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Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study

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ABSTRACT

Objective To directly compare the efficacy of natalizumab and fingolimod in patients with active relapsing-remitting multiple sclerosis.

Methods This phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study was conducted at 43 sites in nine countries. Patients were randomised (1:1) to intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for ≤52 weeks. Enrolment-related early study termination precluded assessment of the primary endpoint (evolution of new on-treatment gadolinium-enhancing (Gd+) lesions to persistent black holes). Unplanned exploratory analyses of secondary endpoints evaluated the effects of treatment on the development of new T1 Gd+ lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes.

Results The intent-to-treat population comprised 108 patients (natalizumab, n=54; fingolimod, n=54); 63 completed ≥24 weeks of treatment. Due to the limited numbers of events and patients at risk, MRI and relapse outcomes were reported over up to 24 and 36 weeks, respectively. The mean number of new T1 Gd+ lesions was numerically lower with natalizumab than with fingolimod by 4 weeks; accumulation rates were 0.02 and 0.09 per week, respectively, over 24 weeks (p=0.004). The cumulative probability of developing ≥1 lesion at 24 weeks was 40.7% with natalizumab versus 58.0% with fingolimod (HR=0.60; 95% CI 0.31–1.16; p=0.126); the corresponding probabilities for ≥2 lesions were 11.5% vs 48.5% (HR=0.25; 95% CI 0.09–0.68; p=0.007). No significant between-group differences were observed for the other MRI outcomes at 24 weeks. The cumulative probability of relapse over follow-up was 1.9% with natalizumab versus 22.3% with fingolimod (HR=0.08; 95% CI 0.01–0.64; p=0.017). Adverse events were consistent with known safety profiles.

Conclusions These results suggest that natalizumab is more efficacious than fingolimod in reducing multiple sclerosis relapses and T1 Gd+ lesion accumulation in patients with active disease.

Trial registration numbers NCT02342704; EUCTR2013-004622-29-IT; Post-results.

Strengths and limitations of this study

- This study is the first randomised controlled trial to compare the efficacy of natalizumab and fingolimod in patients with relapsing-remitting multiple sclerosis.
- The primary endpoint, evolution of new on-treatment gadolinium-enhancing lesions to persistent black holes, could not be assessed due to early study termination.
- Secondary endpoints, including the effects of treatment on the development of new T1 gadolinium-enhancing lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes, were assessed over a relatively short treatment period of 24–36 weeks.

INTRODUCTION

Natalizumab and fingolimod are well-established, efficacious disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS), demonstrating reductions in clinical and radiological measures of disease activity in pivotal placebo-controlled trials.[1–5] Previous analyses have indicated that both natalizumab and fingolimod exhibit beneficial effects quickly (within 2 months) after treatment initiation,[6–9] which may be an important consideration in treatment selection, especially in patients with active disease. However, evidence regarding the relative efficacy of natalizumab and fingolimod has, to date, been limited to retrospective analyses of registry datasets.[10–22] While the majority of these studies reported improved outcomes with natalizumab compared with fingolimod,[10 12–15 18–21] several found no difference in clinical outcomes between the two therapies.[16 17] However, one study found that the

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reduction in annualised relapse rate (ARR) after 1 year of treatment was significantly greater with natalizumab than with fingolimod, whereas treatment persistence was significantly higher in patients treated with fingolimod.[22]

This study reports results from REVEAL, a 1-year, randomised, rater-blinded and sponsor-blinded, prospective head-to-head study comparing natalizumab and fingolimod in patients with active RRMS. Although early study closure precluded analysis of the primary efficacy endpoint, available MRI data were used in unplanned exploratory analyses of secondary endpoints to directly compare natalizumab versus fingolimod efficacy within 4 weeks of therapy initiation. In addition, relapse data were analysed to assess ARRs and the cumulative probability of relapse over the duration of the study.

