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Multiple sclerosis in the real world: a systematic review of fingolimod as a case study

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Abstract (290 words)

Introduction: The aim of our study was to systematically review the growing body of published literature reporting on one specific multiple sclerosis (MS) treatment, fingolimod, in the real world to assess its effectiveness in patients with MS, evaluate methodologies used to investigate MS in clinical practice, and describe the evidence gaps for MS as exemplified by fingolimod.

Methods: We conducted a PRISMA-compliant systematic review of the literature (cut-off date: 4 March 2016). Published papers reporting real-world data for fingolimod with regard to clinical outcomes, persistence, adherence, healthcare costs, healthcare resource use, treatment patterns, and patient-reported outcomes that met all the eligibility criteria were included for data extraction and quality assessment.

Results and discussion: Based on 34 included studies, this analysis found that fingolimod treatment improved outcomes compared to the period before treatment initiation and was more effective than interferons or glatiramer acetate. However, among studies comparing fingolimod with natalizumab, overall trends were inconsistent: some reported natalizumab to be more effective than fingolimod and others reported similar effectiveness for natalizumab and fingolimod. These studies illustrate the challenges of investigating MS in the real world, including the subjectivity in evaluating some clinical outcomes and the heterogeneity of methodologies used and patient populations investigated, which limit comparisons across studies. Gaps in available real-world evidence for MS are also highlighted, including those relating to patient-reported outcomes, combined clinical outcomes (to measure overall treatment effectiveness), and healthcare costs/resource use.

Conclusions: The included studies provide good evidence of the real-world effectiveness of fingolimod and highlight the diversity of methodologies used to
assess treatment benefit in clinical practice. Future studies could address the evidence gaps found in the literature and the challenges associated with researching MS when designing real-world studies, assessing data, and comparing evidence across studies.

Keywords: Clinical practice, Effectiveness, Fingolimod, Multiple sclerosis, Real-world data, Systematic review

Abbreviations: AHSCT, autologous hematopoietic stem cell transplant; ARR, annualized relapse rate; BVL, brain volume loss; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; HRQoL, health-related quality of life; IFN, interferon; MS, multiple sclerosis; NA, not applicable; NEDA, no evidence of disease activity; NS, not significant; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRO, patient-reported outcome; RCT, randomized controlled trial; RRMS, relapsing–remitting multiple sclerosis; RWD, real-world data; SR, systematic review.
1. Introduction

In multiple sclerosis (MS) research, randomized controlled trials (RCTs) have demonstrated the efficacy of MS treatments according to relapses, disability, and magnetic resonance imaging (MRI) outcomes, and in some cases according to patient-reported outcomes (PROs) [1-3]. The protocol-driven approach to data generation in RCTs provides high-quality evidence in a carefully selected group of patients who are treated under ideal, controlled conditions [3, 4]. In the real world, however, the population of patients with MS who are eligible to receive disease-modifying therapies (DMTs) is much more heterogeneous than that treated in RCTs [4], and patient medication-taking behavior and patient monitoring are not constrained by protocol [4, 5]. These factors can influence clinical outcomes, and as a result, data generated from RCTs may not be generalizable to the clinical practice setting [4, 6].

Real-world studies complement RCTs by investigating a more diverse group of patients than those included in clinical trials, providing real-world data (RWD) that can be generalized across the population of patients with MS who are treated and monitored according to standard clinical practice [4]. Real-world studies are often observational in nature, and can collect RWD prospectively during routine patient visits or retrospectively from existing data sources, such as patient registries, medical records, or administrative claims databases [4, 7]. Medical records and registries generally report clinical information collected by physicians [7]. Conversely, administrative claims databases, which capture diagnosis codes and payment data for the insured population, may require proxy measures to identify patients with MS and certain clinical outcomes, such as relapses [7-10]. RWD expand the evidence base for MS, give insight into the short-term and long-term safety and effectiveness
of DMTs for MS as well as patient persistence with, and adherence to, therapies in clinical practice, and can provide insight into healthcare resource use and costs that are often not measured in RCTs [3, 4, 7, 11].

Injectable, infusible, and oral therapies, which can have different mechanisms of action, are approved to treat patients with MS, and several new treatments are in development [1, 12]. A need therefore exists to understand the comparative benefits of different DMTs in this complex and evolving landscape. Fingolimod (Gilenya®, Novartis Pharma AG, Basel, Switzerland), the first oral therapy approved to treat relapsing MS, has demonstrated efficacy in reducing relapses, delaying disability progression, and improving MRI and brain volume loss (BVL) outcomes in phase 3 RCTs compared with placebo or intramuscular interferon (IFN) beta-1a [13-16].

