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ORIGINAL RESEARCH

Cost-Effectiveness of Dimethyl Fumarate Compared to Teriflunomide for Relapsing Remitting Multiple Sclerosis Patients in Italy

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ABSTRACT

BACKGROUND: The objective of this economic analysis was to compare the cost-effectiveness of dimethyl fumarate vs teriflunomide for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) in the Italian setting. Additionally, the cost-effectiveness analysis was used to predict some patient-relevant outcomes such as burden of relapses and survival with disability over time.

METHODS: A Markov model was used to conduct the cost-effectiveness analysis. The model measured health outcomes and costs of RRMS patients treated with either dimethyl fumarate or teriflunomide. Data from a published mixed treatment comparison were used for efficacy and safety input. Local economic data were used to calculate costs. A supplementary analysis was carried out to assess ICER variability over time from the Italian National Healthcare Service (NHS) and societal perspectives. Further analyses were conducted to compare clinical effectiveness of the alternatives over time, in terms of incidence of relapses, proportion of patients with EDSS (Expanded Disability Status Scale) score ≤3 and EDSS score ≥6.

RESULTS: In the base-case analysis (lifetime horizon; societal perspective) dimethyl fumarate was dominant over teriflunomide (6.526 vs 5.953 QALYs – quality-adjusted life-years; € 1.01 M vs € 1.03 M). The most relevant cost savings (per-patient) with dimethyl fumarate were related to relapses (-€ 5,096), inpatient care (-€ 5,767), informal care (-€ 9,603), long-term absence/early retirement (-€ 14,187). The additional analysis of ICER by time horizon shows that dimethyl fumarate is cost-effective vs teriflunomide (i.e., ICER <€ 50,000 per QALY gained) at already 6 years and at 15 years in societal or NHS perspectives, respectively. Results favoured dimethyl fumarate vs teriflunomide also for: cumulative burden of relapses (-0.23 and -1.37 relapses saved per patient already at 1 year and 10 years, respectively), proportion of patients with mild disability (+4.0% at 10 years), proportion of patients with severe disability (-4.0% at 10 years).

CONCLUSIONS: Dimethyl fumarate is dominant (societal perspective), or cost-effective (NHS perspective), referring to a threshold of € 50,000 per QALY gained, vs teriflunomide for the first-line treatment of RRMS, in the Italian setting.

Keywords

Dimethyl Fumarate; Teriflunomide; Relapsing-Remitting Multiple Sclerosis; Cost-Effectiveness; Quality-Adjusted Survival

INTRODUCTION

Multiple Sclerosis (MS) is a demyelinating disease that affects the central nervous system (brain and spinal cord). In 2019, MS prevalence was about 2.8 million subjects worldwide [1], 750 thousand in Europe [2] and 122 thousand in Italy, where every year new 3,400 cases are diagnosed [2,3].

MS onset can occur at any age of life, but is mostly observed in young adults, aged between 20 and 40 years old [4,5]. This brings considerable clinical and economic burden on patients, healthcare systems and society [6-8].

In Italy, the annual societal costs of MS amount to about € 5 billion [3]. Studies on the economic impact for society (i.e. evaluating both healthcare and non-healthcare direct and indirect costs) show that the annual costs per patient are in the range of € 45 thousand [3].

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Reasonably, the economic burden of MS increases with the severity of the disease and its associated disability, ranging from about € 18,000 for patients with mild disability, up to € 84,000 for the most severe patients [3].

Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS. About 85% of patients with MS have a relapsing-remitting form at disease onset [9]. Within 20-25 years, ~60-70% of RRMS patients enter a second disease phase characterized by continuous, irreversible neurological decline unassociated with relapses (secondary progressive form – SPMS) [9]. The remaining 15% of patients have a primary progressive form (PPMS) at diagnosis [9].

Several decades ago, the approval and introduction of the first-generation therapies for RRMS (interferon β-1b, interferon β-1a, glatiramer acetate) dramatically changed the natural history of the disease. As a matter of fact, these therapies had and still have an important role in the RRMS therapeutic algorithm, as they can prevent relapses, reduce disease activity, and consequently delay disease progression and disability accumulation (disease-modifying therapies, DMTs). However, despite the unprecedented efficacy in this therapeutic area, it was quite clear to the scientific community that treatment with injectable therapies in RRMS was only partially addressing the unmet medical need of RRMS [10-12], with some clinical issues remaining open. Limited efficacy in managing highly active forms, limited duration of effect, discomfort of patients for injectable therapies driven by tolerability issues, were some of the main drawbacks associated with first-generation therapies. Such limitations pushed scientists to develop new options to manage patients more appropriately during both the initial phases of the disease, and in patients with refractory disease [10-12].

The first-line oral therapies dimethyl fumarate (delayed-release dimethyl fumarate, also known as gastro-resistant dimethyl fumarate, trade name: Tecfidera® [13,14]) and teriflunomide (trade name: Aubagio® [15,16]) have been developed to effectively prevent relapses, delay disability progression in RRMS, overcome the typical issues of first-generation therapies, improve patients' quality of life and finally provide physicians with therapeutic options with novel mechanisms of action. While the increase in the number of therapeutic options is certainly a great opportunity for patients and physicians, who can "personalize" treatment, multiple options pose important questions regarding economics, i.e. prescribing cost-effectively. In this paper, we aimed to compare costs and outcomes of delayed-release dimethyl fumarate (hereafter defined as "dimethyl fumarate", for simplicity), vs. teriflunomide in the Italian population, according to the approved indication, for the treatment of adult patients with RRMS. The rationale for choosing dimethyl fumarate and teriflunomide is that it was intended to compare the two first-line oral therapies for the treatment of RRMS.

MATERIALS AND METHODS

Study design

This cost-effectiveness analysis was carried out by adapting a Markov model (previously in other cost-effectiveness evaluations in RRMS [17-20]), to the Italian setting. The model was developed to simulate the clinical and economic outcomes of a hypothetical cohort of RRMS patients, that could either receive dimethyl fumarate (240 mg twice a day) or teriflunomide (14 mg daily). More specifically, this model is a cohort-based Markov model in which patients are able to progress through a series of disability health states (measured through the Expanded Disability Status Scale -EDSS- [21]).

At the beginning of the simulation, patients enter the model and are allocated in different EDSS health states, according to their baseline characteristics. During model simulation, patients can experience: i) disease progression (EDSS increase); ii) disease improvement (EDSS decrease); iii) stable disease (unchanged EDSS score). Furthermore, patients can also progress to the SPMS form, where they will progress at a faster rate. Patients transitioning from RRMS to SPMS will also transition from EDSS score "x" (in the RRMS form) to EDSS score "x+1" (in the SPMS form). After transition to the SPMS form, patients can either progress to a higher EDSS state, or remain in their current state.