METHODS

REVEAL was a phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study conducted at 43 sites in nine countries between October 2014 and May 2016 (planned overall duration, 68 weeks) in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines (clinicaltrials.gov identifier NCT02342704; EudraCT identifier EUCTR2013-004622-29-IT).[23] The REVEAL investigators are listed in online supplemental table 1. All sites received institutional review board approval (see online supplemental table 2), and all participants provided written informed consent. REVEAL was designed to include approximately 540 patients. However, after 1 year of enrolling patients, only 111 patients had been enrolled. The decision to terminate the study due to slow enrolment was made by the sponsor (Biogen) in November 2015. Outcome data were not made available until May 2016, and all scheduled MRI scans were evaluated in a blinded manner. Thus, the study termination decision was made without knowledge of the results.

Patients were aged 18–60 years and had active RRMS not previously treated with natalizumab, fingolimod or immunosuppressants, with ≥1 new T1 gadolinium-enhancing (Gd+) lesion within the 6 months prior to screening or ≥2 new T2 lesions on brain MRI within the 6 months prior to screening (compared with a T2-weighted scan 18 months before screening) as well as an Expanded Disability Status Scale (EDSS) score ≤5.5. Included patients could have previously been treated for ≥6 months with glatiramer acetate or an interferon beta formulation if they had ≥9 T2-hyperintense lesions on brain MRI and experienced ≥1 relapse while on therapy within the 6 months prior to screening. Multiple sclerosis (MS) treatment–naïve patients and patients who had previously been treated for <6 months with glatiramer acetate or an interferon beta formulation were included only if they had ≥2 disabling relapses within the 12 months prior to screening. Patients with progressive MS were excluded.

Following a 4-week screening period, patients were randomly assigned (1:1) to open-label intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for up to 52 weeks, then followed for up to 64 weeks. MRI scans were scheduled every 4 weeks for the first 24 weeks and then at 36 and 52 weeks. A follow-up visit approximately 12 weeks after the last dose of study drug was planned.

Relapses and adverse events (AEs) were assessed at scheduled visits. A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occurred fewer than 30 days after the onset of a protocol-defined relapse were considered part of the same relapse. MS relapses were not considered AEs, and MS relapses resulting in hospitalisation did not need to be reported as serious AEs (SAEs). However, any MS relapse that was complicated by other SAEs was reported as an SAE.

The intent-to-treat (ITT) population for efficacy analysis comprised all randomised subjects given ≥1 dose of study drug who provided any efficacy assessments. The primary endpoint (the evolution of new on-treatment T1-weighted Gd+ lesions to persistent black holes over 52 weeks) could not be assessed due to the lack of 52-week data. Secondary endpoints included the number of new T1 Gd+ lesions, the cumulative probability of developing new T1 Gd+ lesions, the number of new/newly enlarging T2 lesions, T1 and T2 lesion volumes and relapse outcomes. MRI and relapse outcomes were assessed over the study duration according to the protocol. However, due to the limited numbers of events and patients at risk, MRI outcomes were reported over up to 24 weeks, while relapse outcomes were reported over up to 36 weeks. Other secondary endpoints, including the time to complete recovery from the first relapse, proportion of patients with no evidence of disease activity and change from baseline in information processing speed as measured by the Symbol Digit Modalities Test, were not interpretable due to the early closure of the study. Safety was assessed based on AEs, laboratory measurements, vital signs and physical examinations.

Treatment groups were compared using negative binomial regression models, and Cox regression models were developed for probability analyses. P values for comparisons in new T2 lesions and lesion volume changes were determined using a Wilcoxon rank-sum test.

A diffusion tensor imaging substudy, which included healthy volunteers, was conducted to assess brain tissue damage and recovery in patients with active RRMS. Due to study termination, results were unevaluable.

