ORIGINAL RESEARCH ARTICLE

Comparative Effectiveness and Cost-Effectiveness of Natalizumab and Fingolimod in Patients with Inadequate Response to Disease-Modifying Therapies in Relapsing-Remitting Multiple Sclerosis in the United Kingdom

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Abstract

Background Patients with highly active relapsing-remitting multiple sclerosis inadequately responding to first-line therapies (interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, known collectively as "BRACETD") often switch to natalizumab or fingolimod.

Objective The aim was to estimate the comparative effectiveness of switching to natalizumab or fingolimod or within BRACETD using real-world data and to evaluate the cost-effectiveness of switching to natalizumab versus fingolimod using a United Kingdom (UK) third-party payer perspective.

Methods Real-world data were obtained from MSBase for patients relapsing on BRACETD in the year before switching to natalizumab or fingolimod or within BRACETD. Three-way-multinomial-propensity-score–matched cohorts were identified, and comparisons between treatment groups were conducted for annualised relapse rate (ARR) and 6-month–confirmed disability worsening (CDW6M) and improvement (CDI6M). Results were applied in a cost-effectiveness model over a lifetime horizon using a published Markov structure with health states based on the Expanded Disability Status Scale. Other model parameters were obtained from the UK MS Survey 2015, published literature, and publicly available UK sources.

Results The MSBase analysis found a significant reduction in ARR (rate ratio [RR] = 0.64; 95% confidence interval [CI] 0.57–0.72; $p < 0.001$) and an increase in CDI6M (hazard ratio [HR] = 1.67; 95% CI 1.30–2.15; $p < 0.001$) for switching to natalizumab compared with BRACETD. For switching to fingolimod, the reduction in ARR (RR = 0.91; 95% CI 0.81–1.03; $p = 0.133$) and increase in CDI6M (HR = 1.30; 95% CI 0.99–1.72; $p = 0.058$) compared with BRACETD were not significant. Switching to natalizumab was associated with a significant reduction in ARR (RR = 0.70; 95% CI 0.62–0.79; $p < 0.001$) and an increase in CDI6M (HR = 1.28; 95% CI 1.01–1.62; $p = 0.040$) compared to switching to fingolimod. No evidence of difference in CDW6M was found between treatment groups. Natalizumab dominated (higher quality-adjusted life-years [QALYs] and lower costs) fingolimod in the base-case cost-effectiveness analysis (0.453 higher QALYs and £20,843 lower costs per patient). Results were consistent across sensitivity analyses.

Extended author information available on the last page of the article

Conclusions This novel real-world analysis suggests a clinical benefit for therapy escalation to natalizumab versus fingolimod based on comparative effectiveness results, translating to higher QALYs and lower costs for UK patients inadequately responding to BRACETD.

Key Points for Decision Makers

The increasing availability of real-world evidence in multiple sclerosis (MS) allows for a novel collaborative effort to design and conduct a real-world registry analysis of highly active MS treatment escalation alternatives in alignment with established cost-effectiveness modelling approaches for MS.

Results from the MSBase registry suggest that treatment escalation to natalizumab is more effective on relapse- and disability improvement-based outcomes compared to switching between BRACETD treatments or escalating to fingolimod.

Results from our cost-effectiveness analysis also indicate that switching to natalizumab improves lifetime clinical and economic outcomes compared with switching to fingolimod for patients with highly active relapsing-remitting MS with inadequate response to first-line therapies from a United Kingdom payer perspective.

1 Introduction

Cost-effectiveness analyses are the cornerstone of health technology appraisals (HTAs) used by many payers globally to inform drug pricing or reimbursement decisions. Traditionally, such analyses have focused on newly approved drugs and relied primarily on clinical trial evidence. However, with the emergence of longitudinal disease registries and the expansion of treatment alternatives in conditions such as multiple sclerosis (MS), payers and HTA agencies are increasingly requesting real-world evidence when re-evaluating drugs that are already reimbursed.

Large disease registries, like the international MSBase registry [1], frequently provide independent analysis for clinical comparisons. This paper describes a novel collaborative effort to design a real-world registry analysis of MS treatments in alignment with established health economic modelling requirements in MS. Acknowledging that the methodologies and terminologies for real-world clinical outcome

analysis in MS and for health economic (or pharmacoeconomic) analysis differ meaningfully, this paper represents a unique effort in the MS literature to join these approaches in pursuit of improved understanding of the benefits and value of treatment alternatives in MS.

Disease-modifying therapies (DMTs) for relapsing-remitting MS (RRMS), the most common MS subtype, reduce the frequency of relapses and the accumulation of disability that contribute to the burden of MS for patients and caregivers [2–5]. The prevailing treatment strategy in RRMS involves escalation of DMTs, where patients with inadequate response to first-line treatment options (interferon-based therapies [Betaferon®/Betaseron (US)®, Rebif®, Avonex®, Extavia®], glatiramer acetate [Copaxone®], teriflunomide [Aubagio®], and dimethyl fumarate [Tecfidera®], known collectively as "BRACETD") switch to more effective therapies, such as natalizumab (Tysabri®) or fingolimod (Gilenya®), among others [5]. While these escalation DMTs are more efficacious, they carry increased risks of rare but serious adverse events (AEs) (e.g. progressive multifocal leukoencephalopathy [PML], secondary autoimmunity, cardiac arrhythmias, and breast cancer) [6]. Since relapses remain the most widespread measure of disease activity, at least one relapse in the year prior to switching therapy was used to define a patient with inadequate response to MS treatment. This definition mirrors the current approved European Medicines Agency regulatory indication for both natalizumab and fingolimod; however, it is recognised that this definition continues to evolve in the scientific community.

Real-world evidence has an established role in characterising the natural history and burden of RRMS in economic evaluations of DMTs [7–10]. Real-world data (RWD) from disease registries such as MSBase [1] are increasingly used to study the comparative effectiveness of DMTs for RRMS, especially escalation alternatives such as natalizumab and fingolimod [11, 12]. The objective of this study was to design and conduct a comparative effectiveness analysis using RWD from MSBase for use in a pharmacoeconomic model to estimate the cost-effectiveness from a United Kingdom (UK) third-party payer perspective of switching to natalizumab compared with switching to fingolimod in patients with highly active RRMS (HA-RRMS) with inadequate response to BRACETD.

2 Methods

2.1 Study Population

The population for the comparative effectiveness and cost-effectiveness analyses comprised adults with HA-RRMS with inadequate response (defined as ≥ 1 relapse in the year before switching) after ≥ 1 year on a first-line DMT (BRACETD) who switched to natalizumab, fingolimod, or another BRACETD. Patients switching to another BRACETD were included as a common reference group in the comparative effectiveness analysis to facilitate extrapolation and post-discontinuation scenarios

for natalizumab and fingolimod in the cost-effectiveness analysis.