In the RRMS form, treatment with dimethyl fumarate and teriflunomide have the effect of modifying the natural disease progression, by reducing disease activity and delaying disability accumulation. Furthermore, it is assumed that: i) treatment with DMTs does not have any effect in preventing transition from RRMS to SPMS and delaying disability progression within the SPMS form; ii) treatment with DMTs is interrupted when patients reach an EDSS score ≥7 or when they switch to the SPMS form (any EDSS level).

Overall, the model consists of 21 health states: 10 states corresponding to the possible 10 disability levels (i.e. EDSS scores) in the RRMS form; 10 states corresponding to the possible 10 EDSS disability levels in the SPMS form; 1 death health state. A graphical illustration of the Markov model is shown in Figure 1. In the base-case analysis, dimethyl fumarate was evaluated vs. teriflunomide, adopting: i) societal perspective (i.e. including direct and indirect costs); ii) 50-year time horizon (lifetime); iii) 3.5% discount rate on both outcomes and costs, as recommended by NICE (National Institute for Health and Care Excellence) [22]. One-year cycles were used for this Markov model.

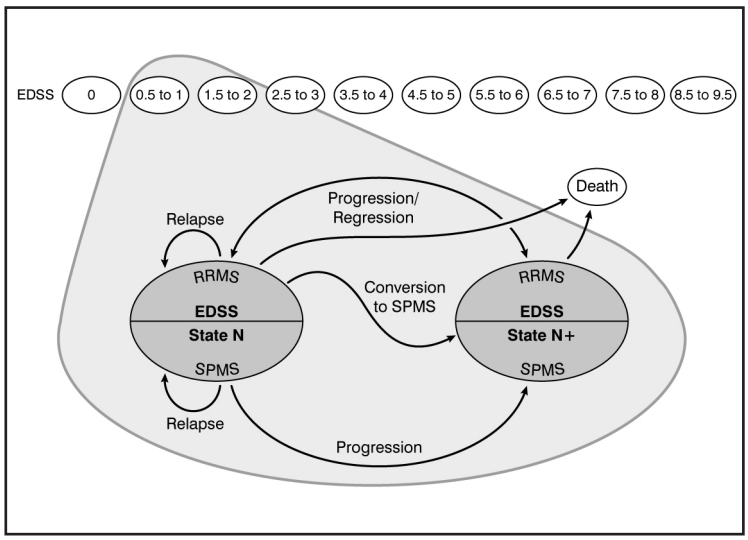

Figure 1. *Scheme of the Markov model used for the analysis (adapted from [19])*
EDSS = expanded disability status scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Data source

Baseline characteristics

The analysis refers to a hypothetical cohort of Italian patients affected by RRMS. It is assumed that the analysed patient population would have same baseline characteristics as observed in the clinical trials DEFINE and CONFIRM [23,24]. At baseline, patients have a mean age of 37.8 years, and 28.6% of them are men. The distribution of patients by EDSS score at model entry is shown in Table I (average EDSS score: 2.72).

Natural history

Natural history of disease has been conventionally measured through two main parameters: i) annual incidence of relapses; ii) annual EDSS progression probabilities. Data on annual relapse rates (Table 1) were obtained from i) dimethyl fumarate clinical trials [23,24], documenting relapse occurrence in the 12 months before study entry for RRMS patients with EDSS score ≤5; ii) from the study conducted by Patzold et al. [25], for RRMS patients with EDSS levels >5; iii) from the elaboration of a survey conducted in the UK [26], for patients affected by SPMS form.

Data on natural disease history (Supplementary Table I and Supplementary Table II), inform on how RRMS patients progress in disease severity in absence of treatment. They were elaborated from dimethyl fumarate clinical trials (CONFIRM, DEFINE [23,24]) and the London Ontario database, one of the most comprehensive and long-lasting observational registries on patients with multiple sclerosis [27-29].

Age- and sex-specific all-cause mortality rates for the general population were obtained from the Italian mortality tables [30]. These mortality rates were then adjusted by the MS-related additional risk of death [31].

Treatment efficacy

Treatment with DMTs like dimethyl fumarate or teriflunomide modify the natural history of the disease, i.e. reduce incidence of relapses and delay disability progression, compared to no treatment/placebo. Estimates of treatment efficacy for both therapies vs. placebo were extracted from the Mixed Treatment Comparison (MTC) conducted by Hutchinson et al. [32]. The MTC calculated risk ratios for relapses and hazard ratios for disability progression, for

Baseline data	EDSS level									
	0	1	2	3	4	5	6	7	8	9
Proportion of patients (%)	5.05	8.52	34.08	22.94	20.64	8.65	0.12	0.00	0.00	0.00
ARR (n of events per year)										
RRMS form, natural history	1.26	1.32	1.32	1.35	1.36	1.43	1.18	1.23	1.23	1.23
SPMS form, natural history	0.00	0.00	0.91	1.64	1.05	1.27	1.10	0.82	0.82	0.82

Table I. *Distribution of patients by EDSS at model entry and ARRs, in absence of treatment [23-29]*
ARR = annualized relapse rate; EDSS = expanded disability status scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Treatment	Disability progression at 12 weeks: HR vs. placebo (CI 95%)	ARR: RR vs. placebo (CI 95%)
Teriflunomide – 14 mg daily	0.7106 (0.5736-0.8803)	0.7113 (0.6224-0.8129)
Dimethyl fumarate – 240 mg twice daily	0.6051 (0.4713-0.7767)	0.5269 (0.4507-0.6159)
Placebo	Reference	Reference

Table II. *Treatment efficacy vs. placebo for relapse rate and disability progression [32]*
ARR = annualized relapse rate; CI = confidence interval; HR = hazard ratio; RR = risk ratio

both dimethyl fumarate and teriflunomide, compared to placebo. Both treatment effect ratios on ARR and disability progression are summarized in Table II.

To model disability worsening, annual probabilities of disability progression, in absence of treatment (placebo) were used. Annual values were taken from: i) dimethyl fumarate clinical trials (CONFIRM, DEFINE [23,24]) for RRMS EDSS states up to 7; ii) from the London Ontario dataset [27] for RRMS EDSS states 7 to 9 and for the SPMS form (Supplementary Table I); iii) from the London Ontario dataset [27], for transition probabilities from RRMS to SPMS (Supplementary Table II).

Adverse events

Adverse events (serious and non-serious) occurring in ≥5% patients in dimethyl fumarate studies and with an incidence difference of >3% between dimethyl fumarate and teriflunomide, were included in the analysis (Supplementary Table III). Annual incidence rates of treatment-related AEs were gathered from Hutchinson et al. systematic review and mixed treatment comparison [32]. Both effects and costs associated with AEs were analysed.