Patient involvement

Patients were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

The ITT population (table 1) comprised 108 patients (see online supplemental figure 1); 63 patients (58.3%;

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Table 1 Baseline demographics and characteristics

Characteristic	Natalizumab (n=54)	Fingolimod (n=54)
Age, years		
Mean (SD)	38.2 (8.8)	34.9 (8.7)
Median (min, max)	40 (21, 55)	35 (19, 55)
Sex, n (%) female	37 (68.5)	38 (70.4)
EDSS score		
Mean (SD)	2.5 (1.3)	2.6 (1.3)
Median (min, max)	2.0 (0.0, 6.0)	2.5 (0.0, 5.5)
Time since the first MS symptoms, mean (SD), years	8.1 (7.7)	6.8 (7.0)
Time since MS diagnosis, mean (SD), years	5.0 (5.8)	4.5 (5.8)
Prior MS treatment, n (%) of patients*	26 (48.1)	28 (51.9)
Time since most recent relapse, mean (SD), days	86.8 (58.8)	91.2 (91.4)
Number of relapses in the past year, mean (SD)	1.9 (0.7)	1.9 (0.6)
Number of Gd+ lesions		
Mean (SD)	2.4 (3.7)	2.5 (4.9)
Median (min, max)	1 (0, 14)	1 (0, 28)
T2 lesion volume, mL		
Mean (SD)	11.9 (9.4)	10.9 (10.4)
Median (min, max)	8.5 (0.7, 40.1)	7.7 (0.1, 43.2)
T1-non-enhancing lesion volume, mL		
Mean (SD)	2.3 (2.4)	2.4 (3.4)
Median (min, max)	1.3 (0, 8.6)	1.1 (0, 15.3)

*Most commonly glatiramer acetate (natalizumab, n=7; fingolimod, n=9) and interferon beta (subcutaneous (SC) interferon beta-1a: natalizumab, n=10; fingolimod, n=6; intramuscular interferon beta-1a: natalizumab, n=4; fingolimod, n=10; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=5; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=2).
EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhanced; max, maximum; min, minimum; MS, multiple sclerosis.

Table 2 Treatment exposure and safety outcomes

Characteristic	Natalizumab (n=54)	Fingolimod (n=54)
Study drug exposure, days		
Mean (SD)	183.0 (90.9)	182.6 (101.8)
Median (range)	197 (1–364)	172 (1–362)
Patients receiving treatment at each time point, n (%)		
Baseline	54 (100)	54 (100)
Week 4	52 (96.3)	50 (92.6)
Week 8	50 (92.6)	47 (87.0)
Week 12	45 (83.3)	45 (83.3)
Week 16	42 (77.8)	40 (74.1)
Week 20	36 (66.7)	35 (64.8)
Week 24	32 (59.3)	31 (57.4)
Week 32	25 (46.3)	23 (42.6)
Week 40	11 (20.4)	13 (24.1)
Week 52	2 (3.7)	1 (1.9)
Treatment-emergent AEs, n (%) of patients	23 (42.6)	32 (59.3)
Most commonly reported events, n (%) of patients*		
Headache	6 (11.1)	4 (7.4)
MS relapse	1 (1.9)	8 (14.8)
Hypoesthesia	0	3 (5.6)
Migraine	0	3 (5.6)
Upper respiratory tract infection	1 (1.9)	5 (9.3)
Urinary tract infection	2 (3.7)	3 (5.6)
Lymphocyte count decreased	0	5 (9.3)
Alanine aminotransferase increased	0	3 (5.6)
Anxiety	1 (1.9)	3 (5.6)
Fatigue	3 (5.6)	0
Oropharyngeal pain	3 (5.6)	1 (1.9)
Serious AEs, n (%) of patients	0	2 (3.7)
Second-degree atrioventricular block	0	1 (1.9)
Migraine with aura	0	1 (1.9)
Events leading to study discontinuation, n (%) of patients†	1 (1.9)	3 (5.6)
Second-degree atrioventricular block	0	1 (1.9)
Infusion site rash	1 (1.9)	0
Alanine aminotransferase increased	0	1 (1.9)
Aspartate aminotransferase increased	0	1 (1.9)
Headache	0	1 (1.9)
Patients who discontinued, n (%)	53 (98.1)‡	51 (94.4)§

