Cost-utility of First-line Disease-modifying Treatments for Relapsing–Remitting Multiple Sclerosis

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ABSTRACT

Purpose: This study evaluated the cost-effectiveness of first-line treatments of relapsing–remitting multiple sclerosis (RRMS) (dimethyl fumarate [DMF] 240 mg PO BID, teriflunomide 14 mg once daily, glatiramer acetate 20 mg SC once daily, interferon [IFN]-β1a 44 μg TIW, IFN-β1b 250 μg EOD, and IFN-β1a 30 μg IM QW) and best supportive care (BSC) in the health care payer setting in Finland.

Methods: The primary outcome was the modeled incremental cost-effectiveness ratio (ICER; €/quality-adjusted life-year [QALY] gained, 3%/y discounting). Markov cohort modeling with a 15-year time horizon was employed. During each 1-year modeling cycle, patients either maintained the Expanded Disability Status Scale (EDSS) score or experienced progression, developed secondary progressive MS (SPMS) or showed EDSS progression in SPMS, experienced relapse with/without hospitalization, experienced an adverse event (AE), or died. Patients' characteristics, RRMS progression probabilities, and standardized mortality ratios were derived from a registry of patients with MS in Finland. A mixed-treatment comparison (MTC) informed the treatment effects. Finnish EuroQol Five-Dimensional Questionnaire, Three-Level Version quality-of-life and direct-cost estimates associated with EDSS scores, relapses, and AEs were applied. Four approaches were used to assess the outcomes: cost-effectiveness plane and efficiency frontiers (relative value of efficient treatments); cost-effectiveness acceptability frontier, which demonstrated optimal treatment to maximize net benefit; Bayesian treatment ranking (BTR); and an impact investment assessment (IIA; a cost-benefit assessment), which increased the clinical interpretation and appeal of modeled outcomes in terms of absolute benefit gained with fixed drug-related budget. Robustness of results was tested extensively with sensitivity analyses.

Findings: Based on the modeled results, teriflunomide was less costly, with greater QALYs, versus glatiramer acetate and the IFNs. Teriflunomide had the lowest ICER (24,081) versus BSC. DMF brought marginally more QALYs (0.089) than did teriflunomide, with greater costs over the 15 years. The ICER for DMF versus teriflunomide was 75,431. Teriflunomide had >50% cost-effectiveness probabilities with a willingness-to-pay threshold of <€77,416/QALY gained. According to BTR, teriflunomide was first-best among the disease-modifying therapies, with potential willingness-to-pay thresholds of up to €68,000/QALY gained. In the IIA, teriflunomide was associated with the longest incremental quality-adjusted survival and time without cane use. Generally, primary outcomes results were robust, based on the sensitivity analyses. The results were sensitive only to large changes in analysis perspective or mixed-treatment comparison.

Implications: The results were sensitive only to large changes in analysis perspective or MTC. Based on the analyses, teriflunomide was cost-effective versus BSC or DMF with the common threshold values, was dominant versus other first-line RRMS treatments, and provided the greatest impact on investment. Teriflunomide is potentially the most cost-effective option among first-line treatments of

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Key words: cost-effectiveness, dimethyl fumarate, economic evaluation, glatiramer acetate, interferon-β, teriflunomide.

INTRODUCTION

Multiple sclerosis (MS)—a chronic progressive, autoimmune, inflammatory disease—affects >2 million people worldwide. Approximately 89% of cases are classified as relapsing–remitting MS (RRMS) at the time of diagnosis.[1] MS prevalence is particularly high in the United Kingdom, the United States, Canada, Germany, and Scandinavia.[2,3] In Finland, MS prevalence varies regionally, from 100 to 200 per 100,000 inhabitants.[4–7]

In young adults with MS, prognosis is based on an individual's factors.[1] The progression and accumulating disability cause a significant human and economic burden[8–15] and the need for support.[16]

The risk for death among Finnish patients with MS is 2.8-fold compared with that in the general population, being 3.4-fold in women and 2.2-fold in men as early as 2 to 10 years after diagnosis.[17] Relapse, MS progression, and disability level (eg, higher Expanded Disability Status Scale [EDSS] score[18]) are associated with a higher risk for mortality,[17,19,20] additional costs,[9–14] and quality of life (QoL) losses.[9,10,12,14,21–24]

MS treatment with disease-modifying therapies (DMTs) is aimed at decreasing the inflammatory activity leading to relapses, stopping or slowing progression of residual disability, and, eventually, delaying the progression to the secondary progressive phase. However, long-term prognosis among treated patients is largely unknown. Based on Finnish drug reimbursement and sales data,[25] commonly used first-line DMTs include injectable DMTs, namely glatiramer acetate (GA), interferon (IFN)-β1a IM, IFN-β1a SC, and IFN-β1b SC.

Dimethyl fumarate (DMF) and teriflunomide are new oral DMTs reimbursed as the first-line treatment of RRMS in Finland. The efficacy and safety of DMF 240 mg BID for established MS have been studied in the Phase III CONFIRM (Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis)[26,27] and DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS)[28,29] trials (ClinicalTrials.gov identifiers: NCT00451451 and NCT00420212, respectively). The efficacy and safety of teriflunomide 14 mg once daily for established MS have been demonstrated in the Phase III TEMSO (Teriflunomide Multiple Sclerosis Oral Teriflunomide for Relapsing Multiple Sclerosis)[30–33] and TOWER (Teriflunomide Oral in People With Relapsing Multiple Sclerosis)[34,35] trials (NCT00134563 and NCT00751881, respectively), and in patients with a first clinical episode suggestive of MS in the TOPIC (Oral Teriflunomide for Patients with a First Clinical Episode Suggestive of Multiple Sclerosis)[36] trial (NCT00622700). Effectiveness of teriflunomide compared with IFN-β1b SC has been demonstrated in the Phase III TENERE (Teriflunomide and Rebif® in Patients with Relapsing Multiple Sclerosis)[37] trial (NCT00883337).

We evaluated the cost-utility of injectable and oral first-line DMTs in the Finnish population of patients with RRMS, based on a decision-analytical model. To our knowledge, there are no previously published journal articles on the cost-utility of first-line oral DMTs in a European setting or on oral and injectable DMTs for first-line treatment of RRMS. In addition, progression of RRMS in Finnish patients has not been assessed before, and the 4 different approaches elaborating the key results from MS cost-utility analysis have not been previously reported.

MATERIALS AND METHODS

The cost-utility of the first-line DMTs in the Finnish RRMS population was assessed in a decision-analytical modeling framework[38] by implementing a Markov cohort model with mutually exclusive health states in Excel 2007, including Visual Basic for Applications (Microsoft Corporation, Redmond, Washington). The modeling approach followed the Finnish guidance for health economic analyses.[39]

The primary outcome of analysis was the modeled incremental cost-effectiveness ratio (ICER), reported as Euros per quality-adjusted life-year (€/QALY) gained. The interpretation of ICER is challenging in Finland because the decision maker's willingness-to-pay (WTP) threshold per QALY gained has not been publicly declared,[40] and significant variation in

decision maker WTP between diseases may exist.[41] Based on our experience, the UK thresholds[42,43] could be applicable in Finland, so that values of $<\sim$€25,000 or €25,000–37,000/QALY gained would indicate most plausible or plausible cost-effectiveness, respectively; and, on average, €55,000/QALY gained could be acceptable for end-of-life treatment based on the UK population-weighted decisions. This applicability of UK thresholds is based on the observation that many articles from Finland[41,44–55] have referred to a WTP threshold of $\sim$€50,000/QALY gained, which is probably based on the so-called "dialysis argument."[41] The Finnish Medicines Agency has considered that €68,000/QALY gained approaches the maximum cost-effectiveness threshold for a life-threatening cancer[56]—a result well in line with earlier Finnish average findings.[41]

The health care payer setting, which is recommended in the Finnish guidance for health economic analyses,[39] was used in the modeling. This model includes direct health and social care costs, and excludes income transfers (taxes) and indirect costs (eg, time costs, disability payments, presenteeism, absenteeism, and informal care). A scenario analysis, including productivity losses,[14] was performed to assess the robustness of this direct-costing perspective. A summary of the modeled key research questions is given in Table I as an extended PICO framework, which is used to capture and clarify the essential parts of complicated cost-effectiveness assessment in a sensible order (namely, PICOSTEPS: P, patients; I, interventions; C, comparator; O, outcomes; S, setting; T, time horizon; E, effects; P, perspective; and S, sensitivity analyses).

A relatively straightforward, limited cost–benefit analysis (clinical value analysis) approach was recently developed.[46] As a secondary complementary analysis, an impact investment assessment (IIA) was carried out to increase the clinical appeal and interpretation of the primary outcome results.[46] The IIA here covered a fixed drug-related budget based on the most affordable DMT and incremental quality-adjusted survival or time to cane use (EDSS score, 6) versus best supportive care (BSC; trial comparator). The outcome (impact on investment [II]) of the IIA was the duration of benefit obtained in comparison with BSC with the fixed budget. This IIA incorporated an explicit minimal willingness-to-invest (WTI) value for DMT based on the most affordable DMT and, thus, demonstrated the mean absolute cost–benefit in terms of a single unit:

$$\mathrm{II} = (\text{Drug health benefit}_i \text{ vs BSC}) * \frac{(\text{Assumed drug-related minimal WTI})}{(\text{Drug-related cost}_i)} \quad \text{(Equation 1)}$$

where *i* indicates a particular drug treatment.

Consequently, the result of the IIA is a standardized benefit (II) obtained with the given WTI (in fact, the WTI can be greater than the minimum assumed here, and the benefit increases accordingly).

Patients

Finland's MS research registry data were used to define the cohort characteristics in the model. Based on the MS research registry data (713 ambulatory patients from Finland, with MS diagnosed in 1991–2010 and an EDSS score of 0–6.5 observed at baseline; see Supplemental Material A in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028), the mean age of modeled patients was 35.64 years, and the female/male ratio was 2.57. The distribution of EDSS scores at baseline is shown in Figure 1.