EDSS level	With relapses		Without relapses	
	RRMS	SPMS	RRMS	SPMS
0	0.8660	0.8223	0.8752	0.8315
1	0.8250	0.7814	0.8342	0.7905
2	0.7710	0.7274	0.7802	0.7365
3	0.6855	0.6418	0.6946	0.6509
4	0.6161	0.5725	0.6253	0.5816
5	0.5350	0.4913	0.5442	0.5005
6	0.4463	0.4027	0.4555	0.4118
7	0.3346	0.2909	0.3437	0.3000
8	-0.0068	-0.0505	0.0023	-0.0413
9	-0.1793	-0.2229	-0.1701	-0.2138

Table III. *Utilities weights by EDSS level, MS form and relapse health state [23,24,26]*
EDSS = expanded disability status scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

Quality of life data

Utility weights for patients affected by RRMS, stratified by EDSS level (Table III), were obtained from dimethyl fumarate trials [23,24] organizing the observations for each EDSS state and calculating the average EQ-5D (EuroQoL, 5 dimensions) score for each state. Disutility values were applied to RRMS utility values to calculate utility weights in: i) SPMS health states (RRMS utility minus 0.0437); ii) relapse health states (RRMS utility minus 0.0092); iii) health states with AEs (RRMS utility minus the sum of specific disutility values of individual AEs).

Both disutility scores associated with SPMS and relapse were retrieved from the survey conducted in the UK [26] and apply on annual basis (entire cycle duration). AE-related disutilities depend on the type and se-

Costs (€)[1]	EDSS level									
	0	1	2	3	4	5	6	7	8	9
Societal perspective										
RRMS	4,609	4,609	4,609	4,609	20,969	20,969	20,969	38,971	38,971	38,971
SPMS	10,070	10,070	10,070	10,070	45,811	45,811	45,811	85,137	85,137	85,137
NHS perspective										
RRMS	2,382	2,382	2,382	2,382	7,636	7,636	7,636	8,633	8,633	8,633
SPMS	5,204	5,204	5,204	5,204	16,681	16,681	16,681	18,861	18,861	18,861

Table IV. *Annual disability-related costs, by MS form and perspective [33,34]*
[1] Relating to RRMS form and EDSS levels <7, to avoid double counting DMT costs, disease management costs (e.g. monitoring, etc.) were subtracted from this calculation and considered in other calculation sections of the model
EDSS = expanded disability status scale; NHS = National Healthcare Service; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

verity of the AE itself, and have a temporary effect on patients' quality of life (from a minimum of one day per year, up to a maximum of six months per year, for some events such as fatigue and flu-like symptoms) and are reported in Supplementary Table III. Since AE-related disutilities were not available in literature, they were estimated and validated by clinical experts.

Economic data

The economic analysis was conducted adopting the societal perspective and considering the following costs: i) treatment with DMTs; ii) administration; iii) monitoring; iv) adverse events; v) relapses; vi) EDSS.

Disability-related costs, including indirect costs (loss of work productivity and absenteeism), were obtained from an elaboration of the data of the study conducted by Battaglia et al. 2017 [33] and Karampampa et al. [34]. Table IV shows disability-related annual costs included in the model, expressed in Euro and inflated from 2015 to February 2020 (coefficient 1.026) [35].

Annual treatment costs with DMTs (dimethyl fumarate and teriflunomide) were calculated using the ex-factory prices per pack (Table V), including the temporary law reductions and discounts granted to the Italian National Healthcare Service (NHS), multiplied by the number of packs needed to cover 1 year of treatment. No administration costs were included, as both drugs are administered orally. Annual monitoring costs were calculated assuming that patients would be compliant with main recommendations for the follow-up of RRMS [36,37] (Table V). These costs take into account the number of annual examinations (magnetic resonance imaging, blood count, kidney and liver function, etc.) and annual visits (neurological).

The cost of relapse management (cost per episode) was obtained from Battaglia et al. 2017 (€ 2,600 and € 1,497, respectively for societal and NHS perspectives, in December 2015 [33]) and then inflated from 2015 to February 2020 (€ 2,668 and € 1,536, respectively; coefficient 1.026) [35]. Finally, treatment-related adverse event costs were calculated by multiplying the unit costs in the Italian practice (Supplementary Table V), by the respective annual incidence rates of treatment-related AEs (Supplementary Table III).

It was assumed that mild-to-moderate events were managed either by general practitioners (GPs) [38] or specialized neurologists [39], while severe events were managed in the hospital setting (either day-hospital or standard admission [40,41], depending on the event). All economic inputs are summarized in Table V.

Additional analyses on time horizon and clinical outcomes

A supplementary analysis was carried out to assess ICER variability over time, in both Italian NHS and societal perspectives.

Further analyses were conducted to compare the clinical effectiveness of the two treatments over the time horizon, in terms of: i) incidence relapse rates; ii) percentage of patients with EDSS score ≤3; iii) percentage of patients with EDSS score ≥6.

Sensitivity analyses

Both univariate deterministic and multivariate probabilistic sensitivity analyses were conducted to identify model parameters with the largest effect on incremental cost-effectiveness ratio (ICER), and to evaluate the overall robustness of the base-case analysis.

For the deterministic sensitivity analysis, the baseline value of each parameter (dimethyl fumarate relapse rate, dimethyl fumarate disability progression rate, teriflunomide relapse rate, teriflunomide disability progression rate) was modified to the upper and lower limits of its 95% confidence inter-

Description of costs	Value (€)	Source/Note
Drug acquisition costs		
Dimethyl fumarate	1,153.00 (56 capsules, 240 mg)	Ex-factory price[1] (Official Journal 19, 2015 [13])
Teriflunomide	1,027.75 (28 tablets, 14 mg)	Ex-factory price[1] (Official Journal 187, 2014 [15])
Administration costs		
Dimethyl fumarate	0.00	Assumption, as both drugs are administered orally
Teriflunomide	0.00	
Monitoring costs		
Dimethyl fumarate (Year 1)	912	[36,37]
Teriflunomide (Year 1)	977	
Dimethyl fumarate (Year 2)	334	
Teriflunomide (Year 2)	350	
Adverse events costs		
Dimethyl fumarate	32	Mild to moderate: GP [38] or specialist [39] visit; Severe: DH or hospital admission [40,41]
Teriflunomide	11	
Relapse management costs	2,668	Battaglia et al. 2017 [33], expressed in Euro (February 2020) [35]

Table V. *Economic data included in the analysis*

[1] It does not include temporary law reductions and any discounts applied to public structures of Italian NHS

DH = day hospital; DMT = disease-modifying therapies; GP = general practitioner

val (95% CI). If the CI was not available, a variation of ± 10% from the baseline value (EDSS state costs, relapse costs, patient utilities, natural history relapse rates) was used.

Three additional deterministic sensitivity analyses were conducted. In the first analysis, the Italian NHS perspective was adopted with lifetime horizon. In the second and third analyses, a shorter time horizon was used (15 years) to run both the Italian societal perspective and the Italian NHS perspective analyses.

