## Author contributions

Pinheiro B, Costa J and Miguel LS were involved in all phases of the work, including conception and design, analysis and interpretation of the data, the drafting of the paper and critical revision for intellectual content.

Guerreiro R participated in the conception, the drafting of the paper and critical revision for intellectual content.

All authors approved the final version of the published manuscript and agree to be accountable for all aspects of the work.

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