Model

The clinical course of MS was modeled (Figure 2)[73,74] to capture all relevant evidence,[38,39,43] as no direct comparison is currently available. Models are always hypothetical and contain an element of uncertainty, but when relying on conservative and fair structure and estimates—and keeping the modeling assumptions in mind—they can produce useful information for decision making.

In the model shown in Figure 2, patients with RRMS either maintained the same EDSS or transited to another EDSS health state as the disease progressed, developed secondary progressive MS (SPMS), transited to another EDSS state in SPMS, or died (EDSS score, 10; absorbing state) within the 1-year model cycles. Within each cycle, patients experienced a relapse (with/without hospitalization) and/or an adverse event (AE). The relative effects of DMTs were implemented as modifiers of the modeled clinical course of MS. Midcycle estimates (life-table method of half-cycle correction[75–77]) were used to avoid over- or underestimation of modeled outcomes.

Table I. PICOSTEPS: Summary of the research questions.

PICOSTEPS	Description
P: Patients	Finnish adults with incident RRMS and EDSS scores 0.0–6.5 at baseline based on data from a Finnish MS registry
I: Interventions	DMTs: DMF 240 mg PO BID, teriflunomide 14 mg once daily, GA 20 mg SC once daily, IFN-β1a 44 μg SC TIW, IFN-β1b 250 μg SC EOD, IFN-β1a 30 μg IM QW
C: Comparator	Common comparator: BSC (trial placebo)
O: Outcomes	Primary: ICER given as the cost/QALY gained based on the direct cost Secondary: disaggregated and total QALYs (based on EQ-5D-3L) and costs, life-years, years without impaired mobility (EDSS <6; ie, years without cane use), cost-effectiveness plane and efficiency frontiers, cost-effectiveness acceptability frontiers, Bayesian treatment ranking, and cost–benefit assessment. Discounting: 3%/y
S: Setting	Probabilistic decision analytical modeling (Markov cohort model), including 21 health states reflecting the disease progression (modified by treatment efficacy); and events reflecting relapses, AEs, and withdrawals
T: Time horizon	15 years, based on the follow-up data from the Finnish registry, time since diagnosis in a Finnish cost and EQ-5D-3L MS study,[14] years covered by the British Columbia, Canada, registry,[57,58] and approximate time from RRMS to SPMS in the London Ontario MS registry database. For the London Ontario MS registry origins, see Weinshenker et al.[59]
E: Effects	RRMS progression: Finnish MS registry data (see **Supplemental Material A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028). SPMS progression: London Ontario MS registry (see **Supplemental Material A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028). Relapse rates: published elsewhere.[21,60] Relapse-associated hospitalizations: published elsewhere.[30,32,33] Mortality: Finnish MS registry data and statistics[61] with EDSS-related[17] adjustment. EDSS-associated costs and quality of life: estimated from a Finnish study.[14] Relapse costs: Finnish MS registry data. Relapse disutility: Finnish study[14] accounting for hospitalization status and duration.[23,24] 12-wk responses with DMT, annual relapse rates, and withdrawals: mixed-treatment comparison.[62,63] DMT effects on relapses resulting in hospitalizations: published elsewhere.[32,64,65] DMT costs: drugs,[66] monitoring.[67–71] AEs: disutility,[72] duration, costs, and occurrence (see **Supplemental Material B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028).
P: Perspective	Finnish payer perspective. A scenario analysis with a societal perspective.
S: Sensitivity analyses	25 deterministic scenarios: impact of modeling assumptions, result robustness, and generalizability Probabilistic sensitivity analysis: joint uncertainty of the input estimates

AE = adverse event; BSC = best supportive care; DMF = dimethyl fumarate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EQ-5D-3L = EuroQol Five-Dimensional Questionnaire, Three-Level Version; GA = glatiramer acetate; ICER = incremental cost-effective ratio; IFN = interferon; MS = multiple sclerosis; QALY = quality-adjusted life-year; RRMS = relapsing–remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Disease Progression

Disease progression and relapses were modeled independently. Disease progression in terms of the EDSS score development during RRMS was estimated from Finland's MS research registry data, consisting of 2299 EDSS measurements. The probability of transiting from RRMS to SPMS was estimated, and EDSS development during SPMS was based on results

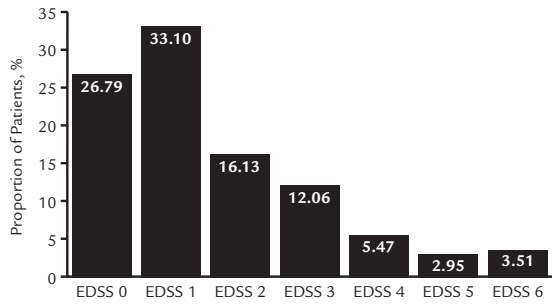

Figure 1. Expanded Disability Status Scale (EDSS) score distribution at the initiation of modeling.

from the London Ontario registry of MS (see **Supplemental Material A** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028). For the origins of registry, see Weinshenker et al.[59] The relapse rates in patients not receiving DMTs were taken from published references.[21,60] The percentage of relapses leading to hospitalization (30.7%) was estimated from the TEMSO trial.[30,32,33]

The annual probability of death was modeled based on Finland's general population mortality rates by applying the observed MS female/male ratio of 2.57 from Finland's MS research registry data to

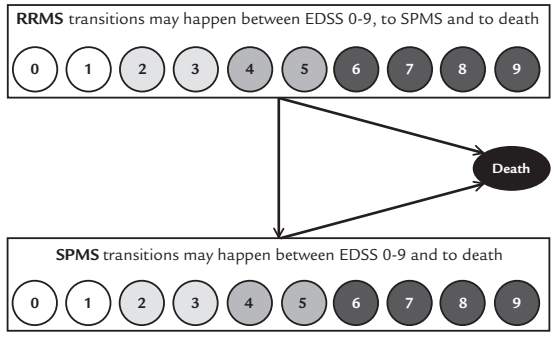

Figure 2. Simplified presentation of the Markov model and its key health states. Relapses and adverse events are not depicted. EDSS = Expanded Disability Status Scale; RRMS = relapsing–remitting multiple sclerosis; SPMS = secondary-progressive multiple sclerosis.

Finland's all-cause age- and sex-specific mortality rates from the year 2014,[61] multiplying the sex-weighted general population mortality rate by the EDSS-specific standardized mortality ratio, and converting the result to give the probability.[78] The EDSS-specific standardized mortality ratio was estimated from Finland's MS research registry results[17] by using linear interpolation:

$$\text{Standardized mortality ratio} = 0.515 * \text{EDSS} + 1.000 \quad \text{(Equation 2)}$$

Treatment Efficacy and Tolerability

Treatment efficacy was assessed by common MS study outcomes: sustaining the same disability status for 12 weeks, annualized relapse rate (ARR), and relapses. Persistence was assessed by withdrawal rates, and tolerability, by AEs. Relative rates of hospitalization in the model were derived from the following clinical trials: IFN-β1a SC, CARE MS I (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis)[64] (assumed to apply to GA and IFN-β1b SC); IFN-β1a IM, TRANSFORMS (Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis)[65]; and teriflunomide, TEMSO[32] (assumed to apply to DMF). Withdrawals were assumed to happen at the initiation of a new model cycle (but not at the start of the first cycle), and patients were assumed to discontinue their current treatment when they progressed from RRMS to SPMS.

Disability progression, ARR, and withdrawal rates were modeled based on a mixed-treatment comparison assessed by the National Institute for Health and Care Excellence.[62,63] To account for new MS diagnostics, earlier treatment, and evidence of decreased ARR over time, the base case analysis included trials that enrolled ≥80% of patients who had RRMS and had been recruiting patients since 2000. In addition, multiway sensitivity analyses (disability progression, ARR, withdrawal rates) of mixed-treatment comparison without year limit and with or without adjustment for placebo relapses were performed.

Treatment safety was modeled using reported AEs from clinical trials or earlier health technology assessments, their costs, and QoL effects (see **Supplemental Material B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028). AEs reported with

similar terms were assumed to be treated similarly and to result in similar QoL loss.

Quality-adjusted Survival

The EuroQol Five-Dimensional Questionnaire, Three-Level Version (EQ-5D-3L) QoL for EDSS scores was modeled on the basis of data from DEFENSE (Burden of Illness in Multiple Sclerosis),[14] a recent cross-sectional survey from Finland. The occurrence and impact[72] of AEs (see **Supplemental Material B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028) and relapses[14,24] were accounted for. Finland's EDSS-related QoL values[14] were deemed acceptable because the mean EQ-5D-3L score in EDSS 0-1 was in line with values from the general population of Finland.[79] However, the study from Finland[14] did not specify QoL related to relapse with and without hospitalizations.

Findings from studies suggest greater disutility for relapse with hospitalization compared with relapses without hospitalization.[23,24] In a US study, the QoL losses in relapsed patients with and without hospitalization were reported as –0.302 and –0.091, respectively.[24] The latter estimate is similar to the Finnish relapse loss, that is, –0.064,[14] which used an extensive 1-year recall period and did not make a distinction between hospitalized and nonhospitalized patients or number of relapses.

To approximate the QoL loss associated with hospitalizations, the Finnish QoL loss was weighted with the observed ratio between the QoL losses for hospitalized and nonhospitalized relapses in the US study[24] (ratio –0.302/–0.091 = 3.3187) to obtain disutility for hospitalized patients in Finland. The applied QoL losses in relapsed patients with and without hospitalization in the model were –0.212 and –0.064, respectively. The QoL effect of relapse was assumed to last for 3 months.[23]

Costs

Annual DMT cost was calculated using the indicated mean dose of each drug and number of doses per year (365.25 d/y), determined for each treatment regimen based on the product labeling. For drugs with multiple package sizes, the drug costs were estimated by weighting of the package costs by their estimated market share (**Table II**). A 100% dose intensity and adherence were assumed.

Administration, monitoring (**Table III**), and AE costs (see **Supplemental Material B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028) were calculated on the basis of resource consumption multiplied by the associated unit costs. DMT-associated resources were based on the product labeling, recommendations in Finland,[1,80,81] publications or earlier assessments (see **Supplemental Material B** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028), and clinical practice.