For the probabilistic analysis, the following distributions were used: lognormal for clinical variables (relapse rates, progression rates and utilities); beta for EDSS transition probabilities to SPMS form and adverse event rates; gamma for costs. A 10% standard error of the mean value of each variable was used to run probabilistic sensitivity analysis.

RESULTS

Base-case

In the base-case analysis (societal perspective and lifetime horizon), dimethyl fumarate was more effective than teriflunomide, both in terms of survival (19.634 and 19.547 life years, LYs, respectively), and quality-of-life-adjusted survival (6.526 and 5.953 QALYs, respectively). The total lifetime cost per patient treated with dimethyl fumarate (€ 1,010,112) was lower than the cost per patient treated with teriflunomide (€ 1,030,436).

Therefore, dimethyl fumarate was dominant (i.e. more effective and less costly) compared with teriflunomide. Table VI illustrates the results of the cost-effectiveness analysis.

The cost saving for patient treated with dimethyl fumarate vs teriflunomide was € 20,324. The saving is mainly evident on cost of relapses (-€ 5,096), inpatient care (-€ 5,767), informal care (-€ 9,604) and long-term absence/early retirement (-€ 14,187).

Additional analyses on time horizon and clinical outcomes

The results of ICER assessment by time horizon and perspective showed that dimethyl fumarate was cost-effective vs. teriflunomide (i.e. ICER <€ 50,000 per QALY gained) at already

Item	Dimethyl fumarate (A)	Teriflunomide (B)	Difference (A-B)
Outcome			
LYs	19.634	19.547	0.087
QALYs	6.526	5.953	0.573
Costs (€)			
Treatment costs[1]	94,637 (9.36%)	72,608 (7.05%)	22,030.04
Adverse events	261 (0.03%)	87 (0.01%)	173.41
Relapse[2]	43,943 (4.35%)	49,039 (4.76%)	-5,096.37
EDSS[2]	871,271.12	908,702.46	-37,431.35
Inpatient care	136,387 (13.50%)	142,154 (13.80%)	-5,766.69
Day admission	34,508 (3.42%)	35,290 (3.42%)	-782.29
Consultations	23,957 (2.37%)	24,795 (2.41%)	-838.21
Tests	12,826 (1.27%)	12,772 (1.24%)	53.81
Medication	20,817 (2.06%)	21,461 (2.08%)	-644.19
Community service	83,676 (8.28%)	88,014 (8.54%)	-4,338.27
Investments	29,022 (2.87%)	30,347 (2.95%)	-1,324.94
Informal care	208,419 (20.63%)	218,022 (21.16%)	-9,603.54
Absence, invalidity and early retirement	321,661 (31.84%)	335,848 (32.59%)	-14,187.04
Total social costs	**1,010,112 (100.00%)**	**1,030,436 (100.00%)**	**-20,324.26**
ICER (€/QALY gained)		**Dimethyl fumarate dominant**	

Table VI. *Results of the incremental cost-effectiveness analysis (base-case: societal perspective and lifetime horizon)*

[1] Including monitoring costs

[2] Including direct and indirect costs

EDSS = expanded disability status scale; ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life years

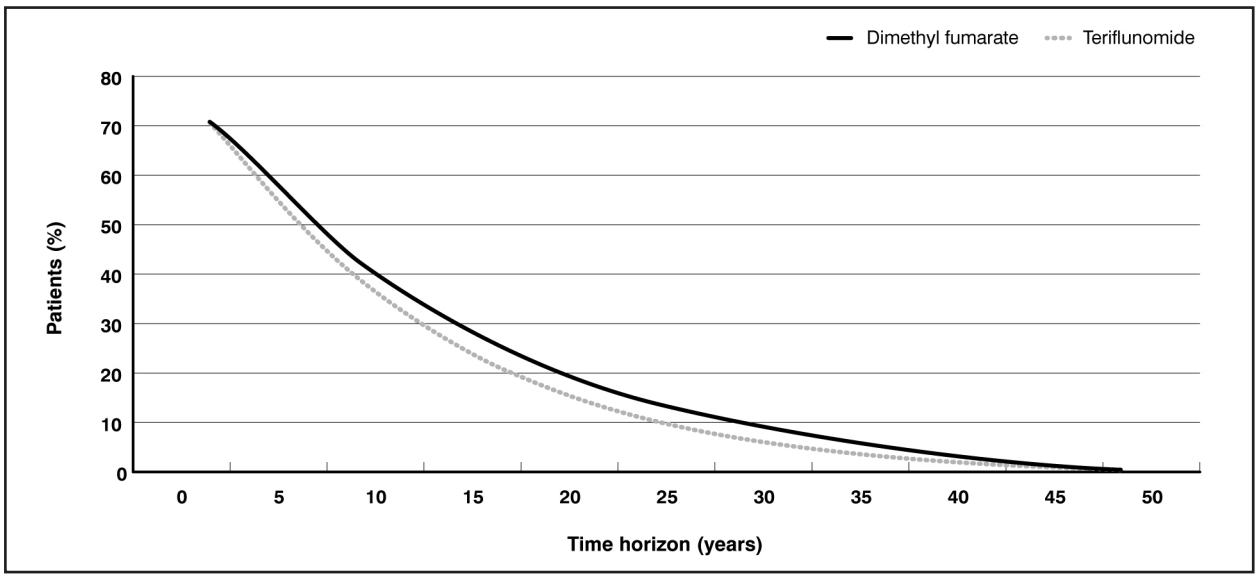

Figure 2. *Proportion of patients with mild disability (EDSS ≤3), over time horizon used in the economic model*