There is also a growing body of RWD being generated for fingolimod in clinical practice from administrative claims databases, MS registries, and patient records [3]. Using fingolimod as a case study, our aim was therefore to systematically review the published literature presenting RWD for this DMT, to assess effectiveness and to explore the methodologies and data sources used to assess MS treatments in clinical practice. A similar approach could be used to assess the body of RWD for other DMTs being used to treat MS in clinical practice.

Various aspects of MS have already been reviewed, including disease biomarkers and the role of inflammation and neurodegeneration in fatigue [17-19]. In this review, we evaluate the RWD for fingolimod for several effectiveness outcomes of interest (clinical outcomes, treatment persistence/adherence, healthcare costs, healthcare resource use, treatment patterns, and PROs), grouping studies into those that assess outcomes after fingolimod initiation (including fingolimod single-arm studies).
or according to the DMT against which fingolimod was assessed. We present the diverse range of methodologies and data sources being used to investigate MS in clinical practice, the challenges of investigating MS in the real world, and the evidence gaps, as exemplified by fingolimod [5]. Finally, we conclude with a summary of our findings and key considerations when conducting or assessing real-world studies.

2. Methods

2.1. Study design and search strategy

This systematic review (SR) was performed according to a prespecified protocol that was defined and agreed by all the authors. A broad search strategy was conducted to identify publications that reported RWD for fingolimod, using Medline®, Medline® In-Process (1946–present), Embase (1974–present), and the Cochrane Library. Supplementary searching of congress abstracts published between 2012 and 2016 and available at the time of searching was also carried out for the Annual Congress of the European Committee for Treatment and Research in Multiple Sclerosis, the Annual Meeting of the American Academy of Neurology, the Annual Meeting of the European Neurological Society, the Joint Congress of European Neurology, the European Academy of Neurology congress, and the International Society for Pharmacoeconomics and Outcomes Research US and EU congresses. SRs and meta-analyses were not included, but their bibliographies were screened for relevant publications, as were the bibliographies of included references. (Complete search strings are shown in Table A.1.)

2.2. Study selection and data extraction
Abstracts and titles of studies were screened by two independent reviewers. A third reviewer resolved any disputes. Publications meeting the inclusion criteria (and none of the exclusion criteria) were obtained as full articles and reassessed against the eligibility criteria (Table 1). The SR process was fully compliant with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3. Results

3.1. Search yields

Electronic searches were conducted on 4 March 2016 (Fig. 1). After screening of titles and abstracts and full paper review, 168 publications were included (34 published papers, 134 congress materials), representing studies that analyzed RWD from patients in over 20 countries (Fig. A.1). Relevant data were extracted from the 34 published papers only, to ensure that sufficient information was available to assess the quality of studies and the robustness of evidence [20-41]. Details of study design, patient characteristics, population size, and outcomes of interest (clinical outcomes, treatment persistence/adherence, healthcare costs, healthcare resource use, treatment patterns, and PROs; see Table A.2 for definitions of the outcomes of interest) were extracted from the included published papers and checked by an independent reviewer. The 34 included published papers present data for fingolimod for over 7000 patient-years (calculated on the basis of the size of the fingolimod cohort and the follow-up time in each study; for publications that provided a range for the follow-up period, the mean follow-up time was calculated and used).

3.2. Characteristics of included published papers
Key study and patient characteristics from the 34 included published papers, which we believe report the results of 34 independent studies, are described in Table A.3. Twenty-one of the 34 studies specified that they were investigating outcomes in patients with relapsing–remitting MS [21-23, 28-31, 34-36, 38, 40-49], one study excluded patients with primary progressive MS [50], and the remaining studies did not exclude patients on the basis of MS type. Twelve studies reported the results of fingolimod single-arm studies: 11 of these studies evaluated outcomes from the start of treatment with fingolimod (baseline), in most cases after discontinuing another DMT [21-23, 28, 33, 39, 40, 44, 46, 48, 49], and one study compared outcomes in patients who remained on fingolimod versus those who discontinued fingolimod treatment [51]. The remaining 22 studies compared fingolimod treatment with other DMTs: seven studies compared fingolimod with IFN and/or glatiramer acetate (GA) [20, 25, 26, 30, 35, 43, 52], 11 studies compared fingolimod with natalizumab [24, 29, 31, 32, 34, 36, 38, 41, 42, 47, 53], three studies compared fingolimod with natalizumab/IFN/GA [27, 37, 50], and one study compared fingolimod with no treatment, first-line treatments (IFN, GA, teriflunomide, azathioprine), natalizumab, rituximab, or immunosuppressive agents (cyclophosphamide/mitoxantrone) [45]. Over half of studies reporting data for IFN and GA did not present data for the individual treatments [23, 30, 35, 37, 43, 45, 52]; therefore, we have not distinguished between the injectable DMTs throughout this review.