In addition to the EQ-5D-3L QoL scores, which are hard to predict with common regressions,[82,83] the DEFENSE survey[14] assessed the costs of patients with MS in Finland. The EDSS-related direct costs were estimated based on data from the DEFENSE survey[14] and are reported in **Table III**. Because of limitations in the assessment of DEFENSE-derived relapse costs, the costs of relapses were estimated from other patients with RRMS in Finland (Tampere; N = 581; data included procedures, hospital visits, hospital stays, and unit cost[70]) using semilog multivariate methodology explained elsewhere.[47,84] Based on this analysis, the additional costs per relapse with and without hospitalization were €5537.57 and €1297.41, respectively.

In a scenario analysis, the relationship between EDSS and annual direct care costs (excluding DMT costs) was estimated based on a nonlinear interpolation of findings reported in a study from Finland,[13] as follows:

$$\text{Annual direct (DMTs excl.) costs} = €(128.44 * \text{EDSS}^2 + 4266.60 * \text{EDSS} - 2480.10), \quad \text{(Equation3)}$$

converted to 2014 real value[71] and with EDSS 0 set to €0. The costs applied in this sensitivity analysis were well in line with those from other MS cost studies from Finland[15] and elsewhere.[9–11]

Apart from the drugs, which were valued at January 2016 prices,[66] health care costs were valued at 2013–2014 real prices. The required inflation adjustments were performed using Finland's official price index for communal health care expenditures or income index.[71,85] The modeled costs and health outcomes were discounted at 3%/y.

Table II. Drug-related use and costs.

DMT	Dose/Amount per Package	Cost per Package,€[*]	Dosage (SPCs)	Use, %	Cost, €
DMF 120 mg[†]	120 mg, 14 tablets	188.37	120 mg PO BID	1.92	14,435/1st y
DMF 240 mg[†]	240 mg, 56 tablets	1151.56	240 mg PO BID	15.33	
	240 mg, 168 tablets	3319.33		82.75	
DMF 240 mg[†]	240 mg, 56 tablets	1151.56	240 mg PO BID	15.33	14,523/2nd y
	240 mg, 168 tablets	3319.33		84.67	
GA 20 mg[‡]	20 mg/mL, 28 × 1 mL	836.11	20 mg SC once daily	100.00	10,907
IFN-β1a 30 μg IM[§]	30 μg/0.5 mL, 4 × 0.5 mL	814.90	30 μg SC QW	100.00	10,630
IFN-β1a 44 μg SC[‖]	44 μg/0.5 mL, 12 × 0.5 mL	897.83	44 μg SC TIW	100.00	11,712
IFN-β1b 250 μg SC[¶]	250 μg/mL, 15 × 1 mL	793.08	250 μg SC EOD	100.00	9656
Teriflunomide 14 mg[#]	14 mg, 28 tablets	1017.89	14 mg PO once daily	15.33	12,023
	14 mg, 84 tablets	2712.79		84.67	

DMT = disease-modifying therapy; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; SPC = summary of product characteristics.
[*]Drug costs are at January 2016 values.
[†]Trademark: Tecfidera® (Biogen, Weston, Massachusetts).
[‡]Trademark: Copaxone® (Teva, Ulm, Germany).
[§]Trademark: Avonex® (Biogen).
[‖]Trademark: Rebif® (EMD Serono, Rockland, Massachusetts).
[¶]Trademark: Betaferon® (Bayer Pharmaceuticals, West Haven, Connecticut).
[#]Trademark: Aubagio® (Genzyme [a Sanofi Company], Cambridge, Massachusetts).

Sensitivity and Generalizability of Results

The robustness and generalizability of the base case results were assessed using various deterministic and probabilistic sensitivity analyses (DSA and PSA, respectively). The base case was based on most credible inputs. DSAs were based on 25 different scenarios, including major or noncredible changes in methods, health risks, treatment, costs, QoL, population, and settings. Means based on all 25 DSA scenarios were also calculated. The details of the DSAs are shown in Table IV.

Probabilistic Sensitivity Analysis

For PSA, a second-order Monte Carlo simulation was used to take into account the joint variation in the economic and clinical outcomes due to sampling uncertainty related to model parameters. The following distributions were used: β for ARR and withdrawal rates, γ for EDSS-related and treatment costs, log-normal for EDSS transitions, disease progression hazard rates, treatment effect on ARR, treatment effect on hospitalization relapse percentage and QoL, and Dirichlet distribution for the percentage of relapses involving hospitalization (see **Supplemental Material C** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028). Based on the PSA, cost-effectiveness acceptability frontiers demonstrated optimal treatment to maximize net benefit with different WTP thresholds, and Bayesian treatment ranking ranked the best treatments.

RESULTS

The average modeled base case results are reported in Table V. The mean projected 15-year total payer's direct costs differed considerably (by 17.2%) between the most affordable (teriflunomide) and the most costly (IFN-β1b SC) DMT. The respective relative QALY gain difference was 9.3%. The maximum relative QALY difference was 10.6% between the 2 DMTs (DMF and IFN-β1b SC).

The modeled key outcome (ICERs €/QALY gained in comparison with BSC alone) ranged considerably, from

Table III. Monitoring and disability (EDSS)-related resource use and costs.

Monitoring	Unit Cost, €*	Resources, First Year/Later Year†				
		DMF	GA	IFNs	Teriflunomide	BSC
Specialist visit	340.76, Including 5% copayment[69]	2/1	2/1	2/1	2/1	0/0
SC training	50.97 Nurse visit[69]	0/0	1/0	1/0	0/0	0/0
Laboratory fee‡	5.47[68]	4/4	0/0	4/1	17/6	0/0
ALT	1.00[67]	4/1	0/0	4/1	17/6	0/0
GGT, creatinine	2.00[67]	4/1	0/0	0/0	0/0	0/0
BC	1.55[67]	0/0	0/0	4/1	0/0	0/0
FBC	6.60[67]	4/4	0/0	0/0	4/1	0/0
MxA	92.50[70]	0/0	0/0	1/1	0/0	0/0
TSH	2.50[67]	0/0	0/0	1/0	0/0	0/0
UT	5.84[68]	4/1	0/0	0/0	0/0	0/0
MRI, head	335.58[69]	1/0.5	1/0.5	1/0.5	1/0.5	0/0
Phone call§	9.56 After tests[69]	2/3	0/0	2/0	15/5	0/0
Disability related						
EDSS score[14]	–	0/1	2/3	4/5	6/7	8–9
Direct health care costs, €‖	–	1108/1446	2890/3470	3909/5656	7919/12,185	15,718
Direct non–health care costs, €	–	49/834	1693/4526	5767/15,289	18,749/32,364	68,852

ALT = alanine aminotransferase; BC = blood count; BSC = best supportive care; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FBC = full blood count; GA = glatiramer acetate; GGT = gamma-glutamyl transferase; MRI = magnetic resonance imaging; MxA = protein induced by interferon-alfa/β; TSH = thyroid-stimulating hormone; UT = urine test.

*Pre-2013 nontariff costs[14,68,69] were indexed to the 2014 price level using official communal price index for health care services.[71]

†Unless otherwise noted.

‡Fixed laboratory fee for each test taking time.

§Phone call after laboratory tests if specialist visit not arranged.

‖Estimated costs of disease-modifying therapies (DMTs) were excluded based on the digitalization and estimation of DMT costs in Figure 4 in Ruutiainen et al.[14]

24,081 (teriflunomide) to 248,652 (GA) per QALY gained, and BSC dominated IFN-β1b SC in the base case. Teriflunomide was estimated to be less costly and more effective (dominant) than injectable first-line DMTs, and DMF had a high ICER of 75,431 versus teriflunomide, resulting from the marginally more QALYs (0.089) with DMF and higher costs versus teriflunomide over 15 years. (Table V and Figure 3).

If the WTP threshold for additional QALY gained is set to the most plausible level (€25,000), only teriflunomide represents a cost-effective alternative to BSC alone, based on the modeling. If the WTP is between €37,000 (plausible) and €55,000 (end of life) per QALY gained, only teriflunomide and DMF represent cost-effective alternatives to BSC alone. However, with a modeled ICER of 75,414 for DMF versus teriflunomide, DMF is unlikely to be considered cost-effective in the Finnish setting given the unofficial assumed WTP thresholds detailed in Materials and Methods.

The cost–benefit analysis type IIA utilized the minimal mean expected DMT-related discounted

Table IV. Details of deterministic sensitivity analyses.

Category	Scenario
Discounting	No discounting
	Discounting with 5%/y
Health risks	British Columbia, Canada, RRMS EDSS development, based on patients more than 28 years old[57]
	Alternative natural relapse source[86]
	Rate for relapses leading to hospitalization based on the 1:2.75 ratio from Tampere data (26.7% of annual relapses result in hospitalization when adjusting for covariates including also EDSS score; N = 581; mean age at relapse, 40 y)
	Relapse time, 2 mo
	Relapse time, 4 mo
Treatment	DMT discontinuation when EDSS 7 and over was reached, based on reimbursement criteria
	Disability progression and ARR set to the lower 95% credibility interval threshold of MTC results
	Disability progression and ARR set to the higher 95% credibility interval threshold of MTC results
	Alternative source disability progression, ARR, and withdrawal rates from the MTC: no year limit and adjustment for placebo relapses
	Alternative source disability progression, ARR, and withdrawal rates from the MTC: no year limit
	Time with AEs doubled (same as doubling AE disutility for those AEs that last a shorter time than the model cycle)
	Time with AEs halved (same as halving AE disutility)
Costs	EDSS costs based on the other Finnish source[13] at 2014 values[61]
	Monitoring costs doubled
	Monitoring costs halved
	Relapse cost doubled
	Relapse cost halved
	AE costs doubled
	AE costs halved
	Societal approach (productivity loss included)[14,85]
QoL	Alternative EDSS QoL source[10]
	Similar QoL loss assumed for all relapses[14]
Result generalizability	TEMSO[30,32,33] patient characteristics and placebo transition probabilities for RRMS EDSS

AE = adverse event; ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; MTC = mixed-treatment comparison; QoL = quality of life; RRMS = relapsing–remitting multiple sclerosis; TEMSO = Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis) Oral Teriflunomide for Patients with Relapsing Multiple.

budget per patient (minimum WTI) of €42,077 based on the drug-related costs of IFN-β1a SC. The consequent discounted IIs in terms of incremental quality-adjusted survivals versus BSC were: teriflunomide, 0.337 QALYs gained; DMF, 0.314; IFN-β1a SC, 0.264; GA, 0.120; IFN-β1a IM, 0.119; and IFN-β1b SC, –0.239, all with the assumed WTI. The respective incremental time to cane uses were

Table V. Base case results (3%/y discounting).