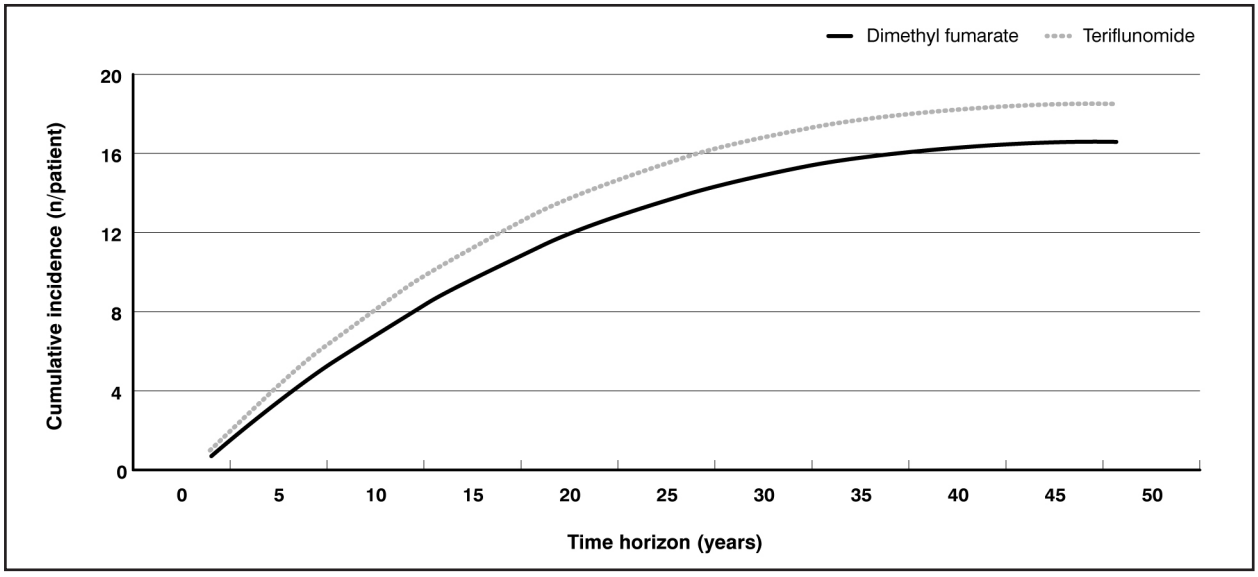

Figure 3. *Incidence of relapses over time horizon used in the economic model*

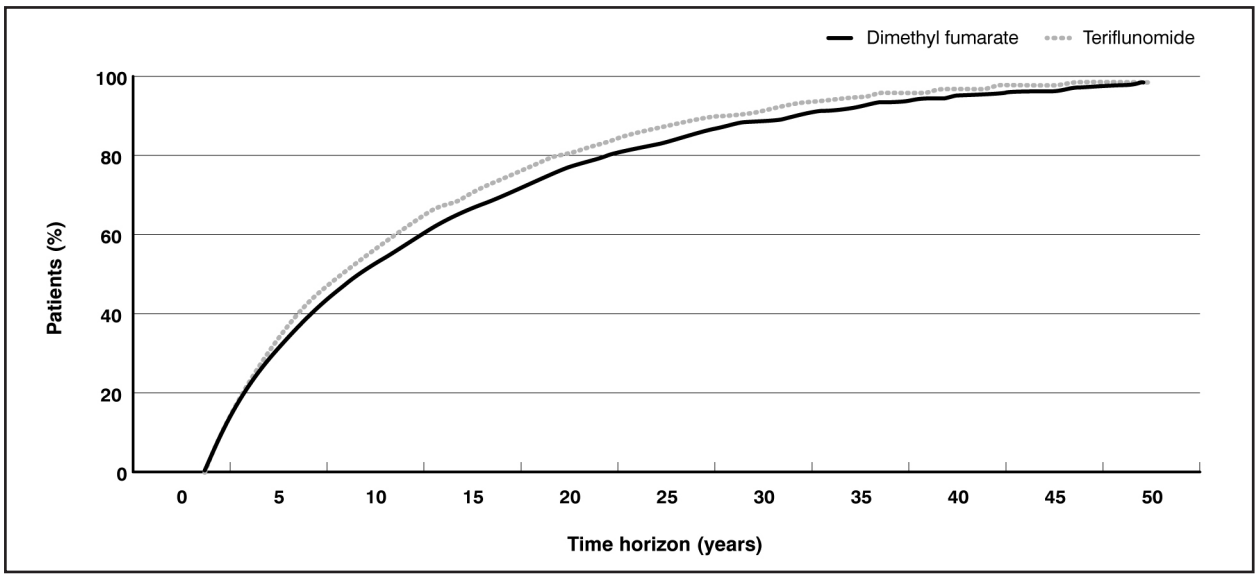

Figure 4. *Proportion of patients with severe disability (EDSS ≥6), over time horizon used in the economic model*
EDSS = expanded disability status scale

6 years, if the societal perspective is adopted, and at 15 years, if the Italian NHS perspective is adopted.

The model also informed on several patient-relevant outcomes such burden of relapses and life years with mild/severe disability (EDSS ≤3; EDSS ≥6). The onset of relapse benefit with dimethyl fumarate occurred quite earlier in time, during the first years of treatment with -0,23 relapse per patient (Figure 3). For instance, at 10 years, patients treated with dimethyl fumarate experienced -1.37 relapses less than patients treated with teriflunomide, which translated into 4% more patients with reduced disability (EDSS ≤3). Then, the benefit (i.e. higher proportion of patients with mild EDSS) has been stable up to year 25, while decreasing afterwards (because of combined effect of disease progression, SPMS transition, and mortality) (Figure 2). The proportion of patients with severe disability (EDSS ≥6), treated with dimethyl fumarate was lower than that treated with teriflunomide already after 3 years from model simulation, and remained steadily lower until about the 35th year (Figure 4).

Sensitivity analysis

One-way deterministic sensitivity analysis showed that dimethyl fumarate was dominant in all tested alternative scenarios, excluding the case of use of the lower limit of the 95% CI for teriflunomide disability progression rate. Moreover, dimethyl fumarate remained cost-effective compared with teriflunomide in the three additional deterministic scenarios tested, with an incremental cost effectiveness ratio ICER below the willingness-to-pay (WTP) threshold of € 50,000 per QALY gained (Table VII).

Figure 5 shows the results of probabilistic sensitivity analysis performed on the base-case, expressed as probability of dimethyl fumarate to be cost-effective or dominant with respect to teriflunomide, below a WTP threshold of € 50,000 per QALY gained.

The acceptability curve of the cost-effectiveness analysis (CEAC, Figure 5) shows that when the willingness to pay (WTP) was € 50,000 per QALY gained, dimethyl fumarate had 78% probability of being cost-effective compared to teriflunomide, based on societal perspective and lifetime horizon. In 72% of the iterations, dimethyl fumarate was dominant over teriflunomide.

Figure 6 shows the results of probabilistic sensitivity analysis performed on the alternative scenario #1 (NHS perspective and lifetime horizon). The CEAC shows that when the WTP was € 50,000 per QALY gained, dimethyl fumarate had 68% probability of being cost-effective compared to teriflunomide, based on NHS perspective and lifetime horizon.