*Treatment-emergent AEs reported by ≥5% patients in either group, listed by MedDRA preferred term.
†With the exception of atrioventricular block, AEs leading to study discontinuation were classified as non-serious events.
‡Forty-nine patients discontinued due to sponsor study termination, two were lost to follow-up, one discontinued due to an AE and one discontinued due to withdrawal of consent.
§Forty-three patients discontinued due to sponsor study termination, three discontinued due to AEs, three discontinued due to physician decision, one was lost to follow-up and one discontinued for another reason.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis.

natalizumab, n=32; fingolimod, n=31) received study treatment through 24 weeks, whereas only 3 (2.8%; natalizumab, n=2; fingolimod, n=1) were treated through 52 weeks (table 2). Median (range) follow-up time was 40.1 (7.1–64.7) weeks for natalizumab and 36.7 (7.0–64.1) weeks for fingolimod.

The mean number of new T1 Gd+ lesions was 63% lower in the natalizumab group than the fingolimod group at 4 weeks (p=0.353) and ≥70% lower at 12 weeks (p=0.030; figure 1), a difference that was maintained (with reduced patient numbers) through 24 weeks (p=0.008). Over 24 weeks, new T1 Gd+ lesion accumulation was lower among natalizumab-treated than fingolimod-treated patients (0.02 vs 0.09 new lesions per week; p=0.004). Over the entire follow-up period, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to develop ≥2 or ≥3 new T1 Gd+ lesions (table 3). No significant between-group differences were observed in other MRI outcomes at 24 weeks; however, all MRI results numerically favoured natalizumab (table 3).

During follow-up in this abbreviated study, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to experience a relapse (table 3). The cumulative probability of relapse over follow-up was 1.9% with natalizumab and 22.3% with fingolimod (HR=0.08; 95% CI 0.01–0.64; p=0.017; figure 2A). Pre-treatment ARRs in the natalizumab and

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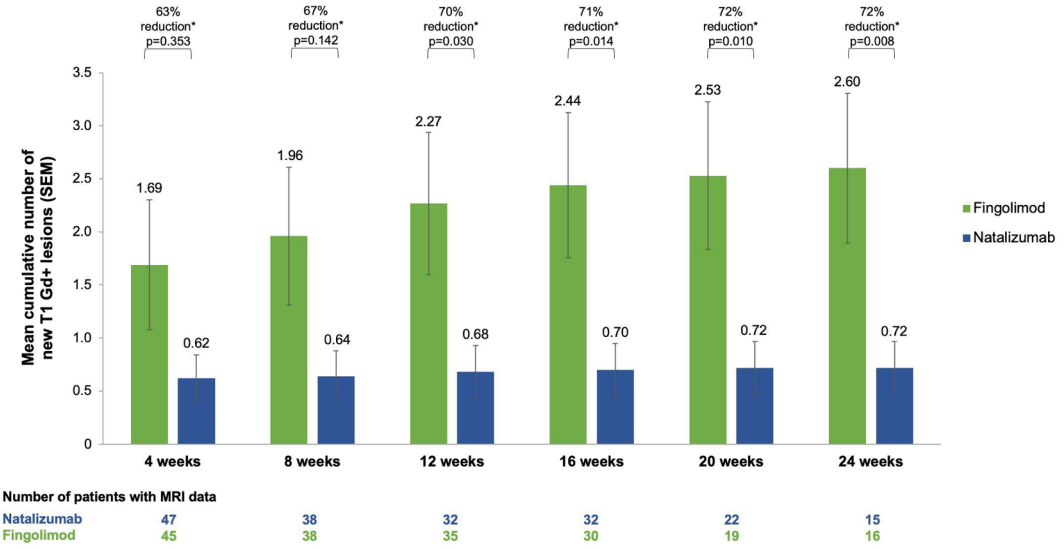

Figure 1 Mean cumulative number of new Gd+ lesions on T1-weighted MRI scans reported over 24 weeks. *Reduction is for natalizumab versus fingolimod. P value is based on a negative binomial regression model adjusted for baseline T1 Gd+ lesion count. Gd+, gadolinium enhancing; SEM, standard error of the mean.