Outcome	DMF	Teriflunomide	IFN-β1a SC	GA	IFN-β1a IM	BSC	IFN-β1b SC
Primary							
ICER vs BSC, €/QALY gained	33,681	24,081	57,690	248,652	244,105	–	Dom.
ICER vs teriflunomide, €/QALY gained	75,431	–	Dom.	Dom.	Dom.	24,081	Dom.
Secondary							
ICER vs BSC, €/y without cane gained	24,692	17,371	43,881	236,722	174,995	–	Dom.
ICER vs teriflunomide, €/y without cane gained	59,512	–	Dom.	Dom.	Dom.	17,371	Dom.
Total costs/patient, €	344,480	337,749	343,619	364,279	358,808	328,403	403,765
Total disease costs	280,427	289,275	301,543	313,535	314,881	328,403	356,527
Direct disability	67,630	69,047	71,430	73,851	73,577	75,721	81,726
Relapses	14,170	15,432	14,854	13,673	16,519	18,290	13,098
Other direct	198,626	204,796	215,258	226,011	224,784	234,392	261,703
Total treatment costs	64,053	48,474	42,077	50,744	43,927	0	47,237
Acquisition, administration	60,932	45,548	39,015	46,916	40,741	0	43,023
Monitoring	2976	2906	2518	2653	2833	0	3226
AEs	145	21	544	1175	353	0	989
Total QALYs/patient	7.808	7.719	7.595	7.475	7.456	7.331	7.063
Total disease QALYs	7.811	7.720	7.596	7.476	7.464	7.331	7.064
Disability QALYs	7.962	7.884	7.755	7.624	7.638	7.524	7.206
QALY loss due to relapses	−0.151	−0.164	−0.159	−0.147	−0.175	−0.193	−0.142
QALY loss due to AEs	−0.003	−0.001	−0.001	−0.001	−0.008	0.000	−0.001
Total life-years	12.098	12.096	12.092	12.087	12.088	12.084	12.074
Years without cane (EDSS <6)	8.393	8.280	8.089	7.894	7.916	7.742	7.252

AEs, adverse events; BSC = best supportive care; DMF = dimethyl fumarate; Dom. = dominated; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; IFN = interferon; QALY = quality-adjusted life-year.

0.467, 0.428, 0.347, 0.126, 0.166, and –0.436 years, respectively. Consequently, teriflunomide was projected to result in the highest II with the assumed WTI.

The results of 1-way and multiway sensitivity and subgroup analyses (Table VI) show that the ranking of DMTs in terms of incremental cost-effectiveness appears to be generally robust for sensible changes in modeling assumptions or input variables. The results were sensitive to large changes in the modeled perspective or mixed treatment comparison. As the base case was performed on the basis of a representative population in Finland with characteristics well in line with the indication for teriflunomide, TEMSO trial results on patients' characteristics and transition probabilities in the placebo group were used in the subgroup analysis. Based on the analysis, the results are also generalizable to an older and more disabled population. Among the 25 modeled DSA scenarios, teriflunomide versus BSC was cost-effective in 72%, 84%, 96%, and 96% of scenarios with WTPs of €25,000, €37,000, €55,000, and €68,000/QALY gained, respectively. DMF versus teriflunomide was cost-effective in 0%, 0%, 4%, and 28% of the 25 DSA scenarios at these respective WTPs.

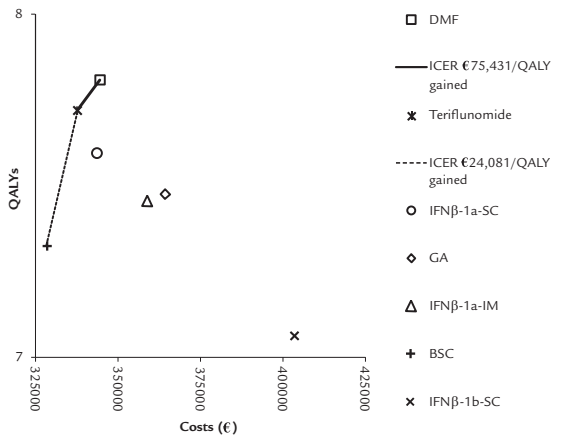

Figure 3. Cost-effectiveness plane and cost-effectiveness efficiency frontiers. BSC = best supportive care; DMF = dimethyl fumarate; GA = glatiramer acetate; ICER = incremental cost-effectiveness ratio; IFN = interferon; QALY = quality-adjusted life-year.

For the results of the modeled PSA, see Supplemental Material C in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.01.028. In summary, the PSA results were in line with the deterministic results—teriflunomide dominated injectable first-line DMTs, and DMF had a high mean ICER of 76,803 (2.5%–97.5% percentile, 52,105–139,595; 96% and 75% of ICERs exceeded 55,000 and 68,000, respectively) versus teriflunomide. Teriflunomide had >50% cost-effectiveness probabilities at WTPs of <€77,416/QALY gained versus other first-line DMTs. According to the Bayesian treatment ranking, teriflunomide was the first-best among the DMTs with all unofficial WTP thresholds from Finland mentioned earlier.

DISCUSSION

The findings from this modeling study of first-line DMTs for RRMS over 15 years suggest that teriflunomide 14 mg saves costs in comparison with all other reimbursed first-line DMTs in Finland; is cost-effective in comparison with DMF 240 mg at the cited threshold values; dominates injectable first-line DMTs; and, as a complementary result, is associated with the most value gained versus BSC as per the limited DMT-related budget (WTI). In some earlier cost-utility analyses of first-line DMTs for RRMS,[87–91] DMTs in comparison with BSC have been found not to be cost-effective based on the commonly cited threshold values—the situation was similar with GA, IFN-β1a IM, and IFN-β1b SC. These outcomes were largely explained by drug prices and clinical parts of the analysis, that is, short-term efficacy and tolerability and long-term efficacy and persistence of treatments.

The findings from the cost–benefit analysis type IIA based on the WTI seemed to follow the primary outcomes, yet a clear distinction on modeled II for teriflunomide versus BSC in comparison with other DMTs versus BSC was demonstrated with the assumed minimal DMT-related WTI of €42,077/patient. The IIA developed recently is a clinical value-assessment method that could increase clinical interpretation and appeal of the results, and indicate best IIs. However, based on the findings from Soini et al,[46] IIA cannot fully substitute the primary cost-effectiveness analysis outcomes if it ignores everything other than drug costs, differences in QoL, differences in AEs, and discounts and mixes the time horizons (ie, costs and benefits are gained from different timelines). Thus, IIA can easily result in investment biases and partial optimization of limited budgets. IIA, as such, probably should not be used as a primary method without acknowledging its limitations—here, the objective of the IIA was only to elaborate and complement the primary outcome based on a clear DMT-related cost and DMT-related II approach. In this study, the IIA was based on a modeling approach capable of synthesizing all of the known evidence. Comprehensive methods and data were needed for a valid IIA.

In addition to modeling methods, data validity and generalizability can be an issue in decision-analytical modeling. For example, the DEFENSE survey[14] is the most comprehensive, recent, and up-to-date assessment of the MS burden in Finland. However, the results from DEFENSE, as such, should be interpreted with caution. There are various reasons for this: the DEFENSE setting was cross-sectional, with varying patient recall (ie, recall bias can be an issue and there was no link between the cost outcomes and varying recall time, eg, relapses and EDSS-related costs); the base population was limited to active Finnish Neuro Society members, with only 36.9% of invited members participating in the survey (ie, about 10% of the Finnish Neuro Society); EDSS was self-assessed

Table VI. Scenario analysis results.