Alternative Scenario	Perspective	Time horizon	ICER (€/QALY gained)
#1[1]	Italian NHS	Lifetime	19,691.41
#2	Societal	15 years	-25,348.32 Dominant
#3	Italian NHS	15 years	41,189.50

Table VII. *Sensitivity analysis: results of alternative scenarios*
[1] Supplementary Table V
ICER = incremental cost-effectiveness ratio; NHS = National Healthcare Service; QALY = quality-adjusted life years

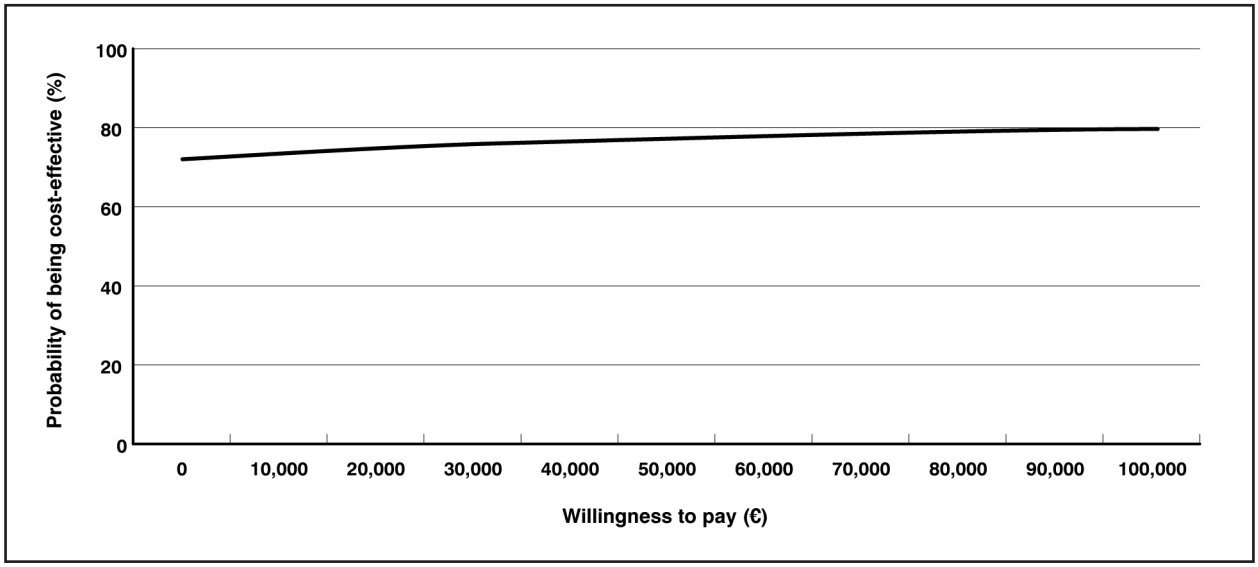

Figure 5. *Probabilistic sensitivity analysis: acceptability curve of dimethyl fumarate vs. teriflunomide (base-case: societal perspective and lifetime horizon)*

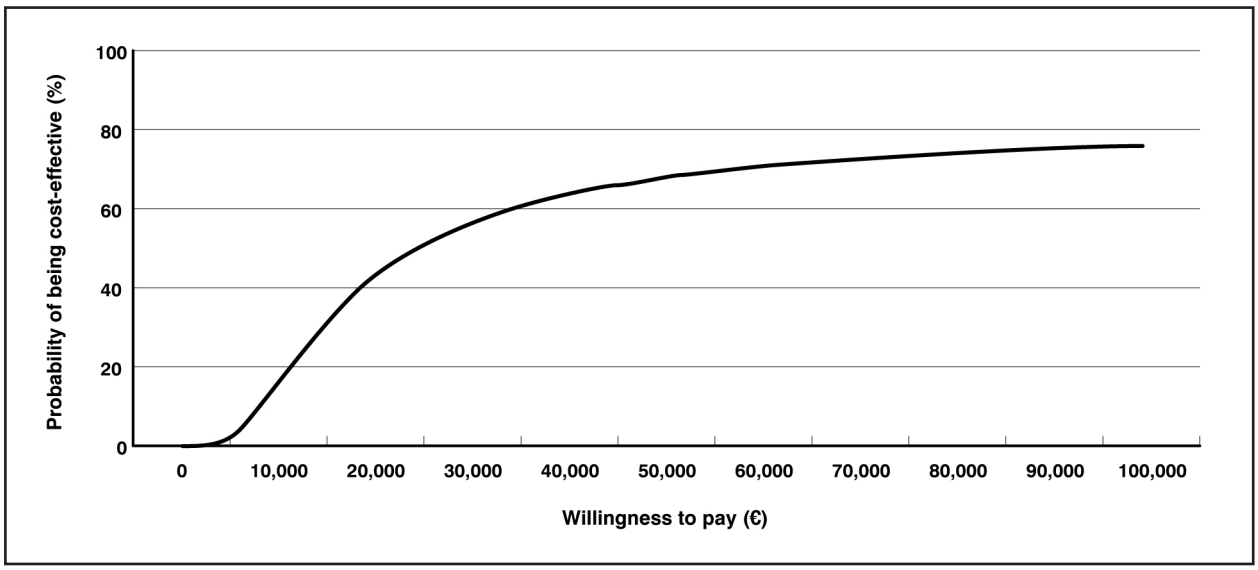

Figure 6. *Probabilistic sensitivity analysis: acceptability curve of dimethyl fumarate vs. teriflunomide (alternative scenario #1: NHS perspective and lifetime horizon)*

DISCUSSION

With this analysis, we aimed to compare costs and outcomes of dimethyl fumarate and teriflunomide, two oral DMTs indicated as first-line treatment of RRMS. The results of this 1:1 comparison showed that dimethyl fumarate was cost-effective vs. teriflunomide for the treatment of RRMS.

In fact, dimethyl fumarate was dominant (i.e. lower costs and better health outcomes) in the societal perspective analysis and remained highly cost-effective vs. teriflunomide (ICER <€ 50,000 QALY gained), when the Italian NHS perspective was considered. In base-case, dimethyl fumarate was more effective than teriflunomide, both in terms of survival (19.634 and 19.547 LYs, respectively), and quality-of-life-adjusted survival (6.526 and 5.953 QALYs, respectively). The total lifetime cost per patient treated with dimethyl fumarate (€ 1,010,112) was lower than the cost per patient treated with teriflunomide (€ 1,030,436).

In this analysis, we chose to set up a base-case looking at the societal perspective, because we wanted to capture the entire spectrum of costs (including out-of-pocket expenses, reduced/lost productivity, formal and informal caregiving, home adaptations, etc.), which are extremely relevant for conditions like multiple sclerosis, as shown in literature [7,33,34]. Interestingly, our analysis shows that less than 10% of social costs are allocated to pharmacological treatments, and that other costs drive the economic burden (absence from work, invalidity and early retirement; informal care; inpatient care costs; community service; relapse).

Nonetheless, we also conducted additional analyses reflecting the Italian NHS perspective, as we are aware of the importance of such perspective for budget holders in charge of drug decision making, and of the importance of demonstrating consistent cost-effectiveness of one technology when a subset of costs (direct costs, i.e., drug acquisition, monitoring, adverse events, tests and medication) is considered.

These additional analyses confirmed findings of the base-case analysis, with dimethyl fumarate being cost-effective vs. teriflunomide with an acceptable ICER. Even if no economic acceptability threshold has been officially defined in Italy to date, some proposals have been formulated by some Italian authors [42-45]. In other countries official thresholds are used [22] or thresholds are proposed by authors or organizations [46,47]. For this analysis it was preferred to use the same acceptability threshold used in other dimethyl fumarate economic analyses published in Italy [20,48].