To identify this population in the MSBase registry, longitudinal data from 42,189 patients across 139 MS centres in 39 countries were extracted from the registry database on 13 June 2016. These centres are requested to perform at least a yearly clinical assessment of their patients, although this was not used as an exclusion criterion for the current study. Patients aged ≥ 18 years with RRMS were included in the study population if they met the switch criteria (defined in the paragraph above), had completed ≥ 1 year of uninterrupted treatment with BRACETD before switching, and had ≥ 1 relapse in the year before switching while on BRACETD. The analysis excluded patients

Table 1 Baseline patient characteristics for the MSBase cohorts after matching

Baseline patient characteristics[a]	BRACETD to NTZ (n = 897)	BRACETD to FTY (n = 897)	BRACETD to BRACETD (n = 897)	Standardised differences[b]		
				NTZ vs FTY	NTZ vs BRACETD	FTY vs BRACETD
Age, median (IQR), years	36.9 (30.0–43.1)	37.6 (31.2–44.8)	37.1 (30.5–44.0)	− 0.118	− 0.080	0.035
Sex, female, n (%)	669 (74.6)	641 (71.5)	649 (72.4)	0.070	0.050	− 0.020
EDSS score, median (IQR)	2.5 (1.5–4.0)	2.5 (1.5–4.0)	2.5 (1.5–4.0)	0.138	0.149	0.166
Disease duration, median (IQR), years	7.7 (3.6–12.7)	7.8 (3.8–13.9)	7.7 (3.5–12.6)	− 0.117	0.061	0.171
On-treatment proportion of disease duration[c], mean (SD)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	− 0.096	− 0.141	− 0.049
Number of DMT starts before the switch DMT, mean (SD)	1.7 (0.9)	1.7 (1.2)	1.6 (1.0)	− 0.101	− 0.043	0.188
Number of DMT starts before the switch DMT per disease duration, mean/year (SD)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.124	0.106	− 0.165
Total relapse onsets in the prior 12 months, mean (SD)	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)	0.139	0.165	0.137
Total relapse onsets in the prior 24 months, mean (SD)	2.1 (1.0)	2.1 (1.0)	2.0 (1.1)	0.114	0.188	0.139
Total steroid-treated relapse onsets in the prior 12 months, mean (SD)	1.0 (0.8)	1.0 (0.8)	1.0 (0.8)	0.174	0.131	0.156
Total steroid-treated relapse onsets in the prior 24 months, mean (SD)	1.4 (1.1)	1.4 (1.1)	1.3 (1.1)	0.189	0.179	0.187

BRACETD interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *DMT* disease-modifying therapy, *EDSS* Expanded Disability Status Scale, *FTY* fingolimod, *IQR* interquartile range, *MS* multiple sclerosis, *NTZ* natalizumab, *SD* standard deviation

[a]Baseline patient characteristics prior to matching for the MSBase cohorts are presented in Table S1 (see the Electronic Supplementary Material). Baseline, or time of switch, was defined as the date at which natalizumab, fingolimod, or another BRACETD DMT was initiated. The distributions of BRACETD therapies before (all cohorts) and after (BRACETD cohort only) switching are presented in Table S2

[b]The propensity score algorithm used a calliper width of 0.2 SDs

[c]On-treatment proportion of disease duration refers to the proportion of pre-baseline disease duration spent on a DMT. This captures the time from the first symptoms of MS up to the start of the switch DMTs (including the treatment gap between pre-switch BRACETD and the switch DMT)

with non-BRACETD MS treatments prior to switching. A maximum 6-month treatment gap was allowed at the time of switching, and a minimum 3-month treatment persistence after switching was required. Complete data for all predefined matching variables [baseline patient age, sex, residential country, index year, and other disease and history variables (Table 1)] were included in the three-way-multinomial-propensity-score matching algorithm [13]. The matching variables were chosen based on availability in the MSBase registry and known correlation with treatment outcome based on published literature and previous MSBase research [11, 12]. Baseline, or time of switch, was defined as the date at which natalizumab, fingolimod, or another BRACETD DMT was initiated. Propensity scores were derived for the natalizumab, fingolimod and BRACETD cohorts using a logistic regression with treatment group as the dependent variable. The predefined matching variables

were the independent model covariates. Table S1 (see the Electronic Supplementary Material) presents values for all required variables before matching. Figure 1 presents a Consolidated Standards of Reporting Trials (CONSORT)-like diagram detailing patient selection.

2.2 Comparative Effectiveness Analysis

2.2.1 Outcome Measures

We captured all data included in eligible patients' records beginning at the time of switching and ending with discontinuation of the switch therapy or conversion to secondary progressive MS (SPMS) or last Expanded Disability Status Scale (EDSS) visit recorded in MSBase. All MSBase participating centres are required to have Neurostatus certification to perform EDSS assessments. Comparative effectiveness
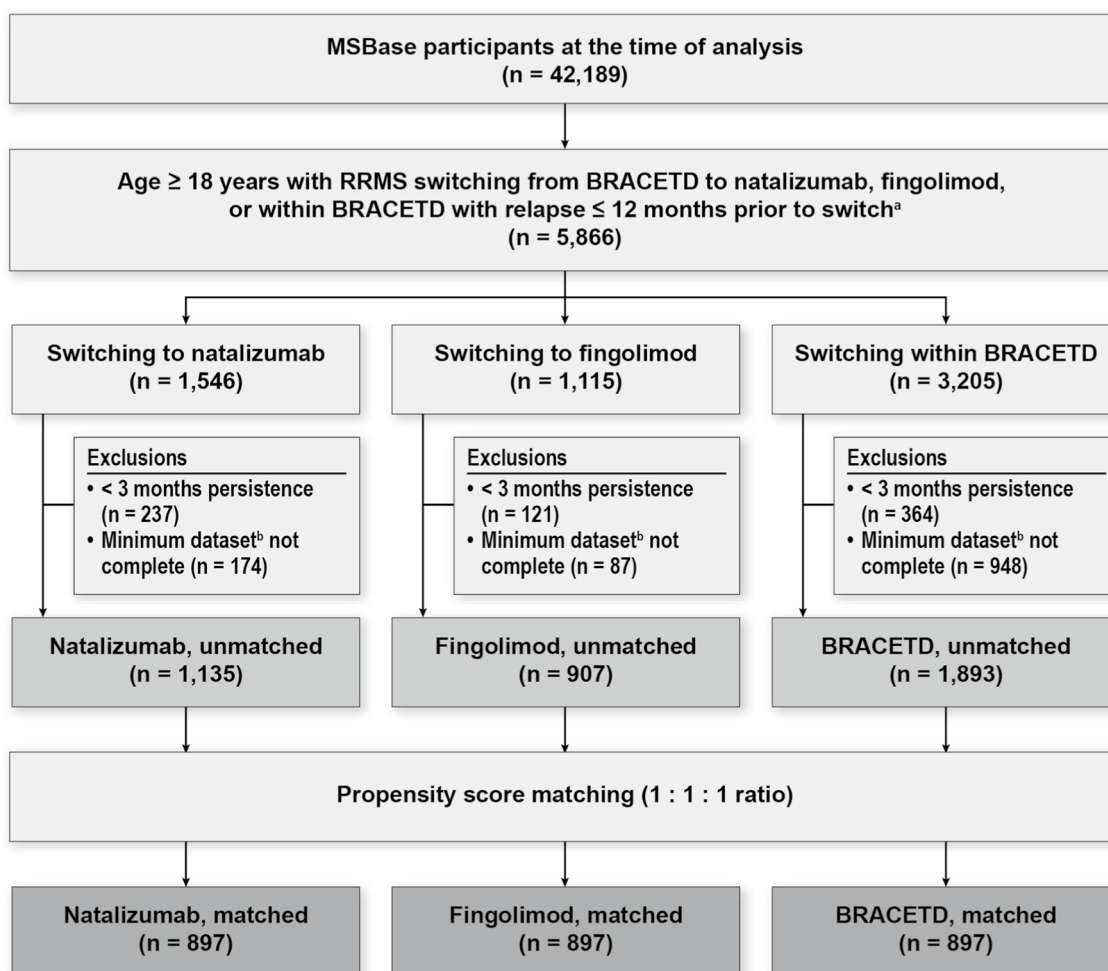
Fig. 1 Patient selection flow chart for MSBase analysis. *BRACETD* interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *RRMS* relapsing-remitting multiple sclerosis. [a]Requires completion of ≥ 12 months uninterrupted treatment with a BRACETD therapy and a < 6-month gap between discontinuing the BRACETD therapy and initiating the switch therapy. [b]All variables included in the propensity score matching algorithm (Table 1 in the main text) were required for inclusion in the analysis

was assessed for four outcomes: annualised relapse rate (ARR), time to first relapse, time to 6-month–confirmed disability worsening (CDW6M), and time to 6-month–confirmed disability improvement (CDI6M).