	DMF		Teriflunomide		IFN-β1a SC		GA		IFN-β1a IM		BSC		IFN-β1b SC		ICER vs BSC, €/Q gained					ICER, €/Q gained
Parameter	t€	Qs	t€	Qs	t€	Qs	t€	Qs	t€	Qs	t€	Qs	t€	Qs	DMF	Teriflunomide	IFN-β1a SC	IFN-β1a IM	IFN-β1b SC	DMF vs Teriflunomide
Treatment scenario*																				
0	344	7.81	338	7.72	344	7.59	364	7.48	359	7.46	328	7.33	404	7.06	33,681	24,081	57,690	244,105	D2	75,431
1	435	9.31	428	9.19	437	9.03	462	8.88	456	8.86	424	8.71	513	8.36	17,117	7690	37,189	200,655	D2	57,611
2	299	7.02	292	6.95	297	6.84	315	6.74	310	6.72	280	6.61	348	6.38	45,200	35,488	71,757	274,356	D2	87,775
3	334	7.83	327	7.75	331	7.65	350	7.55	345	7.52	312	7.41	384	7.19	54,341	43,651	81,243	300,582	D2	100,644
4	352	7.73	346	7.64	351	7.51	372	7.39	367	7.37	338	7.23	412	6.98	28,834	19,963	50,325	226,293	D2	66,678
5	344	7.82	337	7.73	343	7.60	364	7.48	358	7.46	327	7.34	403	7.07	34,577	24,891	59,531	247,709	D2	76,741
6	344	7.86	338	7.77	344	7.65	364	7.52	359	7.51	328	7.40	404	7.11	34,692	24,677	60,243	256,395	D2	79,476
7	344	7.76	338	7.66	344	7.54	364	7.43	359	7.40	328	7.27	404	7.02	32,728	23,514	55,345	232,940	D2	71,778
8	343	7.80	337	7.71	343	7.59	362	7.47	357	7.45	328	7.33	399	7.71	31,961	22,404	55,085	235,817	186,098	73,618
9	323	8.06	317	7.96	314	7.93	318	8.00	322	7.87	328	7.33	325	7.93	D1	D1	D1	D1	D1	67,342
10	375	7.46	362	7.45	389	7.12	429	6.79	408	6.95	328	7.33	513	5.97	366,514	280,158	D2	D2	D2	1,784,824
11	333	7.93	327	7.84	341	7.64	348	7.84	355	7.51	328	7.33	378	7.32	8303	D1	41,383	152,493	D2	62,213
12	344	7.80	335	7.74	335	7.67	342	7.69	353	7.50	328	7.33	357	7.50	33,504	17,031	19,928	146,428	165,735	160,740
13	344	7.81	338	7.72	344	7.59	364	7.48	359	7.49	328	7.33	404	7.06	33,867	24,128	57,848	261,165	D2	77,031
14	344	7.81	338	7.72	344	7.59	364	7.48	359	7.46	328	7.33	404	7.06	33,586	24,057	57,610	236,352	D2	74,624
15	359	7.81	351	7.72	355	7.59	374	7.48	369	7.46	336	7.33	405	7.06	47,405	38,500	72,137	260,027	D2	86,131
16	347	7.81	341	7.72	346	7.59	367	7.48	362	7.46	328	7.33	407	7.06	39,916	31,568	67,235	266,852	D2	76,220
17	343	7.81	336	7.72	342	7.59	367	7.48	357	7.46	328	7.33	402	7.06	30,564	20,338	52,918	232,732	D2	75,036
18	359	7.81	353	7.72	358	7.59	378	7.48	375	7.46	347	7.33	417	7.06	25,050	16,717	44,662	229,887	D2	61,288
19	337	7.81	330	7.72	336	7.59	357	7.48	351	7.46	319	7.33	397	7.06	37,997	27,763	64,204	251,214	D2	82,502
20	345	7.81	338	7.72	344	7.59	365	7.48	359	7.46	328	7.33	405	7.06	33,985	24,135	59,752	246,942	D2	76,825
21	344	7.81	338	7.72	343	7.59	364	7.48	359	7.46	328	7.33	403	7.06	33,529	24,054	56,660	242,687	D2	74,734
22	563	7.81	559	7.72	569	7.59	594	7.48	588	7.46	561	7.33	646	7.06	3760	D1	30,202	215,755	D2	45,370
23	344	6.19	338	6.08	344	5.92	364	5.76	359	5.74	328	5.58	404	5.21	26,393	18,796	45,500	189,710	D2	60,137
24	344	7.87	338	7.78	344	7.65	364	7.53	359	7.53	328	7.41	404	7.11	35,308	25,205	62,785	264,278	D2	79,614
25	335	7.58	328	7.50	332	7.41	350	7.31	345	7.29	315	7.19	383	6.98	52,617	41,397	79,775	304,327	D2	101,341
Mean	355	7.76	348	7.68	355	7.55	374	7.45	370	7.41	339	7.28	413	7.06	33,147	22,608	58,452	244,916	D2	81,704
Δ0	+10.8	-0.04	+10.6	-0.04	+11.2	-0.05	+10.1	-0.03	+11.1	-0.05	+11.0	-0.05	+9.1	0.00	-535	-1473	+762	+810	-43,928	+6273

Δ0 = difference vs base case; BSC = best supportive care; D1 = treatment dominates comparator; D2 = comparator dominates treatment; DMF = dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; ICER = incremental cost-effectiveness ratio; Q = quality-adjusted life-year; QoL =; t€ = cost in thousand Euros.
*Scenarios: 0 = base case; 1 = 0% discounting; 2 = 5% discounting; 3 = British Columbia relapsing–remitting multiple sclerosis (RRMS) Expanded Disability Status Scale (EDSS) transitions[57]; 4 = relapses from Held et al[86]; 5 = percentage of hospital relapses from Tampere; 6 = relapse duration 2 mo; 7 = relapse duration 4 mo; 8 = EDSS 7 stopping rule for disease-modifying therapies; 9 = mixed-treatment comparison (MTC): progression and annualized relapse rate (ARR) with low 95% credible interval (CrI); 10 = MTC: progression and ARR with high 95% CrI; 11 = MTC: no year limit, relapses adjusted; 12 = MTC: no year limit; 13 = time with adverse events (AEs) doubled; 14 = time with AEs halved; 15. EDSS-associated costs from Martikainen and Sintonen[13]; 16 = monitoring costs doubled; 17 = monitoring costs halved; 18 = relapse costs doubled; 19 = relapse costs halved; 20 = AE costs doubled; 21 = AE costs halved; 22 = societal approach[14]; 23 = EDSS-associated quality of life (QoL) from Kobelt et al[10]; 24 = similar QoL loss for all relapses; and 25 = TEMSO[30,32,33] patient characteristics and placebo transition probabilities for RRMS EDSS.

(whereas typically EDSS is assessed by a clinician); the results in patients with RRMS and those with SPMS were not separately reported; the reporting of DMT-related costs in different EDSS classes was unclear; and the adjusted cost (and relapse disutility) results may not have been adequately captured owing to statistical limitations (eg, costs should be assessed with methods that account for both distribution skewness and smearing).[47,84] Finally, dividing the cost level effect of ≥ 1 relapse by the mean number of relapses[14] is potentially an inappropriate statistical approach. Instead, the use of, for example, multilevel/hurdle regression or simple semilog regression with relapses as a continuous variable would have produced more reliable results.

Based on the findings from the extensive sensitivity analyses, the modeled base case results were nonetheless generally robust and generalizable, even when based on the TEMSO trial setting or RRMS transitions from British Columbia, Canada. Because of the potential impact of inherent methodologic issues in the DEFENSE survey,[14] results based on an earlier cost study[13] were used in a sensitivity analysis and demonstrated that the base case analysis was unlikely to overestimate cost differences. The ranking of DMTs in terms of primary outcome appeared to be robust to sensible changes in the input variables.

Based on the trial evidence, the modeled results of this study are valid. Teriflunomide 14 mg once daily was the only first-line DMT, injectable or oral, to show a significant reduction in both ARR and 3-month risk for disability progression compared with placebo in 2 pivotal clinical trials.[32,34] Compared with placebo, teriflunomide significantly reduced the rate of relapses with neurologic sequelae, relapses leading to hospitalization, and relapses requiring intravenous corticosteroids, and teriflunomide-treated patients spent fewer nights in hospital for relapse.[32,35] Teriflunomide 14 mg was associated with a significant decrease in the annual rate of all hospitalizations and emergency visits.[33] In addition, teriflunomide has a consistent tolerability profile, and AEs reported in patients receiving teriflunomide in clinical trials were largely mild to moderate (diarrhea, nausea, and hair thinning being most common) and infrequently led to treatment discontinuation. Patients reported improved treatment satisfaction with teriflunomide compared with IFN-β1a 44 μg.[37] Findings from a pooled analysis of data from teriflunomide trials supported the earlier trial findings.[92] Alanine aminotransferase and blood pressure should be monitored regularly, and complete blood cell counts should be performed based on signs and symptoms (eg, infections) during teriflunomide treatment (European Medicines Agency. Teriflunomide [summary of product characteristics] 2013).

Recently, Teri-PRO (Teriflunomide Patient-Reported Outcomes Study), an international Phase IV real-world study that measured patient-reported outcomes after the initiation of teriflunomide treatment, demonstrated a significant increase in treatment satisfaction in patients who were switched to teriflunomide from other DMTs.[93–95] In that study, a low rate of treatment discontinuation (21.4%) was observed over a 48-week period,[93] which is consistent with the findings from the present modeling study, with those from teriflunomide clinical trials, and with those from other recent real-world studies.[96–102] In Teri-PRO, statistically significant improvements were also seen in QoL (as measured by the MS International QoL scale), particularly on the subscales of activities of daily living, psychological well-being, symptoms, and coping.[94]

In addition, teriflunomide seems to have some benefit in patients who are switched from natalizumab due to a risk for progressive multifocal leukoencephalopathy.[101,102] However, it is important to note that the risk for progressive multifocal leukoencephalopathy, a severe AE that is included in the DMF labeling in Europe[103] and the United States,[104] was not included in the present modeling study.

On the other hand, injection-site or skin reactions, influenza-like symptoms, and neutralizing antibodies are common AEs associated with injectable DMTs and are among the most common reasons for discontinuing injectable DMTs.[105,106] Flushing, hot flushes, and upper gastrointestinal symptoms are the AEs most commonly reported with DMF therapy, according to an assessment by the National Institute for Health and Care Excellence.[75] Based on real-world evidence, AEs relating to DMF therapy can more frequently result in treatment discontinuation in comparison with teriflunomide[96,97]—an observation not accounted for in the present study; in fact, the modeling assumed a lesser withdrawal rate in DMF users compared with teriflunomide users.

Among earlier cost-effectiveness studies of first-line MS DMTs,[87–91,107–111] only 1 includes oral DMTs (DMF, teriflunomide, US setting).[111] In the present modeling study, teriflunomide 14 mg and DMF 240

mg were cost-effective treatments versus BSC at the WTP threshold values of €37,000 or €55,000/QALY gained. However, at the most plausible WTP of €25,000/QALY gained versus BSC, only teriflunomide 14 mg was cost-effective. Furthermore, DMF 240 mg was not cost-effective versus teriflunomide 14 mg at Finland's unofficial WTP threshold values.