Table 3 Key MRI and clinical outcomes

Outcomes	Natalizumab (n=54)	Fingolimod (n=54)	HR (95% CI)*	P value†
MRI outcomes: T1 Gd+ lesions				
Cumulative probability of developing new T1 Gd+ lesions over study, %				
≥1	40.68	57.99	0.60 (0.31–1.16)	0.126
≥2	11.54	48.48	0.25 (0.09–0.68)	0.007
≥3	10.02	41.38	0.24 (0.08–0.77)	0.016
Number of patients with new T1 Gd+ lesions from baseline to 24 weeks, n/N (%)	16/47 (34.0)‡	24/45 (53.3)‡	NA	0.062
Change from baseline in T1 Gd+ lesion vol to 24 weeks, mean (SD)	0.5 (31.2)§	1.8 (19.7)§	NA	0.532
MRI outcomes: T2 lesions				
Number of patients with new/newly enlarging T2 lesions at 24 weeks, n/N (%)	6/15 (40.0)	10/16 (62.5)	NA	0.21
Number of new/newly enlarging T2 lesions at 24 weeks per patient, mean (SD)	1.3 (2.5)§	1.9 (2.2)§	NA	0.263
Change from baseline in T2 lesion volume to 24 weeks, mean (SD)	0.1 (4.4)§	3.3 (5.0)§	NA	0.053
Relapse outcomes				
Cumulative probability of relapse over study, %¶	1.9	22.3	0.08 (0.01–0.64)**	0.017
ARR on study (95% CI)	0.02 (0.00–0.13)	0.20 (0.11–0.37)	0.09 (0.01–0.72)††	0.023‡‡

*All HRs and rate ratios compare natalizumab to fingolimod.
†P value based on a Cox model adjusted for the baseline number of Gd+ lesions, age, baseline EDSS score and years since the first symptom (for the cumulative probability of new T1 Gd+ lesions during follow-up), from a χ^2 test between the two treatment groups (for the number of patients with new lesions) or based on a Wilcoxon rank-sum test between the two treatment groups (for the number of new/newly enlarging T2 lesions and changes in lesion volume).
‡Includes patients with new T1 Gd+ lesions at any time point after baseline. Not all patients received treatment through 24 weeks.
§Natalizumab, n=15; fingolimod, n=16. Includes only patients who had MRI data through 24 weeks.
¶Cumulative probabilities at 36 weeks are reported, as no relapse events were observed after 36 weeks.
**Based on Cox model adjusted for the number of relapses in the year before baseline, age, baseline EDSS score and years since the first symptom.
††Value indicated is a rate ratio based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since the first symptom, baseline EDSS score and baseline age.
‡‡P value based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since the first symptom, baseline EDSS score and baseline age.
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; NA, not applicable.

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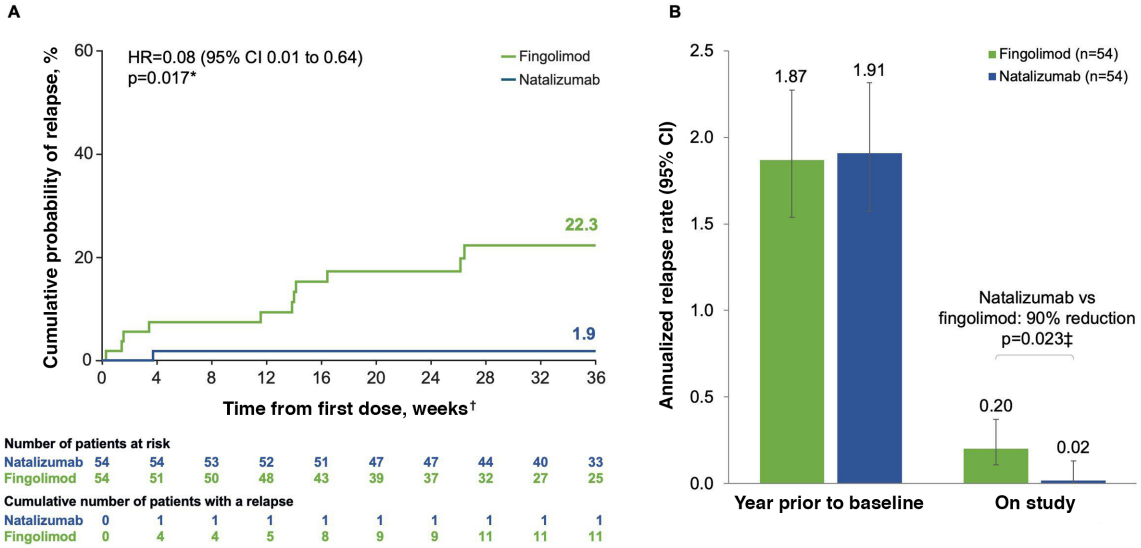