A relapse was defined as occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 h, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse [14]. Relapses were confirmed by the treating physician; confirmation with EDSS scores or magnetic resonance imaging (MRI) was not required. CDW6M was defined as an increase in EDSS score of at least 1 point from baseline sustained between two follow-up visits separated in time by no less than 6 months (1.5 points if EDSS at baseline was 0; 0.5 points if the baseline EDSS $\geq$ 5.5). CDI6M was defined as a decrease in EDSS score of at least 1 point from a baseline EDSS equal to or above 2 sustained between two follow-up visits separated in time by no less than 6 months. EDSS scores within 30 days of a relapse were not considered for CDW6M or CDI6M. Similarly to previous studies [11], CDW6M and CDI6M were modelled as separate outcomes. Six-month confirmation of disability changes was required for the primary analysis based on regulatory preferences [15]. A 3-month confirmation definition was used in a scenario analysis.

For use in the cost-effectiveness analysis, EDSS transition probability matrices were estimated. The entries in these matrices reflect the probabilities of moving between pairs of EDSS scores during a yearlong interval. For the transition matrix analysis, confirmation of changes in EDSS were not required so that patients could contribute multiple distinct yearly intervals to the analysis.

2.2.2 Statistical Analysis

All statistical analyses were performed using Stata version 16 (RRID:SCR_012763) and R Project for Statistical Computing version 3.6.3 (RRID:SCR_001905). We compared outcomes between the three treatment groups. We used a generalised estimated equation Poisson regression model to analyse ARRs, overall and by baseline EDSS. Time to first relapse, disability worsening, and disability improvement utilised a Kaplan–Meier approach and a marginal Cox regression model that adjusted for matching but not for any other covariates. Disability worsening and improvement analyses required the inclusion of data from patients with $\geq$ 3 EDSS scores (baseline, change from baseline, and confirmation). Statistical tests appropriate for the clustered nature of the matched design were used. Matched triplets were censored at treatment end or last-recorded on-treatment visit. The *p* value for the significance threshold was set at 0.05.

In the transition matrix analysis, EDSS scores at the beginning and end of distinct yearly intervals were identified for all patients in each matched cohort. EDSS scores reported within 90 days of each time point were considered valid, and non-integer EDSS scores were rounded down in alignment with the cost-effectiveness model structure. All valid yearly intervals were used to estimate the probability of transitioning between each possible pair of EDSS scores within a year [16]. Following Markovian principles, all valid yearly intervals were given the same weight, including multiple intervals observed for the same patient and intervals occurring during different years of the follow-up period.

2.3 Cost-Effectiveness Analysis

We developed a cost-effectiveness model in alignment with UK guidelines [17] to compare predicted costs and health outcomes and to estimate the cost-effectiveness of switching to natalizumab compared with switching to fingolimod in patients with HA-RRMS with inadequate response to BRACETD. The model was programmed in Microsoft Excel (RRID:SCR_016137) for Windows with Visual Basic for Applications (Microsoft Corporation, Redmond, Washington).

2.3.1 Modelling Approach

The model tracked a cohort of patients with RRMS over their remaining lifetimes as they experienced disability worsening or improvement and relapses associated with RRMS, conversion to SPMS, disability worsening and relapses associated with SPMS, and death. We used a Markov-based structure with an annual cycle length and integer EDSS-based health states, consistent with previous cost-effectiveness analyses (Fig. 2) [10, 18]. The analysis was conducted over a lifetime horizon from a UK National Health Service perspective. Scenario analyses considered shorter time horizons and a societal perspective.

The model structure included separate EDSS health states for RRMS (EDSS 0–9.0) and for SPMS (EDSS 1.0–9.0). Disability worsening was possible in both RRMS and SPMS; disability improvement was assumed possible in RRMS only. Conversion from RRMS to SPMS was assumed to be associated with a 1-point EDSS increase, consistent with modelling precedent in MS, based on the expectation that conversion to SPMS increases disability. Transitions of $\geq$ 1.0 EDSS score in a single cycle were allowed.

The cost-year was 2019 Great British Pound (GBP; £). All costs and health outcomes were discounted at 3.5% annually [17]. Alternative discounting rates were considered in scenario analysis.

Fig. 2 Model structure diagram for cost-effectiveness analysis. *BRACETD* interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *EDSS* Expanded Disability Status Scale, *RRMS* relapsing-remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis. Note: While not shown in the figure, EDSS changes of more than one level are permitted. [a]Death is reachable from all health states
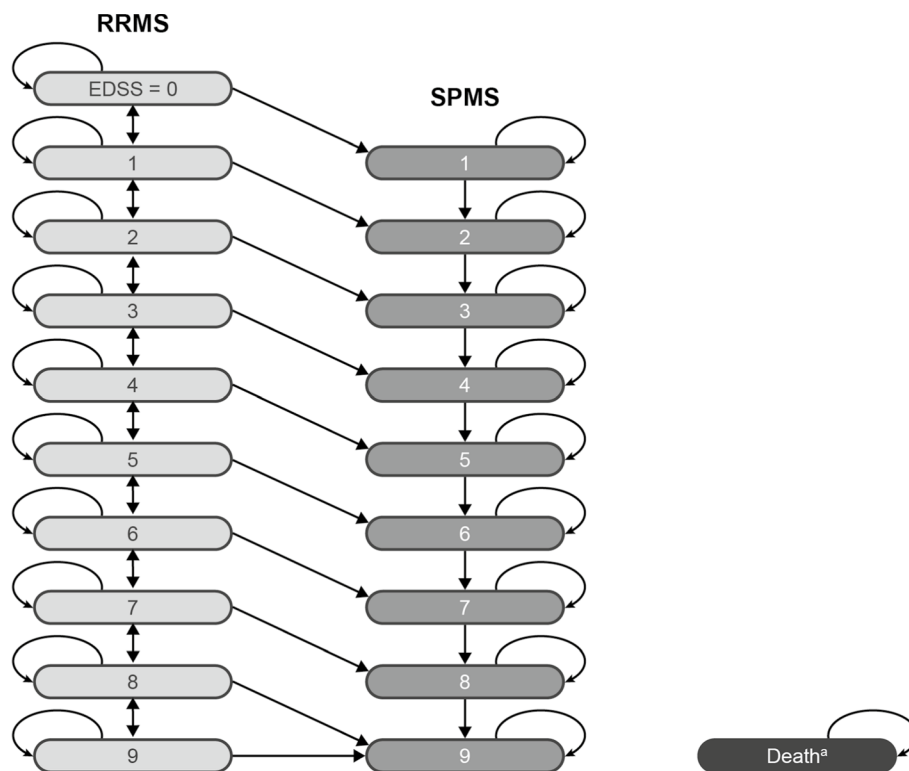
2.3.2 Data Sources

Data were drawn from RWD sources wherever possible, with synthesised clinical trial data, the published literature, and other publicly available data sources used when necessary (Figure S1, see the Electronic Supplementary Material).

2.3.2.1 Clinical Data from MSBase The primary RRMS clinical data used in the cost-effectiveness analysis were drawn from the results of the MSBase comparative effectiveness analysis: baseline patient age, sex, and EDSS distribution (Table S3, see the Electronic Supplementary Material); hazard ratios (HRs) for disability worsening and improvement and rate ratios (RRs) for relapses for natalizumab and fingolimod (reference = BRACETD) (Table 2 and Tables S4–S7); and treatment-specific annual EDSS transition probability matrices and ARRs for each MSBase treatment group (Tables S9–S12). The MSBase results estimated for the matched cohorts were used for the base-case cost-effectiveness analysis; estimates for the unmatched cohorts were considered in scenario analysis.

Because the MSBase cohorts had insufficient patient numbers at EDSS ≥ 7.0, we followed precedent from the MS modelling literature [10, 18] and used transition probabilities from the British Columbia Multiple Sclerosis (BCMS) database [8] and ARRs from a previous analysis [19] (Table S8) to estimate these values. The transition probability matrix and ARR extrapolation methodologies are described in

Tables S9 and S10, respectively, for the matched BRACETD cohorts. The same methodologies were used for the matched natalizumab and fingolimod cohorts (Tables S11 and S12).