Overall health care efficiency, low drug prices, and costly health care resources may be reasons behind the results from the present analysis. However, the health care setting in Finland can be regarded as a robust default setting and as a benchmark for health economic assessments for many reasons. Most important, the productivity and efficiency of the Nordic health care systems are high, as demonstrated in multiple studies of the health care system in Finland.[112–114] Social security code and national registries cover all citizens in Finland, and one of the most advanced biobank laws is in use for the willing. Furthermore, Finland has a low pharmacy purchase price for reimbursed drugs[44] among European countries, and tendering or patient access schemes have not been possible for reimbursed drugs,[115] eliminating uncertainties about drug prices in Finland. Finland also has national lists for health care unit costs[68,69] and official indexes based on national statistics.[71,85] In some countries, such information does not exist. Currently, Finland is undergoing health care, social welfare, and regional government reform,[116] which is likely to result in digitized service solutions for the primary (eg, benchmarking service producers) and secondary (eg, market access to new drugs and devices) uses of national, areal, local, and biobank health care and social welfare data in terms of effectiveness and cost-effectiveness.[117] Furthermore, the Finnish parliament recently received a proposal for a risk-sharing scheme centered around an agreement-based conditional reimbursement from the government of Finland. However, the official wholesale price in the application would still need to be affordable, and the risk-sharing scheme would be available only through the optional application process.[118,119] This development has the potential to further increase the efficiency of Finland's health care system and the relevance of modeling-based health economic assessments. Finally, Finland's guidance for health economic analyses[39] is well in line with many other cost-effectiveness analysis guidelines.[43,120–128]

Health economic modeling is needed to handle the multidimensional assessment challenge, to summarize the trial evidence and local input data, to enable extrapolations and discounting, and to produce results in terms of generalizable outcomes with standard interpretation. In the future, it will be necessary to assess the effects of the risk-sharing scheme with some treatments. Thus, by necessity, health economic models are simplifications of a very complicated reality. Here, these assumptions are discussed.

In the model, potential treatment sequences were excluded, and switching between different DMTs was not accounted for. However, dropping out of first-line DMT altogether was included. To analyze the cost-utility of first-line RRMS DMTs, a sequential approach was not needed. A sequential approach would be more viable in later treatment line assessment or in health technology assessment searching for the optimal treatment sequence. Furthermore, there was no gold standard treatment sequence based on Finnish data, and the treatment of patients with RRMS seemed to be guided by per-patient decisions (which are probably affected by disease severity, disease progression, patient/clinician preferences, and potential DMT-related AEs).

In the selected modeling approach, all DMTs compared were handled equally by assuming similar treatment after the first-line DMT, and the result was not jeopardized by inherent and potentially problematic assumptions related to second- and later-line DMT efficacy, tolerability, and washout. Furthermore, in a sequential model, the result may be confounded by potential population changes between the treatment lines. In the present analysis, the results were directly related to differences due to the first-line DMT. In the evaluation, the first-line DMTs were being compared against each other, which potentially was associated with less uncertainty and fewer assumptions, and also in reduced bias and confounding in comparison with a sequential approach relying on multiple additional assumptions due to lack of data. Furthermore, all of the DMTs in the comparison were pharmacy prescription drugs, which overcomes issues of comparing intravenously administered hospital drugs (eg, further-line or high-activity MS treatments) and pharmacy prescription drugs[44,47] and are currently subject to public reimbursement in Finland.

In earlier cost-effectiveness analyses of treatments for diseases other than MS, if the treatment sequence

included treatment options that were not the most cost-effective, the incremental cost-effectiveness of the sequence deteriorated in comparison with base treatments.[45,48,129,130] First-line MS DMTs lacked published cost-utility evidence; thus, there are no supporting publications to benchmark or determine the optimal MS treatment sequence. Furthermore, in these situations, it was more important to know how DMTs perform in comparison with the minimum case (BSC). Based on the Finnish MS research registry data, only a percentage of patients with RRMS are currently actively treated. This may be for reasons connected with efficacy, tolerability, the patient, or the clinician.

Based on the Finnish MS research registry data, MS DMT-related AEs seem to accumulate in some patients. However, owing to the similarity of some AEs produced by frequently used first-line MS injectable DMTs, it is uncertain whether AEs occur in some patients after changing from one first-line DMT to another. Furthermore, no well-controlled research evidence exists demonstrating the clinical gains or benefits of switching the first-line DMT.

EDSS transitions in this modeled evaluation were based on data from Finland (RRMS) and London, Ontario, Canada (SPMS),[59] because these were most comprehensive for the setting and because they included survival data and were recorded and checked by clinical experts. Other examples of EDSS data include the British Columbia database,[57,58,131,132] the Lyon MS Cohort,[133] the Rennes MS Database,[134] and the Sonya Slifka Longitudinal MS Study.[135] The effects of RRMS EDSS transitions were tested in sensitivity analyses, and the relative results remained unchanged. In fact, the recently published RRMS transitions from British Columbia, Canada[57] agree with those from Finland.

Last, in addition to clinical real-world evidence, future real-world studies should collect real-world data to support modeled economic evaluations. They should, accordingly, include comprehensive assessments of the EDSS specified separately for RRMS; SPMS and primary progressive MS; relapses; AEs and withdrawals; comorbidities; patient income; and the impact of these outcomes on resource use, costs, QoL, and mortality. This real-world evidence may be obtainable using structural treatment-monitoring systems and long-term registry data with sufficient data coverage and could enable the use of event-based or microsimulation methods in the assessments. In addition, IIA type analysis should be used to increase the clinical appeal of complex analyses.

CONCLUSIONS

Data presented from the present modeling study highlight the cost-effectiveness of teriflunomide 14 mg once daily compared with DMF 240 mg BID when the commonly cited threshold values are taken into account. In the present modeling study, teriflunomide 14 mg also dominated all other commonly used first-line DMTs for RRMS in Finland and was associated with the highest II.

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CONFLICTS OF INTEREST

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SUPPLEMENTAL MATERIAL

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SUPPLEMENTARY MATERIAL

Supplement A. EDSS-based RRMS and SPMS transition matrices

EDSS[1] is the key outcome in the assessment of MS disability progression. In the Finnish Pirkanmaa-Seinäjoki-Vaasa MS registry, there were 1359 patients with MS with EDSS assessment data available, with altogether 2458 measurements. These patients were identified from administrative registries. The data collection, case ascertainment procedure, and ethical permits have been described in detail elsewhere.[2,3] Incident MS cases diagnosed in the study region that fulfilled the McDonald[4] criteria were included. The classification of disease course to RRMS was performed using standardized definitions.[5]

A total of 1242 patients had RRMS, and these patients with RRMS had altogether 2299 EDSS measurements between August 27, 1986, and December 31, 2010. Women accounted for 69.8% of the patients. In all, 62.2% of the EDSS assessments were carried out at the beginning of a DMT episode with an EDSS score of 0–7. In 2010, EDSS values were assessed for all patients alive (July 1, 2010, assumed, if no specific day shown in the data).

EDSS Transitions in RRMS

Figure A.1 shows all EDSS measurements over time for descriptive purposes. As can be seen, most EDSS measurements were performed for patients with RRMS (green colored dots). The figure also shows that there was censoring in the EDSS measurements in EDSS classes 6.5–9.5.

For descriptive purposes, combined Figure A.2 shows the development from one EDSS measurement to the next among patients with RRMS, conditional on particular EDSS scores.

EDSS development over time needs to be modeled in order to estimate the progression of MS. MS progression for the model was estimated using integer RRMS EDSS scores (halves rounded up; 9.5 assumed to be 9.0 because the patient is alive when EDSS is 9.5). The JAGS software V3.3.0,[6] which is a statistical program capable of analyzing Bayesian hierarchical models by Markov Chain Monte Carlo (MCMC)

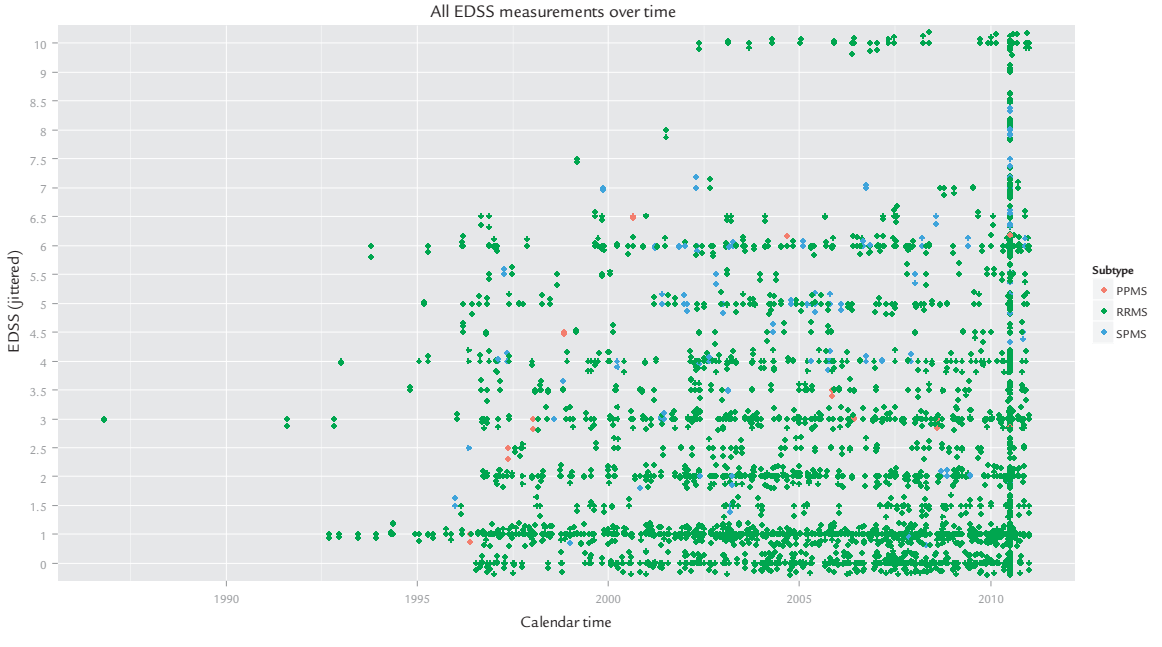

Figure A.1. All EDSS measurements (jittered to prevent over-plotting) over time, by MS type (RRMS, green; PPMS, red; SPMS, blue). EDSS = Expanded Disability Status Scale; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