Figure 2 Impact of natalizumab versus fingolimod treatment on relapse outcomes, shown as (A) Kaplan-Meier survival curve of time to relapse over 52 weeks and (B) ARRs before study and on study. *Natalizumab versus fingolimod, based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since the first symptom. †The x-axis has been truncated at week 36, as no events were observed after week 36. ‡P value is based on a negative binomial model of ARR with treatment as effect, adjusted for number of relapses in the year before baseline, years since the first symptom, baseline EDSS score and baseline age. ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.

fingolimod treatment groups were 1.91 and 1.87, respectively (figure 2B). The on-treatment ARR was 0.02 in the natalizumab group (a 99% reduction) and 0.20 in the fingolimod group (an 89% reduction). The on-treatment ARR was 90% lower with natalizumab than with fingolimod (p=0.023).

Treatment-emergent AEs were reported for 42.6% and 59.3% of natalizumab- and fingolimod-treated patients, respectively, including two serious AEs, both in patients on fingolimod (table 2). All safety findings were consistent with the known safety profiles for natalizumab and fingolimod.[24 25]

DISCUSSION

These unplanned exploratory analyses of REVEAL secondary endpoints indicate that natalizumab reduces T1 Gd+ lesion accumulation and relapse disease activity soon after initiation, consistent with previous clinical trial findings.[6 7] Treatment effects on MRI outcomes were observed within 4 weeks of starting natalizumab.

While both treatments were efficacious in patients with active RRMS, reduction in disease activity, measured by the number of new T1 Gd+ lesions and relapses, occurred more rapidly and to a greater extent with natalizumab than with fingolimod. These results extend previous findings of the efficacy advantage of natalizumab over fingolimod in preventing relapses and reducing disease activity from comparative analyses of patients with active RRMS or prior treatment failure followed up for 1–2 years in real-world settings.[10–13 15 19] No significant between-group differences were observed for other MRI outcomes, such as lesion volume and the number of new/newly enlarging T2 lesions.

Safety findings in this study were consistent with the established profile of each treatment, with no new safety concerns noted.[24 25]

Although REVEAL was designed as a randomised controlled trial, results should be interpreted with caution, as analysis of the primary endpoint was not possible due to early study closure. However, the bias in the results due to early study termination is unlikely based on the timing of the decision (before outcome data availability) and the blinding of the sponsor and MRI readers. Secondary efficacy evaluations were limited to a relatively short treatment period of 24–36 weeks, precluding meaningful assessment of EDSS score change. A further limitation is that the long-term consequences of these relatively short-term findings are unknown.

In conclusion, the results suggest a greater benefit with natalizumab than with fingolimod in reducing relapse rates and T1 Gd+ lesion accumulation in patients with active RRMS. The onset of efficacy occurred more rapidly with natalizumab than with fingolimod, which may be an important consideration for treatment selection in patients with active disease, who need swift and effective control of disease activity.

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Contributors HB, DJ, DLA, MF, JG and P-RH contributed to study design. HB, SL, DJ, DLA, MF, JG, SS, NC and P-RH were involved in analysis and interpretation of data. HB, SL and P-RH contributed to manuscript development. HB, SL, DJ, DLA, MF, JG, SS, NC and P-RH revised the manuscript for intellectual content.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by ethics committees for all participating study centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Datasets from this study are not publicly available. Requests for de-identified data should be made to Biogen via established company data-sharing policies as detailed on the website http://clinicalresearch.biogen.com/.

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