The MSBase analysis provided two options for modelling the effectiveness of natalizumab and fingolimod: (1) direct use of treatment-specific EDSS transition matrices and ARRs by EDSS for natalizumab and fingolimod; and (2) application of HRs for disability worsening and improvement to the BRACETD EDSS transition matrix and RRs for relapse to the ARRs for BRACETD, yielding comparative effectiveness-adjusted transition matrices and ARRs for natalizumab and fingolimod. In the base-case cost-effectiveness analysis, the model used the first option for the follow-up duration observed in MSBase before switching to the second option for long-term extrapolation. The use of each approach individually was considered in scenario analysis.

2.3.2.2 Other Clinical Data Treatment-specific dosing regimens, including administration and monitoring requirements, for natalizumab (300 mg every 4 weeks) and fingolimod (0.5 mg daily) are detailed in Table S13 (see the Electronic Supplementary Material). Annual treatment discontinuation rates (Tables 2 and S14) and AE incidence rates (Table S15), including serious AEs other than PML, for natalizumab and fingolimod were extracted from published trials [20–22]. Annual discontinuation rates reflected all-cause discontinuation and were estimated from the intention-to-treat (ITT) populations of the pivotal studies

Table 2 Treatment-specific comparative effectiveness outcomes, costs, discontinuation rates, and adverse event outcomes used in the cost-effectiveness model

	Natalizumab	Fingolimod
Comparative effectiveness outcomes (reference = switching to BRACETD)[a]		
Mean (SD) years of follow-up	2.56 (1.71)	2.05 (1.27)
Rate ratio for ARR (95% CI)	0.64 (0.57–0.72)	0.91 (0.81–1.03)
Hazard ratio for CDW6M (95% CI)	1.01 (0.73–1.40)	1.08 (0.78–1.50)
Hazard ratio for CDI6M (95% CI)	1.67 (1.30–2.15)	1.30 (0.99–1.72)
EDSS transition matrix for RRMS	See Table S11	See Table S12
ARRs by EDSS for RRMS	See Table S11	See Table S12
Treatment costs per year[b]		
Acquisition (all years)	£14,740	£19,176
Administration (year 1)	£2909	£615
Administration (year 2+)	£2909	£0
Monitoring (year 1)	£372	£695
Monitoring (year 2+)	£352	£376
Treatment discontinuation[c]		
Discontinuation per year	6.3%	10.3%
AE outcomes per year on treatment (weighted average including PML)[d]		
Costs	£141	£347
Utility decrement	0.0063	0.0073

AE adverse event, *ARR* annualised relapse rate, *BRACETD* interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *CDI6M* 6-month–confirmed disability improvement, *CDW6M* 6-month–confirmed disability worsening, *CI* confidence interval, *EDSS* Expanded Disability Status Scale, *OWSA* one-way sensitivity analysis, *PML* progressive multifocal leukoencephalopathy, *PSA* probabilistic sensitivity analysis, *RRMS* relapsing-remitting multiple sclerosis, *SD* standard deviation

[a]Detailed comparative effectiveness outcomes are described in the Sect. 3 and are presented in Fig. 3 and the Electronic Supplementary Material (Tables S4–S7 and Tables S9–S12). Uncertainty parameters and distributions used in the OWSA and PSA are presented with the supplementary tables

[b]Acquisition costs (from UK list prices [23]) were varied in the OWSA only, while administration and monitoring costs (from resource utilisation frequencies and standard UK unit costs [24–27]) were varied in the PSA and OWSA. See Table S13 for details on specific resources used and their respective unit costs. For all treatment costs, a gamma distribution was used with the standard errors assumed to be 10% of the means

[c]Discontinuation rates (derived from pivotal clinical trials for natalizumab [22] and fingolimod [20, 21]; see Table S14) were varied in the OWSA and the PSA using a beta distribution (sample sizes for beta distribution: $N = 627$ for natalizumab; $N = 856$ for fingolimod)

[d]Source information, uncertainty parameters, and sampling distributions for AE incidence rates, AE costs per event, and AE utility decrements per event are provided in Table S15

Table 3 Direct costs and utility values associated with MS management and relapses

EDSS score	Direct costs[a]		Utility values/decrements[b]	
	RRMS	SPMS	RRMS	SPMS
MS Management	(Annual costs)		(Utility values)	
0	£488	£601	0.908	0.888
1	£887	£1094	0.797	0.777
2	£4611	£5684	0.705	0.685
3	£3656	£4506	0.583	0.563
4	£3474	£4283	0.615	0.595
5	£4850	£5979	0.579	0.559
6	£9602	£11,837	0.490	0.470
7	£15,412	£18,998	0.407	0.387
8	£27,786	£34,252	0.167	0.147
9	£35,545	£42,583	− 0.101	− 0.121
Relapses	(Cost per event)		(Utility decrement per event)	
All EDSS scores	£424	£424	0.013	0.013

Sources: 2015 UK MS burden-of-illness survey [4, 31] (inflated from 2016 to 2019 GBP using the consumer price index for health [27])

EDSS Expanded Disability Status Scale, *GBP* Great British Pound, *MS* multiple sclerosis, *OWSA* one-way sensitivity analysis, *PSA* probabilistic sensitivity analysis, *RRMS* relapsing-remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis

[a]Direct costs by EDSS for both RRMS and SPMS, including relapse costs, were varied for the PSA and the OWSA using a gamma distribution with standard errors assumed to be 20.0% of the means

[b]Utility values by EDSS for RRMS and SPMS without relapse were varied for the PSA and the OWSA using a lognormal distribution (as differences from 1 to allow for negative utility values), with standard errors assumed to be 20% of the means. Relapse utility decrements were varied for the PSA and the OWSA using a beta distribution, with standard errors assumed to be 20% of the means

for natalizumab and fingolimod (see Table S14 for additional details). PML incidence and fatality rates were taken from recent literature (Table S15). In addition to annual discontinuation rates, treatment stopping rules for progression to EDSS ≥ 7.0 and for conversion to SPMS were assumed.

After discontinuation of natalizumab or fingolimod and before conversion to SPMS, the model used the EDSS transition probability matrix from the BCMS database [8] and ARRs by EDSS from the placebo arm of the ITT population from AFFIRM (as in previous economic evaluations) [8, 19]. Data from the London Ontario MS database [7] and from previous cost-effectiveness analyses [19] were used for conversion to SPMS and for EDSS worsening and ARRs in SPMS (Table S16).

A constant standardised mortality ratio (SMR) for patients with MS (SMR = 2.88 [95% confidence interval (CI) 2.71–3.06]) [28] was applied multiplicatively to

age- and sex-specific general population all-cause mortality probabilities from the UK [29]. Alternative mortality ratios by disease severity from an older study [30] were considered in scenario analysis.

2.3.2.3 Cost and Utility Data from the MS Burden-of-Illness Survey

Data from participants in a 2015 UK MS burden-of-illness survey [4, 31] were used to estimate direct and indirect costs and utility values (including those associated with relapses) by EDSS in RRMS and SPMS (Table 3 and Table S17 [see the Electronic Supplementary Material]). Indirect costs include short- and long-term absence, invalidity, and early retirement. A regression analysis was used to adjust the raw societal cost estimates by EDSS levels for differences between RRMS and SPMS, and indirect costs were estimated by subtracting the direct costs from the total societal costs [31]. Indirect costs were used in scenario analysis considering a societal perspective. UK-specific cost and utility estimates from a prior 2005 survey [9] were considered in scenario analysis (Table S18).

2.3.2.4 Other Cost and Utility Data

Annual acquisition costs for natalizumab and fingolimod were based on UK list prices [23] [Table 2 and Table S13 (see the Electronic Supplementary Material)]. Annual administration and monitoring costs, based on treatment-specific resource utilisation frequencies (e.g. physician visits, infusions, MRI scans, and lab tests), were estimated from costing templates, assumptions, and standard UK unit costs [24–26] (Table 2 and Table S13). Because fingolimod is covered by a confidential patient access scheme (PAS) in the UK [32], percentage reductions for the fingolimod acquisition price were considered in scenario analysis.