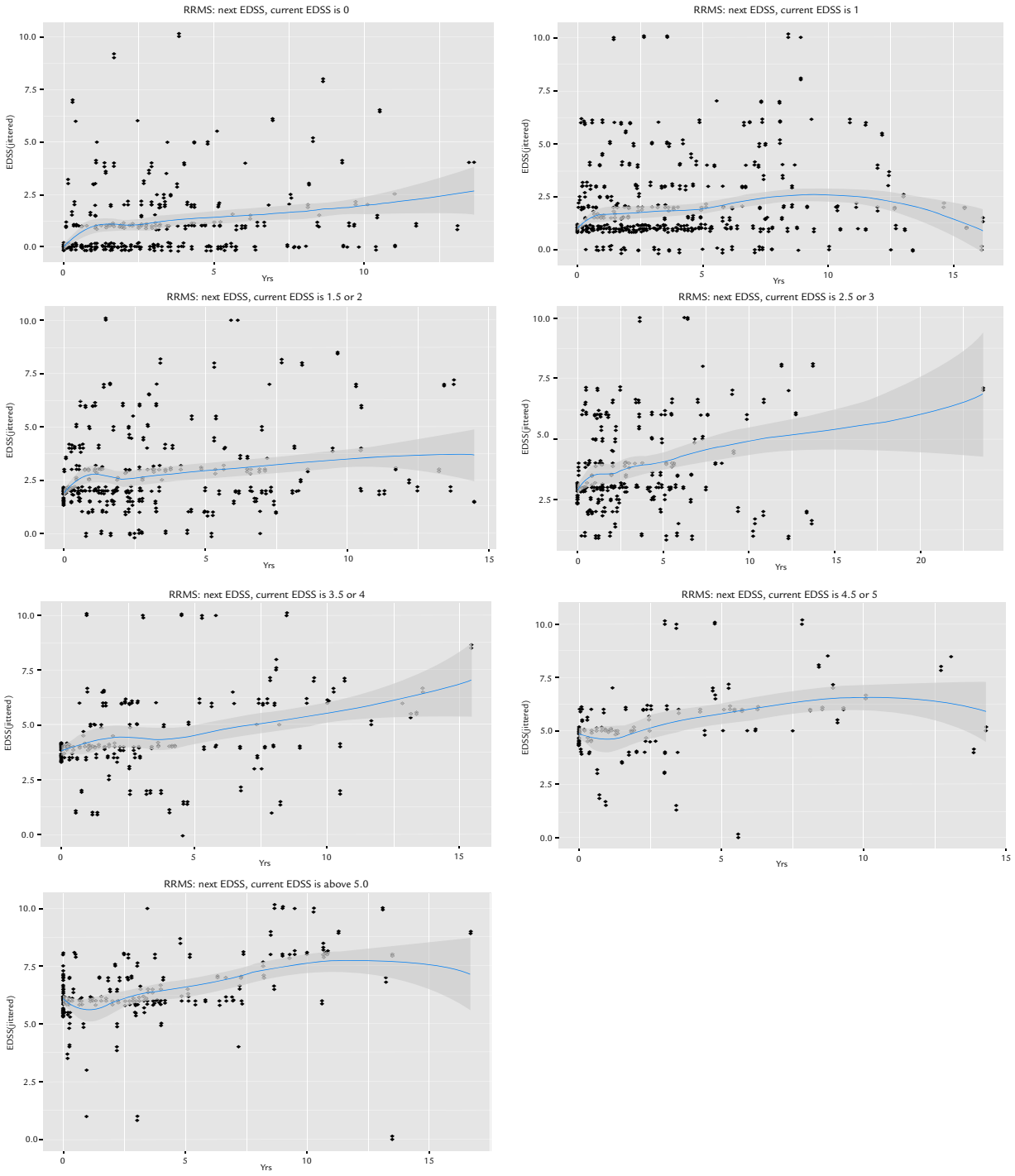

Figure A.2. EDSS development in RRMS population over time showing next EDSS scores. The blue line gives the average expected EDSS over time and the shaded area is the 95% CI obtained by unadjusted local polynomial smoothing of the raw data. CI = confidence interval; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.

Table A.I. Annual transition probability matrix by EDSS for patients with RRMS based on the Finnish data.

From/To	RRMS EDSS 0	RRMS EDSS 1	RRMS EDSS 2	RRMS EDSS 3	RRMS EDSS 4	RRMS EDSS 5	RRMS EDSS 6	RRMS EDSS 7	RRMS EDSS 8	RRMS EDSS 9	RRMS EDSS 10
RRMS EDSS 0	0.67822	0.26314	0.04275	0.01136	0.00364	0.00077	0.00003	0.00003	0.00003	0.00003	0.00000
RRMS EDSS 1	0.11299	0.60711	0.17922	0.06484	0.02725	0.00711	0.00037	0.00037	0.00037	0.00037	0.00000
RRMS EDSS 2	0.01770	0.17312	0.37521	0.22712	0.14263	0.04960	0.00365	0.00365	0.00365	0.00365	0.00001
RRMS EDSS 3	0.00547	0.07282	0.26542	0.25690	0.24007	0.11065	0.01216	0.01216	0.01216	0.01216	0.00002
RRMS EDSS 4	0.00155	0.02710	0.14772	0.21289	0.30097	0.18210	0.03189	0.03189	0.03189	0.03189	0.00009
RRMS EDSS 5	0.00045	0.00981	0.07124	0.13607	0.25204	0.20969	0.08010	0.08010	0.08010	0.08010	0.00031
RRMS EDSS 6	0.00001	0.00027	0.00276	0.00786	0.02314	0.04173	0.23071	0.23071	0.23071	0.23071	0.00141
RRMS EDSS 7	0.00001	0.00027	0.00276	0.00786	0.02314	0.04173	0.23071	0.23071	0.23071	0.23071	0.00141
RRMS EDSS 8	0.00001	0.00027	0.00276	0.00786	0.02314	0.04173	0.23071	0.23071	0.23071	0.23071	0.00141
RRMS EDSS 9	0.00001	0.00027	0.00276	0.00786	0.02314	0.04173	0.23071	0.23071	0.23071	0.23071	0.00141
RRMS EDSS 10	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	1.00000

Table A.II. Annual probabilities of conversion to SPMS from RRMS by EDSS score.

EDSS score	Calculation	Hazard rate of conversion	Calculation	Probability
1	ln(2)/15	0.046210	1-exp(-0.046210)	0.045158
2	0.04621*e^(0.25270*2)	0.076600	1-exp(-0.076600)	0.073739
3	0.04621*e^(0.25270*3)	0.098622	1-exp(-0.098622)	0.093915
4	0.04621*e^(0.25270*4)	0.126975	1-exp(-0.126975)	0.119245
5	0.04621*e^(0.25270*5)	0.163480	1-exp(-0.163480)	0.150817
6	0.04621*e^(0.25270*6)	0.210480	1-exp(-0.210480)	0.189805
7	0.04621*e^(0.25270*7)	0.270993	1-exp(-0.270993)	0.237378
8	0.04621*e^(0.25270*8)	0.348902	1-exp(-0.348902)	0.294538
9[†]				1.000000
10				0.000000

[†]Information for EDSS 9 was not available from the London Ontario dataset. Thus, a 100% conversion rate for patients with RRMS in EDSS 9 was assumed.

simulation methods, was used to estimate the EDSS transition probabilities.

When estimating the RRMS EDSS 0–9 transitions, uniform priors were assumed because no earlier Finnish transition probabilities data were available. Based on a prior knowledge of the data in question, 60% of the mortality was assumed to be MS-related.[7] This estimate was conservative in comparison to other estimates, which have a higher proportion of MS-related mortality (eg, 78.3% in Goodin et al[8]). The results shown in Table A.I are well in line with the recent British Columbia results.[9]

RRMS to SPMS Transition

The hazard rate (HR, λ) for conversion from RRMS EDSS 1 to SPMS was calculated assuming an exponential survival function (ie, a constant hazard of converting to SPMS over time):

$$S(t)=\exp(-\lambda t)$$

λ for an exponential distribution could be estimated from the median time of conversion to SPMS, reported to be 15 years based on London Ontario data,[10,13] ie:

$$\lambda = \ln(2)/15$$

This gives an annual HR of 0.0462 for SPMS-conversion of patients in EDSS 1.

The Finnish dataset includes only a few observations of conversion to SPMS, and an EDSS-specific rate could not be estimated from these. Based on the London Ontario data, the Cox proportional hazards model was:

$$H(t)=H(t)_{EDSS1}.\exp(\beta X)$$

where H(t) is the HR of conversion for any EDSS state; $H(t)_{EDDS1}$, the HR of conversion for EDDS 1; and β, the coefficient (0.25270) of the relationship between EDSS and the HR of progression between the base case EDSS 1 and all other EDSS states.[10,13] Using Bender et al,[11] the relationship was reformulated as:

$$\ln\left[\frac{H(t)}{H(t)_{EDSS1}}\right]=\beta.X$$

Thus:

$$H(t)=\lambda.e^{\beta.X}$$

This was used to derive the HR of conversion from EDSS 1 through each successive stage to EDSS 8 (Table A.II). All estimated HRs were then subsequently converted into probabilities[12]:

$$p=1-\exp(-rt)$$

EDSS Transitions in SPMS

For SPMS transitions, data from the London Ontario MS registry[10,13] were available and used (Table A.III), because the Finnish register data had too few EDSS measurements for patients with SPMS.

Table A.III. Annual transition probability matrix by EDSS for patients with SPMS based on London Ontario data.[10,13]

From/To	SPMS EDSS 0	SPMS EDSS 1	SPMS EDSS 2	SPMS EDSS 3	SPMS EDSS 4	SPMS EDSS 5	SPMS EDSS 6	SPMS EDSS 7	SPMS EDSS 8	SPMS EDSS 9	SPMS EDSS 10
SPMS EDSS 0	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SPMS EDSS 1	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
SPMS EDSS 2	0.000	0.000	0.455	0.375	0.099	0.041	0.027	0.002	0.001	0.000	0.000
SPMS EDSS 3	0.000	0.000	0.000	0.563	0.280	0.088	0.061	0.005	0.002	0.000	0.000
SPMS EDSS 4	0.000	0.000	0.000	0.000	0.482	0.281	0.218	0.013	0.006	0.000	0.000
SPMS EDSS 5	0.000	0.000	0.000	0.000	0.000	0.340	0.597	0.041	0.023	0.000	0.000
SPMS EDSS 6	0.000	0.000	0.000	0.000	0.000	0.000	0.870	0.081	0.048	0.000	0.000
SPMS EDSS 7	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.645	0.349	0.006	0.000
SPMS EDSS 8	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.992	0.008	0.000
SPMS EDSS 9	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000
SPMS EDSS 10	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000

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SUPPLEMENT B. AES: INCIDENCE, TREATMENT COSTS, AND DISUTILITIES

Risks of AEs

Adverse events (AEs) were included to the modeling based on a $\geq$4% difference between active treatment and placebo and/or clear inclusion in a previous NICE HTA submission (Table B.I). Nearly all AEs related to DMF, GA, interferons, and teriflunomide are mild to moderate and of short duration. The reason for not including the AEs with a $<$4% difference between placebo and active treatment and no NICE HTA reference was to simplify the analysis. Recently, the FDA added a progressive multifocal leukoencephalopathy (PML, a very severe AE) scenario to the DMF label. However, possible PML risk with DMF was ignored owing to uncertainty related to exact PML risk (usually PML risk accumulates over time).