There was a diversity of study designs among the 34 included studies. Twenty studies were described as retrospective [20-22, 24-27, 30, 31, 33-37, 39, 40, 44-46, 49], and seven were described as prospective [28, 32, 38, 42, 48, 50, 52]; the reports of the remaining seven studies contained insufficient information to determine whether studies were retrospective or prospective [23, 29, 41, 43, 47, 51, 53]. Nine studies collected results at a single center [28, 30, 31, 39, 41, 44, 46, 49, 51], and 25
studies were conducted at several centers, either within a single country or across different countries [20-27, 29, 32-38, 40, 42, 43, 45, 47, 48, 50, 52, 53]. Study characteristics have been presented for single-arm studies and for studies comparing fingolimod with IFN/GA or natalizumab in Fig. A.2.

In total, 12 studies were identified as being of a high quality [20, 24-27, 29, 35, 37, 38, 42, 43, 52]. This was because they met all of the following criteria: defined the inclusion and exclusion criteria; investigated a representative population (included treatment cohorts of at least 30 patients, collected data from multiple centers); defined outcomes according to objective criteria; had a follow-up period that was regarded by the authors of the present study as being long enough to assess outcomes accurately; and used statistical methodology to reduce bias and confounding (Table A.4). Eighteen studies, which met most but not all the above criteria, were categorized as being of a medium quality [21, 22, 28, 31, 32, 34, 36, 39, 40, 44-51, 53]. The remaining four studies, which did not meet several criteria, were categorized as being of a low quality [23, 30, 33, 41].

3.3. Summary of real-world relapse outcomes

Twenty-seven studies reported relapse outcomes for fingolimod (Table A.5) [21-26, 28-32, 34-38, 41-49, 51, 52].

Fingolimod treatment versus the period before initiation: Nine studies [21, 22, 28, 42, 44, 46-49], which included seven single-arm studies [21, 22, 28, 44, 46, 48, 49], reported improved relapse outcomes after fingolimod initiation based on patient data from MS registries, MS centers, or hospitals. This is consistent with another single-
arm study that reported improved relapse outcomes in patients who remained on fingolimod versus those who discontinued fingolimod [51].

Fingolimod versus IFN/GA: Eight studies compared fingolimod with IFN/GA [25, 26, 30, 35, 37, 43, 45, 52], which included patients discontinuing natalizumab [30, 45, 52]. Seven studies used administrative claims, registry data, or electronic medical records and reported a lower relapse rate with fingolimod compared with IFN/GA [25, 26, 35, 37, 43, 45, 52]. Conversely, in a small, single-center study assessing outcomes after natalizumab discontinuation, the proportions of relapse-free patients were similar for those switching to fingolimod versus those switching to “first-line” treatments, including IFN/GA; however, this study was of a low quality owing to its small size (“first-line” cohort, N < 30 patients) and the lack of detail about how outcomes were assessed [30].

Fingolimod versus natalizumab: Seven studies compared fingolimod with natalizumab [24, 29, 31, 34, 38, 42, 47], and six studies assessed fingolimod as a switch therapy after natalizumab discontinuation [30, 32, 36, 37, 41, 44]. Of studies comparing fingolimod and natalizumab, three studies, using patient records from several centers [29, 47] or an administrative claims database [24], reported similar relapse outcomes with fingolimod and natalizumab treatment [24, 29, 47]. Conversely, four studies reported better relapse outcomes with natalizumab treatment than fingolimod [31, 34, 38, 42]; these studies ranged in scale from those that used patient data from one [31] or two [34] clinics to those that used data from 27 MS centers [42] or an international MS registry [38]. Of studies assessing fingolimod as a switch therapy [30, 32, 36, 37, 41, 44], five studies reported reactivation of relapses after switching to fingolimod [30, 32, 36, 37, 41] and one
study reported no difference in relapse rate [44]. All three studies that provided data on relapses before natalizumab initiation or in the period between treatments (washout period) reported lower relapse rates during fingolimod treatment than in the pre-natalizumab or washout periods [32, 36, 37].