Direct costs and utility decrements per AE, including PML, were derived from estimates and assumptions obtained from the literature, previous HTA submissions for DMTs in RRMS, standard UK unit costs, and clinical experts (Table 2 [weighted outcomes] and Table S15 [detailed outcomes]). Caregiver disutilities by EDSS from a previous analysis [18] were used in scenario analysis considering a societal perspective (Table S17).

2.3.3 Analysis of Uncertainty

The impact of uncertainty in the base-case parameter values on the results of the cost-effectiveness analysis was assessed through one-way and probabilistic sensitivity analyses. The appropriate probability distributions for each parameter type were specified in accordance with best practices [33, 34] (see detailed table notes for specific distributions and uncertainty parameters). The one-way sensitivity analysis considered individual parameters

at the lower and upper bounds of their 95% CIs, while the probabilistic sensitivity analysis sampled all parameters jointly from their respective probability distributions over 10,000 iterations. Additional deterministic scenarios were considered to evaluate the impact of alternative model settings, approaches to using the MSBase results, treatment discontinuation, and other data sources. Due to the limitations of interpreting negative incremental cost-effectiveness ratios, results were presented using a net monetary benefit (NMB) outcome measure assuming a willingness-to-pay threshold of £30,000 per quality-adjusted life-year (QALY) gained [17].

2.3.4 Validation

Cost-effectiveness model validation was performed in alignment with best practices, which emphasize the face validity of the modelling approach and data sources, the internal validity of the model programming and predicted outcomes, and the external validity of the predicted outcomes compared with other published studies [35, 36]. The appropriateness of our approach and data sources was supported by extensive modelling and HTA precedent in MS [10, 18] and the demonstrated clinical relevance of the MSBase registry [37]. The internal validity of the model was evaluated through extreme value testing and a comprehensive review of model logic and calculations by experts not involved in model development (results not shown). Finally, external validity was assessed by comparing our cost-effectiveness results with previously published analyses relying on trial-based efficacy values to compare natalizumab and fingolimod [38–43].

3 Results

3.1 Comparative Effectiveness

3.1.1 Patient Characteristics

Among 3935 patients with RRMS in the MSBase registry meeting the study criteria, 1135 switched to natalizumab, 907 switched to fingolimod, and 1893 switched to another BRACETD (Fig. 1). Table S1 in the Electronic Supplementary Material presents the raw unmatched patient characteristics. The three-way-multinomial-propensity-score matching algorithm [13] accounting for potential differences in baseline characteristics identified 897 matched patients in each cohort for inclusion in the analysis.

After matching, baseline characteristics were well balanced among treatment cohorts (Table 1). For patients switching to natalizumab, fingolimod, or within BRACETD, mean [standard deviation (SD)] post-index follow-up times

were 2.56 (1.71), 2.05 (1.27), and 1.99 (1.52) years, respectively. Before switching, nearly all patients in each matched cohort were being treated with either interferon-based therapies (72.2–81.9%) or glatiramer acetate (15.8–25.1%) (Table S2). Among those switching within BRACETD, 78.9% continued to receive one of these therapies.

3.1.2 Relapses

The ARR for patients switching to natalizumab was significantly reduced compared with patients switching to fingolimod (RR = 0.70 [95% CI 0.62–0.79]) or switching within BRACETD (RR = 0.64 [95% CI 0.57–0.72]). In contrast, the reduction in ARR for those switching to fingolimod compared with those switching within BRACETD (RR = 0.91 [95% CI 0.81–1.03]) was not statistically significant (Fig. 3a).

In the time-to-first-relapse analysis, significant improvements were observed for patients switching to natalizumab (HR = 0.65 [95% CI 0.56–0.76]) and patients switching

to fingolimod (HR = 0.86 [95% CI 0.74–0.99]) compared with those switching within BRACETD. Switching to natalizumab was also associated with an improved time to first relapse compared with switching to fingolimod (HR = 0.76 [95% CI 0.65–0.89]) (Fig. 3b). Tables S4–S7 in the Electronic Supplementary Material further describe the relapse analyses, including data maturity and results for the unmatched MSBase cohorts.

The impact of switching to natalizumab or fingolimod on ARRs in RRMS was also reflected in treatment-specific ARRs by EDSS estimated for use in the cost-effectiveness analysis (Tables S11 and S12). ARRs by EDSS score were also estimated for the unmatched MSBase cohorts (estimates not shown) for use in cost-effectiveness scenario analysis.

3.1.3 Disability Worsening and Improvement

The rates of CDW6M for patients in all three groups were not statistically significantly different from each other
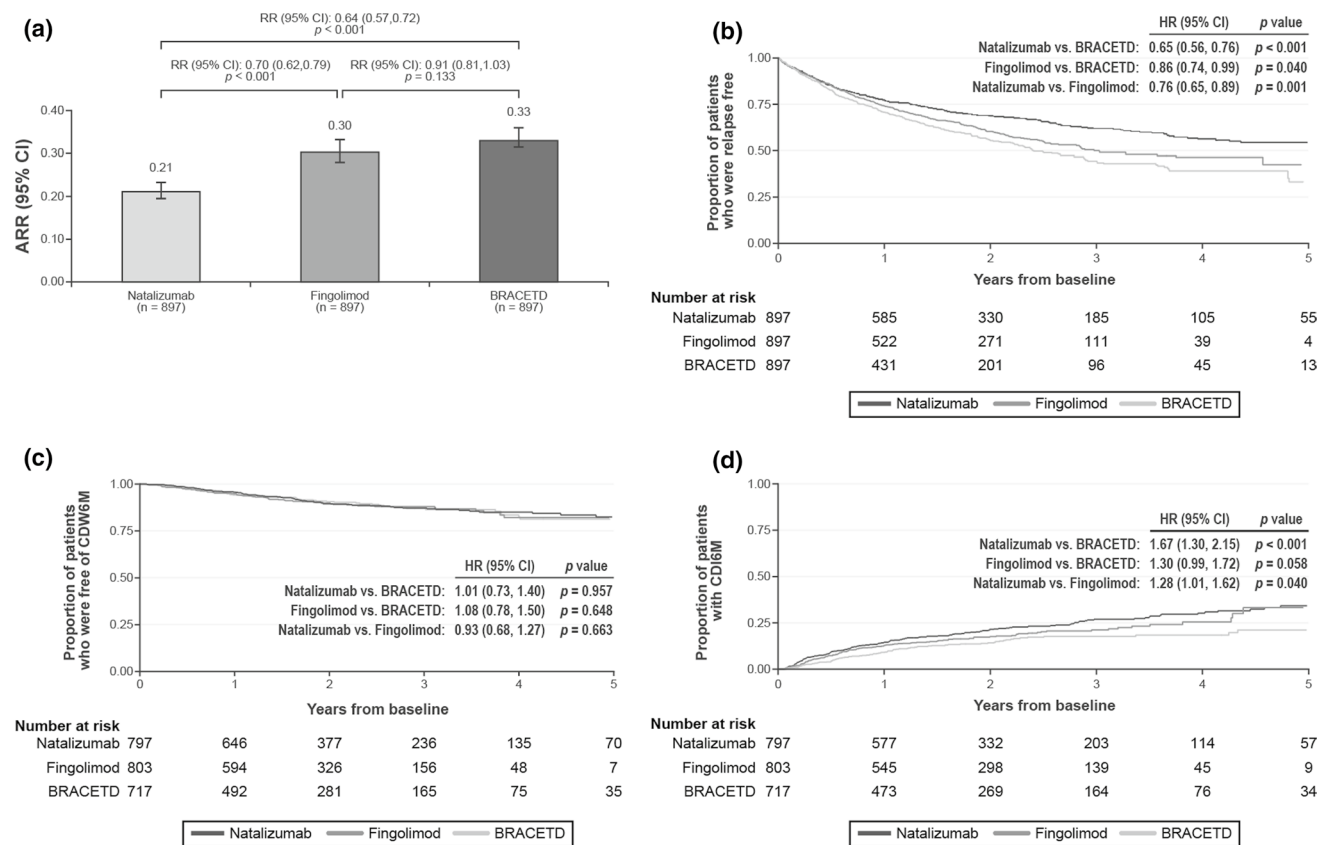
Fig. 3 Comparative effectiveness analysis results for natalizumab and fingolimod compared with BRACETD. *ARR* annualised relapse rate, *BRACETD* interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *CDI6M* 6-month–confirmed disability improvement, *CDW6M* 6-month–confirmed disability worsening, *CI* confidence interval, *HR* hazard ratio, *RR* risk ratio. Note: The com-

parative effectiveness outcomes for ARR (panel **a**), CDW6M (panel **c**), and CDI6M (panel **d**) for natalizumab and fingolimod compared with BRACETD were used in the base-case cost-effectiveness analysis. The time-to-first relapse outcomes (panel **b**) were not used in the cost-effectiveness analysis