Finally, the results of deterministic and probabilistic sensitivity analyses confirm the reliability and robustness of base-case results.

Although we were aware this was a cost-effectiveness assessment, we wanted to provide a more detailed analyses of the clinical outcomes derived from the model simulation. Together with the standard indicators shown in pharmacoeconomic analyses (quality adjusted survival, costs, incremental cost-effectiveness ratios), some additional outcomes were analysed and reported, to investigate the clinical rationale behind the incremental benefit associated with dimethyl fumarate. A conjoint analysis of four indicators, quality adjusted survival, burden

of relapses and life years with mild (EDSS ≤3) and severe (EDSS ≥6) disability is useful to understand the model dynamics and the reason for the clinical benefit. All in all, dimethyl fumarate patients have fewer relapses than teriflunomide patients, which translates into an earlier benefit of reduced disease activity and reduced proportion of patients progressing severe health states. This "early benefit", observed in our simulations since the first years since treatment initiation, transforms into a quality-adjusted survival benefit later in time. In other words, early prevention of relapses delays disability, whose negative effects will be observed later (e.g. due to detrimental quality of life for disease mobility, social functioning, isolation, etc.). These results are driven by the clinical efficacy data used in the model, coming from Hutchinson et al. mixed treatment comparison (MTC) [32], which demonstrate that dimethyl fumarate is statistically superior to teriflunomide in preventing relapses and numerically superior to teriflunomide in delaying disability progression.

MTC results [32] have been confirmed by the results of two real world studies: i) Braune et al. 2018 [49] study that compared dimethyl fumarate versus teriflunomide and other treatments, evaluating the time to first relapse (TTFR) and annualised relapse rate (ARR); ii) Buron et al. 2019 [50] study that compared on-treatment efficacy and discontinuation outcomes in teriflunomide and dimethyl fumarate. In the first study, both outcomes were better in the population treated with dimethyl fumarate compared to teriflunomide; in the second study, a higher relapse-free survival and a lower incidence of discontinuation due to disease breakthrough on treatment with dimethyl fumarate vs. teriflunomide were showed.

From a methodological point of view, this analysis is a revised and updated version of previous cost-effectiveness assessments on the use of dimethyl fumarate as first-line treatment of the RRMS [20,48]. Compared with these previous analyses, the most relevant update consists in the choice of the economic data (source for EDSS costs and updating prices). Given the similarities on methodological approach and model framework, the present analysis is affected by the same limitations that have been extensively reported in previous publications [20,48]. In summary, the lack of one head-to-head study comparing dimethyl fumarate vs. teriflunomide, the impossibility of testing treatment sequences (i.e. add-up a second-line treatment after failure with first-line treatment), the lack of a systematic approach in including all treatment-related adverse events, and finally the lack of quantification of MS intangible costs are the main limitations of the study. As said, a detailed analysis of such limitations and their impact on results has been conducted and documented in previous publications [20,48]. However, the consistent findings from deterministic and probabilistic analyses, together with the additional scenarios, give high level of confidence with regards of analysis robustness.

This assessment intends to support decision makers in their decision on drug access and physicians on appropriate prescription. For the latter, of course, a cost-effectiveness cannot be a tool for decision making, because it does not capture many aspects of the disease and more importantly, because all the patients are different and have different needs, perception, history, etc. However, we believe these types of evaluation can provide prescribers with a "piece of information" that can play a role in the final treatment decision.

CONCLUSIONS

The results of the cost-effectiveness analysis confirm that dimethyl fumarate is an optimal first-line treatment for RRMS compared to teriflunomide in both Italian NHS and societal perspectives and considering a lifetime horizon. In the base-case analysis dimethyl fumarate is dominant (more effective and less costly) compared with teriflunomide. The additional analysis of ICER by time horizon shows that dimethyl fumarate is at least cost-effective option vs teriflunomide (i.e. ICER <€ 50,000 per QALY gained) in societal and NHS perspectives. Results favoured dimethyl fumarate also for less cumulative burden of relapses, higher proportion of patients with EDSS ≤3 and lower with EDSS ≥6 at 10 years. This assessment can support decision makers but also prescribers in their decision.

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Conflicts of interest

LGM declares research grant from Biogen, Almirall, Roche, Bayer. Speaker's fee from Almirall, Roche, Biogen, Bayer.
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SUPPLEMENTARY MATERIALS

From EDSS level	RRMS to RRMS									
	0	1	2	3	4	5	6	7	8	9
0	0.311	0.289	0.312	0.070	0.016	0.001	0.000	0.000	0.000	0.000
1	0.178	0.231	0.419	0.127	0.039	0.004	0.001	0.000	0.000	0.000
2	0.060	0.130	0.493	0.215	0.088	0.011	0.002	0.000	0.000	0.000
3	0.019	0.055	0.299	0.322	0.241	0.044	0.013	0.003	0.004	0.000
4	0.005	0.017	0.127	0.251	0.411	0.121	0.048	0.014	0.007	0.000
5	0.001	0.004	0.033	0.096	0.252	0.295	0.211	0.085	0.023	0.000
6	0.000	0.001	0.009	0.034	0.123	0.257	0.329	0.190	0.056	0.001
7	0.000	0.000	0.003	0.013	0.057	0.169	0.309	0.257	0.189	0.004
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.995	0.005
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000
From EDSS level	**SPMS to SPMS**									
	1	2	3	4	5	6	7	8	9	
1	0.769	0.154	0.077	0.000	0.000	0.000	0.000	0.000	0.000	
2	0.000	0.636	0.271	0.062	0.023	0.008	0.000	0.000	0.000	
3	0.000	0.000	0.629	0.253	0.077	0.033	0.003	0.005	0.000	
4	0.000	0.000	0.000	0.485	0.350	0.139	0.007	0.018	0.000	
5	0.000	0.000	0.000	0.000	0.633	0.317	0.022	0.026	0.002	
6	0.000	0.000	0.000	0.000	0.000	0.763	0.190	0.045	0.002	
7	0.000	0.000	0.000	0.000	0.000	0.000	0.805	0.189	0.006	
8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.926	0.074	
9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	

Supplementary Table I. *Transition probabilities among disability progression levels, by MS form [23,24,27]*
EDSS = expanded disability status scale; RRMS = relapsing remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis

EDSS level	RRMS to SPMS								
	1	2	3	4	5	6	7	8	9
Probability	0.003	0.032	0.117	0.210	0.299	0.237	0.254	0.153	1.000

Supplementary Table II. *Transition probabilities from RRMS to SPMS form [27]*
EDSS=expanded disability status scale; RRMS=relapsing remitting multiple sclerosis; SPMS=secondary progressive multiple sclerosis