3.4. Summary of real-world disability outcomes

Nineteen studies assessed disability after initiation of fingolimod treatment using the Expanded Disability Status Scale (EDSS; Table A.6) [21-23, 28-30, 34-36, 38, 41-44, 46-49, 52].

Fingolimod treatment versus the period before initiation: Nine studies assessed outcomes after fingolimod initiation [21-23, 28, 42, 44, 46, 48, 49], which included eight single-arm studies [21-23, 28, 44, 48, 49]. In four studies disability outcomes were unchanged [23, 28, 44, 48], and in five studies disability outcomes were improved after fingolimod initiation, as measured by EDSS score [21, 22, 28, 42, 49] and as the proportion of patients with no disability progression [28, 46]. Two single-arm studies assessed disability outcomes from baseline in cohorts of patients subdivided by baseline DMT: one study reported a significant difference from baseline in patients switching to fingolimod from IFN/GA but not in patients switching to natalizumab [44]; conversely, in the other study, similar EDSS scores were reported before and after fingolimod initiation regardless of whether patients had previously received IFN/GA or natalizumab [23]. However, the lack of methodological description in this second publication meant that it was not possible to explore the lack of consistency between the two studies [23, 44].
Fingolimod versus IFN/GA: Two studies, using either registry data or patient medical records, compared fingolimod or IFN/GA treatment after discontinuing IFN/GA [35, 43]: one study reported better outcomes for patients switching to fingolimod than to another IFN/GA, as measured by the risk of disability progression and disability regression [35], and the other study reported better outcomes for fingolimod for the proportion of patients free from disability progression but not for the risk of disability progression [43]. One study compared fingolimod and IFN/GA in patients discontinuing natalizumab and reported no significant difference in the proportion of patients with disability progression [52].

Fingolimod versus natalizumab: Six studies compared fingolimod and natalizumab [29, 34, 36, 38, 42, 47], and one study compared outcomes in patients remaining on natalizumab versus those who switched to fingolimod [41]. Of studies comparing fingolimod and natalizumab, five studies reported similar outcomes for fingolimod and natalizumab for EDSS score, time to disability progression, or proportion of patients free from progression [29, 34, 36, 42, 47]. Conversely, the proportion of patients with disability regression was higher for natalizumab than fingolimod ($p < 0.001$) in the sixth study, an international MS registry study [38]. In a small observational study that investigated fingolimod as a switch therapy, EDSS scores were stable in all patients remaining on natalizumab but increased in over a third of patients switching from natalizumab to fingolimod [41].

3.5. Summary of real-world MRI outcomes

Thirteen studies reported MRI outcomes (T2 and gadolinium-enhancing lesions) after initiation of fingolimod (Table A.7) [21-23, 28, 34, 41, 42, 45-49, 51], but none
provided data on BVL.

*Fingolimod treatment versus the period before initiation:* Eight studies presented MRI data after fingolimod treatment [21-23, 28, 42, 46, 48, 49], which included seven single-arm studies [21-23, 28, 46, 48, 49]. Four of these studies reported improved MRI outcomes after fingolimod treatment [21-23, 42] and one study reported no change [46]. Three of the single-arm studies reported that over half of patients receiving fingolimod had no active lesions or new lesions, but did not provide baseline data from before patients initiated fingolimod [28, 48, 49]. One study, using patient data from a medical center, compared outcomes in those who remained on fingolimod versus those who discontinued fingolimod and reported better MRI outcomes in those who remained on fingolimod [51].

*Fingolimod versus natalizumab:* Three studies compared fingolimod and natalizumab [34, 42, 47] and two studies assessed fingolimod as a switch therapy after natalizumab discontinuation [41, 45]. Of studies comparing fingolimod and natalizumab, two studies reported better MRI outcomes in the natalizumab cohort than the fingolimod cohort [42, 47], whereas a third study reported a similar proportion of patients with new lesions in both cohorts [34]. Of the two studies assessing outcomes in patients receiving fingolimod as a switch therapy after discontinuing natalizumab, one study reported that the majority of patients had MRI activity after switching to fingolimod compared with none of the patients who remained on natalizumab [41]. In the other study, similar proportions of patients switching to fingolimod or first-line therapies (including IFN/GA) had radiological reactivation [45], but this was lower than the proportion of patients with radiological reactivation after a switch to no treatment when discontinuing natalizumab [45].
Although reactivation of disease activity may reflect differences in effectiveness between fingolimod and natalizumab, it is more likely that the reactivation of disease activity in the fingolimod cohort is a consequence of natalizumab withdrawal rather than inadequate disease control during subsequent fingolimod treatment.