(Fig. 3c). The rate of CDI6M for patients switching to natalizumab increased significantly compared with that for those switching to fingolimod (HR = 1.28 [95% CI 1.01–1.62]) or switching within BRACETD (HR = 1.67 [95% CI 1.30–2.15]); the increase in the rate of CDI6M for patients switching to fingolimod was not significant compared with that for those switching within BRACETD (HR = 1.30 [95% CI 0.99–1.72]) (Fig. 3d). Tables S4–S7 in the Electronic Supplementary Material further describe the disability worsening and improvement analyses, including 3-month-confirmation results, data maturity, and results for the unmatched MSBase cohorts.

The impact of switching to natalizumab or fingolimod on annual probabilities of transitioning between EDSS scores in RRMS also was reflected in treatment-specific EDSS transition probability matrices estimated for use in the cost-effectiveness analysis (Tables S11 and S12). EDSS transition probability matrices also were estimated for the unmatched MSBase cohorts (estimates not shown) for use in cost-effectiveness scenario analysis.

3.2 Cost-Effectiveness

3.2.1 Base-Case Analysis

The clinical benefits observed in the comparative effectiveness analysis translated to the base-case cost-effectiveness results, where switching to natalizumab versus switching to fingolimod was predicted to lead to fewer lifetime relapses (13.25 vs. 14.27 [undiscounted]) and higher QALYs (7.87 vs. 7.42 [discounted]) (Table 4). The base-case cost-effectiveness analysis assumed that the only event impacting mortality differently between treatments was the occurrence of PML. Despite both treatments having been associated with PML, the relatively higher incidence of this AE for

natalizumab led to the difference in total life-years between the treatments (Table 4). While natalizumab was associated with higher lifetime treatment costs than fingolimod (£3765 higher per patient) because of a longer time on treatment (5.56 vs. 4.31 years), the impact on disability accumulation (Fig. S2, see the Electronic Supplementary Material) and relapses led to lower disease-management and relapse costs for natalizumab versus fingolimod (£24,608 lower per patient) that more than offset the additional treatment costs (Table 4). As a result, natalizumab, in pharmacoeconomic terminology, dominated fingolimod, with higher predicted lifetime QALYs and lower predicted lifetime costs, in the base-case cost-effectiveness analysis (Table 4). At a willingness-to-pay threshold of £30,000 per QALY gained, the base-case NMB was estimated at £34,430 (Table 4).

3.2.2 Sensitivity and Scenario Analyses

In one-way and probabilistic sensitivity analyses, natalizumab remained dominant over fingolimod for all parameters varied (Fig. 4a) and for 99% of the 10,000 Monte-Carlo simulations (Fig. 4b), respectively. The incremental costs and QALYs for the one-way sensitivity analysis are presented in Table S19 (see the Electronic Supplementary Material).

Because fingolimod is covered by a confidential PAS in the UK [32], percentage discounts on the fingolimod list acquisition price were considered in scenario analysis. Natalizumab remained dominant with up to a 25.2% discount on the fingolimod list price and remained cost-effective at willingness-to-pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained with up to 36.2 and 41.7% fingolimod discounts, respectively (Fig. S3).

Additional scenario analyses explored the impact of alternative model settings, approaches to using the MSBase

Table 4 Base-case results for the cost-effectiveness analysis

	Natalizumab	Fingolimod	Incremental (%)
Expected health outcomes			
Time on treatment (years)	5.56	4.31	1.249 (29.0%)
Number of relapses (undiscounted)	13.25	14.27	− 1.021 (− 7.2%)
LYs	20.05	20.15	− 0.103 (− 0.5%)
QALYs	7.87	7.42	0.453 (6.1%)
Expected cost outcomes			
Direct treatment-related costs	£90,621	£86,856	£3765 (4.3%)
Other direct costs (including AEs)	£368,427	£393,034	− £24,608 (− 6.7%)
Total direct costs	£459,047	£479,890	− £20,843 (− 4.3%)
Cost-effectiveness outcomes			
Incremental cost per QALY gained			
Natalizumab dominates fingolimod			
NMB at £30,000 per QALY gained	£34,430		

AE adverse event, *LY* life year, *NMB* net monetary benefit, *QALY* quality-adjusted life-year

(a)

(b)
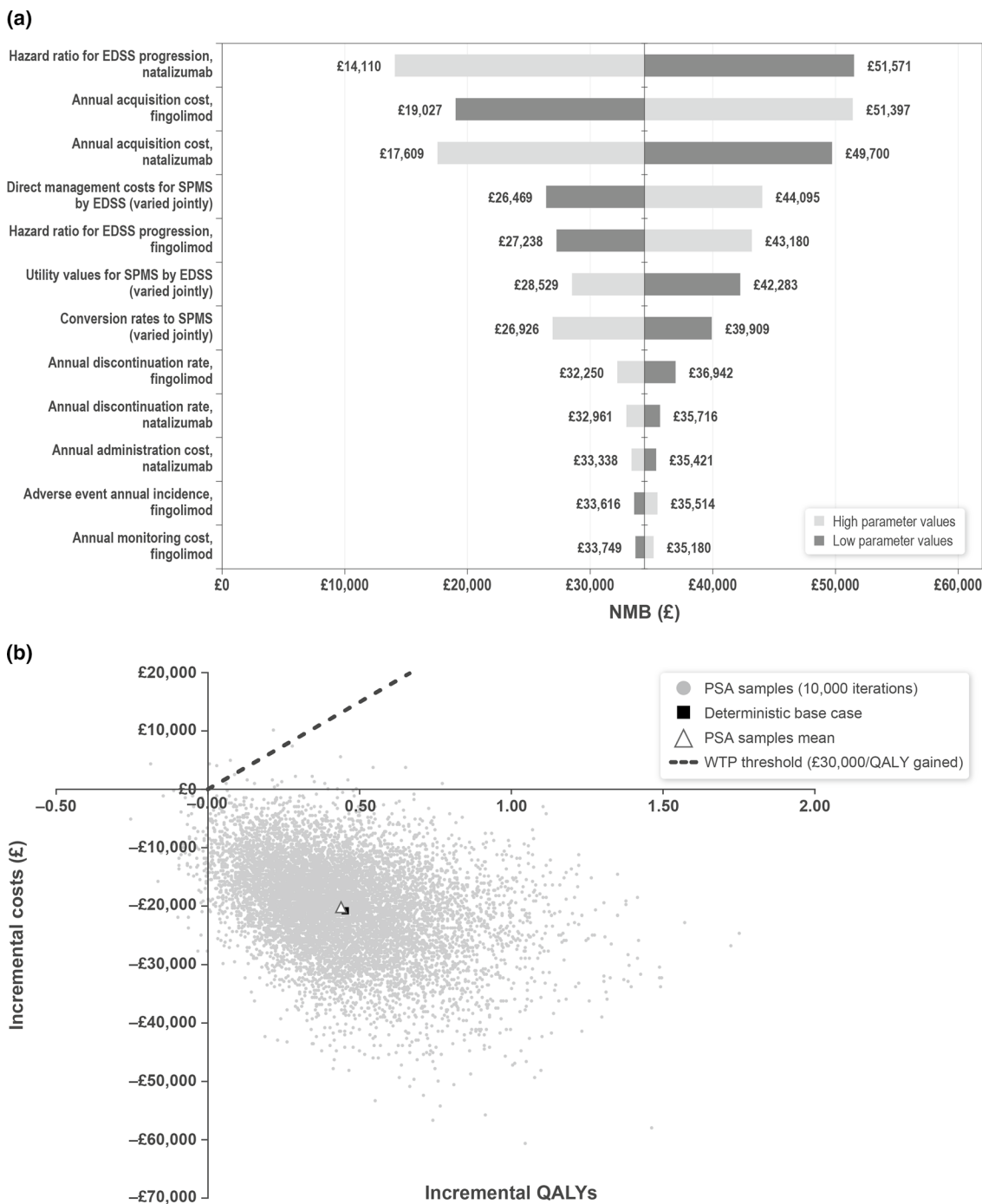
Fig. 4 One-way and probabilistic sensitivity analysis results for cost-effectiveness analysis. *BRACETD* interferon-based therapies, glatiramer acetate, dimethyl fumarate, and teriflunomide, *EDSS* Expanded Disability Status Scale, *NMB* net monetary benefit, *OWSA* one-way sensitivity analysis, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life-year, *SPMS* secondary progressive multiple sclerosis, *WTP* willingness-to-pay. Note: For all parameters varied in the OWSA (panel **a**), natalizumab remained dominant compared with fingolimod. The NMB outcomes were estimated using a WTP threshold of £30,000 per QALY gained. The PSA results are presented in panel **b**