In order to convert risk of AEs from studies to annualized risk of AEs, the risk of AEs was converted to a rate using a standard formula,[1] and the resulting annualized AE rates were then converted back to annualized probabilities/risks (Table B.I).

AEs were assumed to occur at most once per cycle. However, injection-site reaction, fever, and nausea tend to occur after every interferon dose, and chest pain, palpitation, and dyspnea may happen after every GA dose for subjects who have a particular AE. Consequently, the impact of those AEs may be underestimated for interferons and GA.

Treatment of AEs

In Finnish practice, the active treatment of severe AEs takes place in the neurology unit, and moderate AEs result in phone calls to the neurologic department. More severe AEs, including injection-site reactions, chest pain, palpitation, dyspnea, hot flush, and vomiting, require specialist consultation (Table B.II). Chest pain and flushing, palpitation, and dyspnea related to GA are usually transient.[8] Asthenia, chills, diarrhea, flush, hair thinning, and nausea alone do not usually need active treatment; thus, phone contact to the neurologic department was assumed for these. Conservatively,

Table B.I. Annualized risk of AEs associated with treatment.

Treatment	Adverse event (AE)	Annualized probability	Rate source
DMF 240 mg (Tecfidera®)	Flushing	19.0%	Aggregate weighted estimate based on the trials referred to in the HTA submission (NICE)[2]
	Nausea	6.2%	
	Upper abdominal pain	5.1%	
	Vomiting	4.3%	
	Hot flush	3.4%	
GA 20 mg (Copaxone®)	Injection-site reaction	68.4%	Johnson et al[3]
	Dyspnea	6.6%	
	Chest pain, flushing	2.8%	
	Palpitation	2.4%	
IFNβ-1a-SC 44 μg (Rebif®)	Injection-site reaction	38.3%	PRISMS Study Group[4]
	Myalgia	7.0%	
	Neutralizing antibodies	6.5%	
	Fever	6.1%	
IFNβ-1a-IM 30 μg (Avonex®)	Headache	42.6%	Jacobs et al[5]
	Influenza-like symptoms	37.4%	
	Muscle pain	18.5%	
	Nausea	16.9%	
	Neutralizing antibodies	14.0% year 1, 8.0% year 2+	
	Fever	12.5%	
	Asthenia	11.1%	
	Chills	11.1%	
	Diarrhea	8.3%	
IFNβ-1b 250 μg (Betaferon®)	Injection-site reaction	80.0% year 1, 44.0% year 2+	IFNB Multiple Sclerosis Study Group[6]
	Neutralizing antibodies	27.4% year 1, 5.6% year 2+	
	Influenza-like symptoms	8.0% year 1, 5.5% year 2+	
Teriflunomide 14 mg (Aubagio®)	Diarrhea	9.1%	O'Connor et al[7]
	Nausea	6.9%	
	Hair thinning	6.6%	

none of the AEs included were assumed to result in hospitalization.

Ibuprofen is used to treat fever, headache, influenza, muscle pain, and myalgia. Antihistamine is used to treat (at minimum) the hot flush associated with DMF. No other drugs were assumed to be used for the treatment of DMT-related AEs.

QoL Loss of AEs

Resource use and costs associated with AE management are given in Table B.II, and QoL losses and durations associated with AEs are given in Table B.III.

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Table B.II. Resource use and costs (€) associated with AE management.

Adverse event (AE)	Cost (€)	Resources (original unit cost and source)
Asthenia, chills, diarrhea, flush, hair thinning, or nausea	24.43	Phone call (€24.43[9] at 2014 values[10])
Upper abdominal pain	30.73	Phone call (€24.43[9] at 2014 values[10]) + blood test taking (€5.47[11] at 2014 values[10]) + LFT (€1.00[12])
Fever, headache, influenza symptoms, muscle pain, or myalgia	35.18	Phone call (€24.43[9] at 2014 values[10]) + NSAID (ibuprofen 600mg €10.74[13])
Chest pain, flushing, dyspnea, injection-site reaction, palpitation, or vomiting	340.76	Specialist visit (€340.76 incl. 5% copayment[9] at 2014 values[10])
Hot flush	358.12	Specialist visit (€340.76 incl. 5% copayment[9] at 2014 values[10]) + antihistamine (desloratadine 5 mg €17.36[13])
Neutralizing antibodies	438.74	Specialist visit (€340.76 incl. 5% co-payment[9] at 2014 values[10]) + blood test taking (€5.47[11] at 2014 values[10]) + antibody test (€92.50[14])

Table B.III. Quality of life (QoL) loss and its duration associated with AEs.

Adverse event (AE)	QoL loss	Duration	Assumption	Disutility source
Flushing, hair thinning, neutralizing antibodies, or upper abdominal pain	−0.0001	1 year*	Assumption	–
Headache	−0.0827	2 days*	–	Soini and Hallinen[15]
Injection-site reaction		24 hours*	Headache	
Muscle pain or myalgia		1 week*		
Diarrhea	−0.1034	2.5 days[16]	–	
Asthenia or chills		1 week*	Diarrhea	
Fever		24 hours*		
Influenza-like symptoms		1 week[17]		
Vomiting		3 weeks*		
Nausea		1 week*	–	
Chest pain, flushing, dyspnea, or palpitation	−0.1244	24 hours[8]	Somnolence	
Hot flush		3 weeks*		

*Expert opinion.

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SUPPLEMENT C. PROBABILISTIC SENSITIVITY ANALYSIS RESULTS

Probabilistic Results

Table C.I reports the 15-year mean and 2.5%–97.5% percentile results based on 2000 simulations.

Cost-Effectiveness Plane

Figure C.1 shows the joint distributions of 15-year cost-and-effect differences (increments) for the non-dominated teriflunomide (teriflunomide is in the origin of Figure C.1) vs other DMTs.

Cost-Effectiveness Acceptability Frontier

Figure C.2 depicts the cost-effectiveness acceptability frontier (CEAF). Based on the CEAF, teriflunomide had more than 50% cost-effectiveness probabilities with ICERs less than 77,416 vs other first-line DMTs for RRMS (Figure C.2).

Bayesian Treatment Ranking

According to Bayesian treatment ranking, teriflunomide was the best option, with a willingness-to-pay threshold of €0 (99.9%), €25,000 (100.0%), €37,000 (100.0%), €55,000 (96.2%), and €68,000 (75.2%) per QALY gained.

Table C.I. Probabilistic results.

Treatment	Mean QALYs	2.5%	97.5%	Mean costs (€)	2.5%	97.5%
DMF	7.335	6.847	7.781	376,159	335,827	420,955
Teriflunomide	7.242	6.741	7.683	369,045	327,547	415,265
IFNβ-1a-SC 44µg	7.112	6.612	7.556	373,417	329,267	419,587
GA	6.990	6.445	7.457	393,558	352,185	440,894
IFNβ-1a-IM 30µg	6.971	6.415	7.444	387,785	344,135	436,228
IFNβ-1b-SC 250µg	6.575	6.003	7.095	428,286	380,681	482,486

DMF = dimethyl fumarate; GA = glatiramer acetate; IFNβ-1a-SC = interferon beta-1a-subcutaneous; IFNβ-1a-IM = interferon beta-1a-intramuscular; IFNβ-1b-SC = interferon beta-1b-subcutaneous; QALY = quality-adjusted life-year.

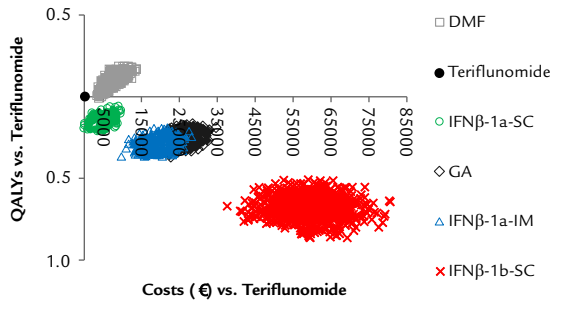

Figure C.1. *Probabilistic incremental cost and QALY results in a cost-effectiveness plane for teriflunomide vs other first-line treatments (2000 simulations)*. DMF = dimethyl fumarate; GA = glatiramer acetate; IFNβ-1a-SC = interferon beta-1a-subcutaneous; IFNβ-1a-IM = interferon beta-1a-intramuscular; IFNβ-1b-SC = interferon beta-1b-subcutaneous; QALY = quality-adjusted life-year.

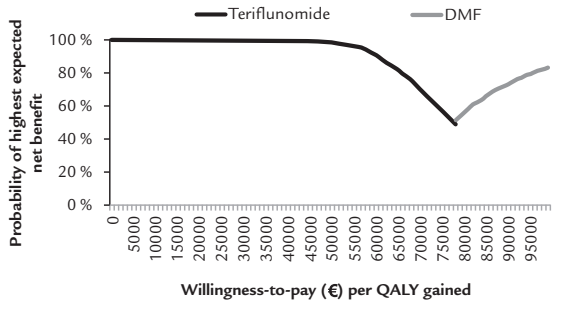

Figure C.2. *Cost-effectiveness acceptability frontier for first-line treatments*. DMF = dimethyl fumarate; QALY = quality-adjusted life-year.