Adverse event	Non-serious adverse event (n/year) [32]		Serious adverse event (n/year) [32]		Disutility value (n)		Disutility duration (days)	
	Dimethyl fumarate	Teriflunomide	Dimethyl fumarate	Teriflunomide	Non-serious	Serious	Non-serious	Serious
Abdominal pain	0.0514	0.0000	0.074	0.000	0.00	0.00	10.50	24.50
Abdominal pain upper	0.0537	0.0000	0.000	0.000	0.00	0.00	10.50	24.50
ALT increased	0.0313	0.1163	0.000	0.000	0.00	0.00	28.00	28.00
Arthralgia	0.0463	0.0998	0.050	0.000	0.00	0.25	10.50	24.50
Atrioventricular conduction block	0.0034	0.0000	0.000	0.000	0.29	0.29	1.00	1.00
Back pain	0.0666	0.0890	0.027	0.000	0.25	0.50	10.50	24.50
Bradycardia	0.0000	0.0000	0.000	0.000	0.00	0.00	14.00	14.00
Chest pain	0.0061	0.0000	0.000	0.000	0.25	0.50	7.00	14.00
Cough	0.0265	0.0000	0.000	0.000	0.00	0.00	7.00	14.00
Depression	0.0371	0.0000	0.018	0.000	0.16	0.56	75.00	365.25
Diarrhea	0.0762	0.1253	0.000	0.000	0.00	0.00	10.50	24.50
Fatigue	0.0666	0.0990	0.000	0.000	0.00	0.00	182.63	182.63

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Adverse event	Non-serious adverse event (n/year) [32]		Serious adverse event (n/year) [32]		Disutility value (n)		Disutility duration (days)	
	Dimethyl fumarate	Teriflunomide	Dimethyl fumarate	Teriflunomide	Non-serious	Serious	Non-serious	Serious
Flu-like symptoms	0.0068	0.0295	0.000	0.000	0.31	0.31	26.00	52.00
Flushing	0.1997	0.0000	0.006	0.000	0.00	0.00	10.50	24.50
Gastroenteritis	0.0292	0.0000	0.143	0.000	0.07	0.07	8.75	8.75
Headache	0.0956	0.1335	0.000	0.000	0.14	0.49	10.50	24.50
Influenza	0.0377	0.0620	0.000	0.000	0.63	0.67	10.50	24.50
Leucopenia	0.0048	0.0000	0.000	0.000	0.00	0.00	28.00	182.63
Lower respiratory tract infections	0.0014	0.0000	0.000	0.000	0.05	0.05	11.70	11.70
Nausea	0.0660	0.1021	0.025	0.000	0.00	0.00	10.50	24.50
Pain in extremity	0.0406	0.0611	0.000	0.000	0.25	0.25	7.00	28.00
Pruritus	0.0434	0.0141	0.000	0.000	0.00	0.00	10.50	24.50
Rash	0.0406	0.0000	0.000	0.000	0.00	0.00	28.00	182.63
Urinary tract infection	0.0764	0.0666	0.009	0.000	0.10	0.10	5.00	5.00

Supplementary Table III. *Annual incidence and disutilities related to adverse events*

Adverse event	Unit cost (€)		Source [38–41]	
	Non-serious	Serious	Non-serious	Serious
Abdominal pain	20.66	20.66	Code 89.7 tariff	
Abdominal pain upper	20.66	20.66		
ALT increased	11.24	31.90	Sum of the tariffs of the codes: 90.10.5; 90.09.2; 90.04.5; 90.23.5; 90.25.5	Sum of the tariffs of the codes: 90.10.5; 90.09.2; 90.04.5; 90.23.5; 90.25.5; 89.7
Arthralgia	20.66	20.66	Code 89.7 tariff	
Atrioventricular conduction block	192.49	1,943.13	Average tariff of DH 138 and DH 139	Average tariff of DRG 138 and DRG 139 + ER
Back pain	20.66	20.66	Code 89.7 tariff	
Bradycardia	192.49	1,566.40	Average tariff of DH 138 and DH 139	Average tariff of DRG 138 and DRG 139
Chest pain	20.66	1,399.00	Code 89.7 tariff	DRG 143 tariff
Cough	20.66	20.66	Code 89.7 tariff	
Depression	87.74	858.00	Code 89.7 tariff + 6 months of treatment with sertraline	DRG 426 tariff
Diarrhea	20.66	1,408.27	Code 89.7 tariff	Average tariff of DRG 182 and DRG 183
Fatigue	0.00	0.00		-
Flu-like symptoms	0.00	20.66	-	Code 89.7 tariff
Flushing	20.66	20.66	Code 89.7 tariff	
Gastroenteritis	183.65	1,408.27	Average tariff of DH 182 and DH 183	Average tariff of DRG 182 and DRG 183
Headache	0.00	20.66	-	Code 89.7 tariff
Influenza	15.48	214.01	GP visit	Average tariff of DH 79 and DH 80
Leucopenia	3.91	28.48	Code 90.70.4 tariff	Sum code 90.70.4 and 89.7 tariffs
Lower respiratory tract infections	15.48	5,327.80	GP visit	Average tariff of DRG 79 and DRG 80
Nausea	0.00	20.66	-	Code 89.7 tariff
Pain in extremity	20.66	30.99	Code 89.7 tariff	Sum code 93.08.1 and 89.7 tariffs
Pruritus	0.00	20.66	-	Code 89.7 tariff
Rash	20.66	218.00	Code 89.7 tariff	DH 447 tariff
Urinary tract infection	20.66	2,296.56	Code 89.7 tariff	Average tariff of DRG 320 and DRG 321

Supplementary Table IV. *Unit costs of adverse events*
DH = day-hospital; DRG = diagnosis-related group; ER = emergency room admission; GP = general practitioner

Item	Dimethyl fumarate (A)	Teriflunomide (B)	Difference (A-B)
Outcome			
LYs	19.634	19.547	0.087
QALYs	6.526	5.953	0.573
Costs (€)			
Treatment costs[1]	94,637 (27.1%)	72,608 (21.5%)	22,030
Adverse events	261 (0.07%)	87 (0.03%)	173
Relapse[2]	25,301 (7.3%)	28,235 (8.4%)	-2,934
EDSS[2]	228,495 (65.5%)	236,472 (70.1%)	-7,977
Inpatient care	136,387 (39.1%)	142,154 (42.1%)	-5,767
Day admission	34,508 (9.9%)	35,290 (10.5%)	-782
Consultations	23,957 (6.9%)	24,795 (7.3%)	-838
Tests	12,826 (3.7%)	12,772 (3.8%)	54
Medication	20,817 (6.0%)	21,461 (6.4%)	-644
Total costs	**348,694 (100.00%)**	**337,402 (100.00%)**	**-11,292**
ICER (€/QALY gained)		**19,691**	

Supplementary Table V. *Results of the incremental cost-effectiveness analysis (alternative scenario #1: NHS perspective and lifetime horizon)*

[1] Including monitoring costs

[2] Including only direct costs

EDSS = expanded disability status scale; ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life years