results, discontinuation assumptions, and data sources. In all scenarios, natalizumab remained dominant compared to fingolimod (Table S20). Of note, shorter time horizons and higher annual discounting rates yielded lower incremental QALYs and lower cost savings, while a societal perspective led to higher incremental QALYs and greater cost savings.

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For the MSBase scenarios, using data from the unmatched cohorts had little impact on the cost-effectiveness results (< £1000 [0.05] difference in incremental costs [QALYs]), while different approaches to modelling treatment effectiveness (3-month disability confirmation, comparative effectiveness-adjusted vs. treatment-specific transition matrices and ARRs) led to larger differences in incremental outcomes. Scenarios considering equal treatment discontinuation rates led to lower incremental QALYs but higher cost savings. Increasing the discontinuation rate of natalizumab by 30% (8.1%) and decreasing the fingolimod one by 30% (7.2%) led to lower incremental QALYs and higher cost savings. Assuming a post-discontinuation treatment cost of £10,000 per year (the approximate annual cost of returning to BRACETD therapy) increased cost savings. Finally, using cost and utility data from the 2005 burden-of-illness survey and considering alternative mortality data by EDSS both led to higher incremental QALYs but lower cost savings (Table S20).

4 Discussion

This study is the first to use real-world effectiveness data in an economic evaluation of DMT escalation options for patients with HA-RRMS. Previously, economic evaluations comparing natalizumab with fingolimod have relied on trial-based efficacy estimates [10, 38, 40, 44]. Furthermore, the integrated approach to analysing comparative effectiveness and cost-effectiveness represents a step forward for the real-world economic evaluation of DMTs for MS and could serve as a model for the use of RWD in economic evaluations.

We conducted a three-way-multinomial-propensity-score–matched analysis to estimate impacts on relapse and disability with natalizumab and fingolimod in this population (Fig. 3). Switching to natalizumab reduced ARR by 30% and increased CDI6M rate by 28% compared with switching to fingolimod. When compared to switching to another BRACETD, switching to natalizumab reduced ARR by 36% and increased CDI6M rate by 67% (all outcomes above were statistically significant). Switching to fingolimod compared with switching to another BRACETD reduced ARR by 9% and increased CDI6M rate by 30% (although neither endpoint reached statistical significance). Time-to-first-relapse results directionally aligned with the ARR results. Conversely, no significant differences on CDW6M were observed among treatments. In the cost-effectiveness analysis based on these RWD estimates, natalizumab dominated fingolimod, leading to 0.453 higher QALYs and £20,843 lower per-patient total costs over a lifetime horizon (equating to a NMB of £34,430 at a willingness-to-pay threshold of £30,000 per

QALY gained) (Table 4). These results were maintained across one-way and probabilistic sensitivity analyses and extensive scenario analyses (Fig. 4 and Table S20).

The comparative effectiveness analysis echoes findings from recent trial-based indirect treatment comparisons [45] and other RWD studies [11, 12, 46, 47] that natalizumab is an effective treatment for this population, with reduced relapse rates and disability improvement as key differentiators from fingolimod and BRACETD. Use of propensity-score matching ensured comparability among three treatment cohorts and allowed the use of the results in the cost-effectiveness analysis to present results comparing natalizumab and fingolimod. The higher effectiveness of natalizumab when compared with fingolimod supports previous findings that natalizumab is more effective than fingolimod among previously treated patients with higher baseline disease activity [48, 49].

The lack of significance in the comparative effectiveness results for fingolimod compared with BRACETD on ARR seemingly contradicts some previously published RWD analyses [50, 51]. The main difference between these studies is that the BRACETD-to-BRACETD switch group of the current study had 15.3% of patients switching to dimethyl fumarate, shown in some studies to have efficacy that is more similar to fingolimod than to other BRACETD therapies [52, 53].

Our cost-effectiveness results are broadly aligned with the results of other cost-effectiveness publications in the literature comparing natalizumab to fingolimod. Of seven publications comparing only these two treatments, natalizumab dominated fingolimod in four studies conducted across different countries (Sweden, the United States, and Colombia) and using different outcome measures (QALY, relapses, and disease progression) [38, 39, 42, 43]. In another study, natalizumab was considered cost-effective in the general RRMS population and dominant in the rapidly evolving severe (RES) sub-population [41]. One UK-based study also focusing on the RES sub-population used a discrete event simulation instead of a Markov model and found natalizumab to be cost-effective in the deterministic analysis at list price [40]. Finally, a study based in Iran concluded that fingolimod was cost-effective versus natalizumab; however, this study did not use clinical trial or registry data and used instead a census method to estimate outcomes for 81 patients with MS in one medical centre [54]. While the results of our study are largely aligned with other literature, care must be exercised when comparing different cost-effectiveness analyses. Costs, including drug costs and overall healthcare costs, tend to vary significantly between countries. The current study is the first to be based on effectiveness data from a large real-world registry, and this and other differences in data sources or outcome measures may also lead to different results. A final potential source of variation relates to the model structure,

although the current model is similar to the majority of modelling approaches in MS in its use of EDSS health states first proposed 2 decades ago in the School of Health and Related Research (ScHARR) model [55].

The results and conclusions of this study are subject to the limitations typical of RWD analyses and economic evaluations. While propensity-score matching accounted for known differences between MSBase cohorts, bias due to unmeasured confounders (e.g. MRI activity) may remain. While the follow-up periods for the MSBase cohorts (means of 2–3 years, and variable among cohorts) were longer than the duration of clinical trials in RRMS (1–2 years), estimation of clinical and economic outcomes in the cost-effectiveness analysis still required significant extrapolation of the clinical benefits suggested by the MSBase results. There were differences in outcome definitions and confirmation requirements for EDSS changes between the MSBase time-to-event and transition matrix analyses, although scenario analyses investigated the impact of alternative MSBase settings on the cost-effectiveness results. Some data required to populate the economic model, such as AEs, discontinuation rates, and post-discontinuation ARRs by EDSS, were derived from the ITT populations of pivotal clinical trials, which were not restricted to patients who had failed a prior BRACETD treatment. The decision to estimate these model inputs from the ITT populations was driven by data availability, but may reduce the external validity of the model. Additionally, because of sample limitations within the MSBase registry at the time of the analysis, newer DMTs for RRMS (e.g. alemtuzumab, cladribine, and ocrelizumab) were not included in this study. Emerging RWD on these comparators [56, 57] may contribute to future evaluations of DMT escalation alternatives.

Finally, the clinical comparative effectiveness results from the MSBase analysis were sourced from an international registry with more than 130 different centres across 39 countries. This increases the applicability of the results to multiple geographies, especially because they reflect real-world clinical practice. Nevertheless, care should be taken because clinical practice, patient characteristics, and other factors may influence clinical outcomes. Conversely, results of a cost-effectiveness analysis often are country specific because inputs such as treatment and other healthcare costs and mortality data, among others, may vary significantly between countries. Adaptations of the current model to Spain and Italy [58, 59] have demonstrated how incremental costs and QALYs can differ across settings even when using the same underlying modelling approach. Therefore, extrapolating the economic implications to settings outside the UK would require additional analyses.

5 Conclusion

Overall, our results suggest that switching to natalizumab improves clinical and economic outcomes relative to switching to fingolimod in patients with HA-RRMS with inadequate response to BRACETD from a UK payer perspective. By relying on real-world effectiveness data from patients treated with natalizumab and fingolimod, this study provides improved external validity relative to trial-based analyses and offers additional evidence of natalizumab's clinical and economic value as a treatment option for RRMS. These results complement the existing body of real-world evidence that should be considered when making individualised treatment decisions, taking into account the available therapies' effectiveness and safety profiles and their impact on healthcare system resources.

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Author Contributions The comparative effectiveness study was conducted by MSBase. TS and HB conducted and supervised the analysis of the MSBase registry data, respectively. The remaining MSBase-affiliated authors contributed to the collection and interpretation of the data. The cost-effectiveness study was conducted by RTI Health Solutions. WH and YZ developed the cost-effectiveness model and contributed to the interpretation of analytical results. IP contributed to the design of the cost-effectiveness model and the interpretation of analytical results. MT provided the country-specific non-clinical inputs for the cost-effectiveness model. CA, TD, UF, and RH supervised the study for both the clinical and cost-effectiveness analysis. Both MSBase and RTI Health Solutions operated under separate research contracts with Biogen and were funded by Biogen. All authors reviewed the data and contributed to the final interpretation of results.

Data Availability The clinical data for this study was obtained under a licence agreement with MSBase (http://www.msbase.org). However, no patient-level data were disclosed as part of the study. Therefore, all data relevant to the study has been presented in the article and Supplementary Materials.

Declarations

Conflict of interest Timothy Spelman is a statistical contractor for the MSBase Foundation and has received compensation for serving on advisory boards for Biogen and speaker honoraria from Novartis and Roche. William L. Herring, Yuanhui Zhang, and Isobel Pearson are employees of RTI Health Solutions, an independent non-profit research organisation, which received funding pursuant to a contract with Biogen. Michael Tempest, Ulrich Freudensprung, Carlos Acosta, and Robert Hyde are employees of Biogen and hold shares or stocks from Biogen as part of their remuneration. Thibaut Dort was an employee and shareholder of Biogen at the time of his passing. Eva Havrdova has received honoraria and research support from Biogen, Merck Serono, Novartis, Roche, and Teva; has served in advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novartis, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education research project PROGRES Q27/LF1. Dana Horakova has received speaker honoraria and consulting fees from Biogen, Merck, Novartis, Roche, Sanofi Genzyme, and Teva and has received support for research activities from Biogen and the Czech Ministry of Education (project Progres Q27/LF1). Maria Trojano has served on scientific advisory boards for Biogen, Novartis, Roche, and Merck; has received speaker honoraria from Biogen, Sanofi, Merck, Roche, Teva, and Novartis; and has received research grants for her Department from Biogen, Merck, Roche, and Novartis. Giovanna De Luca

has served on scientific advisory boards for Merck, Biogen, Novartis, Roche, and Sanofi Genzyme and has received funding for travel and speaker honoraria from Biogen, Merck, Novartis, Sanofi Genzyme, and Roche. Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, and Teva. Her institutions have received research grants from Novartis. Guillermo Izquierdo has received speaking honoraria from Almirall, Biogen, Merck, Novartis, Roche, Sanofi, and Teva. Pierre Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen, Sanofi Genzyme, and Pendopharm and has received grant support from Genzyme and Roche; his institution has also received research grants from Biogen, Sanofi Genzyme, and EMD Serono. Pierre Duquette has received support for organised continuing medical education activities and travel fees to attend advisory meetings from Biogen, EMD Serono, Genzyme, and Novartis. Raed Alroughani has received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche, Sanofi, and Genzyme. Eugenio Pucci has received travel grants from Roche, Novartis, Merck, Genzyme-Sanofi, Biogen, and Teva and received equipment from *Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche*. Franco Granella has received research funding from Biogen and Sanofi Genzyme; fees for advisory boards and speaker honoraria from Biogen, Merck Serono, Novartis, Roche, and Sanofi Genzyme; and travel funding from Biogen, Merck Serono, Roche, and Sanofi Genzyme. Jeannette Lechner-Scott has accepted travel compensation from Novartis, Biogen, and Merck Serono; her institution receives the honoraria for talks and advisory board commitments as well as research grants from Biogen Merck, Roche, TEVA, and Novartis. Patrizia Sola has served on scientific advisory boards for Biogen and Teva; has received funding for travel and speaker honoraria from Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, and Teva; and has received research grants for her institution from Bayer, Biogen, Merck, Novartis, Sanofi, and Teva. Diana Ferraro has received travel funding or speaker honoraria from Merck, Biogen, Sanofi, Novartis, Teva, and Roche and has served on advisory boards for Biogen, Merck, Novartis, Sanofi, and Roche. Francois Grand'Maison has received honoraria or research funding from Biogen, Genzyme, Mitsubishi, Novartis, Ono Pharmaceuticals, and Teva Neuroscience. Murat Terzi has received travel grants from Merck & Co., Novartis, Bayer-Schering, and Teva Pharmaceutical Industries and has participated in clinical trials by Sanofi-Aventis, Roche, and Novartis. Csilla Rozsa has received speakers' honoraria from Biogen, Merck Serono, Roche, and Sanofi Genzyme; travel grants from Biogen, Merck, and Sanofi Genzyme; and fees for advisory boards from Biogen, Merck Serono, Novartis, and Teva. Cavit Boz has received conference travel support from Biogen, Novartis, Bayer-Schering, Merck, and Teva. Raymond Hupperts has received nurse support from Merck and Sanofi and has served on advisory boards for Sanofi, Biogen, and Roche. Vincent Van Pesch has received travel grants from Merck, Biogen, Sanofi, Bristol Meyer Squibb, Almirall, and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Bristol Meyer Squibb, Merck, Almirall, and Novartis Pharma. Celia Oreja-Guevara has received honoraria for speaking and consulting fees from Biogen, Celgene, Alexion, Merck, Novartis, Roche, Sanofi Genzyme, and Teva. Anneke van der Walt is an employee of Monash University and has accepted travel compensation from Merck, Biogen, and Roche; she has received honoraria for talks, steering committee activities, and research grants from Roche, Merck, Biogen, and Novartis. Vilija Jokubaitis is an employee of Monash University; she has accepted travel compensation from Biogen, Merck, and Roche and speakers' honoraria from Biogen and Roche. Tomas Kalincik has served on scientific advisory boards for Roche, Sanofi Genzyme, Novartis, Merck, and Biogen and a steering committee for the Brain Atrophy Initiative supported by Sanofi Genzyme; has received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sa-

nofi Genzyme, Teva, BioCSL, and Merck; and has received research support from Biogen. Helmut Butzkueven is an employee of Monash University and has accepted travel compensation from Merck, Biogen, and Roche; his institution receives honoraria for talks, steering committee activities, and research grants from Roche, Merck, Biogen, Genzyme, Novartis, and Medday Pharma.

Ethics approval and consent Informed consent from all patients according to local laws is required for participation in MSBase, and the project has received human research ethics committee approval or an exemption at each contributing centre.

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