3.6. Summary of real-world persistence/adherence outcomes

Twenty-three studies reported on persistence/adherence in patients receiving fingolimod (Table A.8) [20-22, 24-28, 31-35, 38-40, 43, 44, 46, 48-51].

Fingolimod treatment versus the period before initiation: In the 12 studies assessing persistence with fingolimod following its initiation [21, 22, 28, 32, 33, 39, 40, 44, 46, 48, 49, 51], two studies reported that the majority of patients at an MS center were still receiving fingolimod at follow-up (follow-up was at 6.8 months in one study; length of follow-up was not defined in the other study) [33, 40]. This is consistent with 10 other studies using registry data or patient records in which a small proportion of patients discontinued fingolimod [21, 22, 28, 32, 39, 44, 46, 48, 50, 51].

Fingolimod versus IFN/GA: Of seven studies comparing fingolimod and IFN/GA [20, 25-27, 35, 43, 50], six studies of registry, administrative claims, or MS center data reported better persistence/adherence for fingolimod compared with IFN/GA, according to the risk of discontinuation [20, 27, 43], the risk of non-adherence [20, 27], and the proportion of patients persistent with treatment [20, 25, 27, 35, 43, 50]. In another study of administrative claims data, patients discontinuing IFN reported higher persistence after a switch to fingolimod than those switching to GA, although the difference was not significant [26].
Fingolimod versus natalizumab: Seven studies compared fingolimod and natalizumab [24, 27, 31, 34, 38, 50, 53]. Three studies using administrative claims or registry data reported that similar proportions of patients were persistent with fingolimod and natalizumab [24, 38, 53]. Conversely, four studies, using medical records, registry data, or administrative claims data, reported better outcomes for fingolimod than natalizumab, according to the risk of discontinuation/non-adherence [27] and the proportion of patients discontinuing treatment [27, 31, 34, 50].

Based on these studies reporting on persistence/adherence, the main reasons for discontinuing fingolimod were ineffectiveness or tolerability issues/adverse events [21, 22, 28, 32, 34, 39, 43, 46, 48-51, 53], although one study also reported conversion to secondary progressive MS as a key reason for discontinuing fingolimod treatment [49].

3.7. Summary of real-world combined measures of disease activity

Ten studies included combined measures of disease activity as an outcome of interest [29-31, 43, 45-49, 51].

Fingolimod treatment versus the period before initiation: Three studies assessed the proportion of patients without relapses, disability progression, and MRI activity after fingolimod initiation [46, 48, 49]. One of these studies reported a significantly higher proportion without disease activity after fingolimod initiation ($p < 0.05$) [46]. The remaining two studies reported that almost half of patients receiving fingolimod were
free from disease activity, but did not provide baseline data for before patients initiated fingolimod [48, 49]. Consistent with these studies, one study at a single MS center reported better outcomes for the proportion of relapse- and MRI activity-free patients in those who remained on fingolimod versus those who discontinued fingolimod treatment [51].

**Fingolimod versus IFN/GA:** One multicenter study compared fingolimod and IFN/GA and reported better outcomes for fingolimod, according to the proportion of patients who were relapse- and disability progression-free ($p < 0.03$) [43].

**Fingolimod versus natalizumab:** Three studies compared outcomes between fingolimod and natalizumab [29, 31, 47] and two studies assessed outcomes in patients switching to fingolimod after discontinuing natalizumab [30, 45]. For studies comparing fingolimod and natalizumab, better outcomes were reported for natalizumab in a single-center study for time to first inflammatory event (relapse or new T1 lesions; $p = 0.041$) [31] and a multicenter study for the proportion of patients free from any disease activity (relapses, disability progression, MRI lesions; $p = 0.014$) [47]. Conversely, a multicenter study reported better outcomes for fingolimod than natalizumab for the proportion of patients free from relapses and disability ($p = 0.05$) [29]. For studies assessing outcomes in patients discontinuing natalizumab [30, 45], one small study at an MS center reported similar proportions of patients with disease reactivation (MRI lesions or severe relapse and increased EDSS score) after switching to fingolimod compared with other therapies (including injectable DMTs) [30]. Conversely, in another study of patients from two MS centers, the proportion of patients with clinical reactivation (relapses and/or disability progression) or rebound activity was lower in the fingolimod cohort than in the first-
line DMT (including injectable DMTs) or therapy-free cohorts [45].

### 3.8. Summary of real-world resource use, PROs, and treatment pathways

Healthcare resource use was investigated in one study of administrative claims data from patients who switched to fingolimod or natalizumab after experiencing disease activity with their current DMT. MS-related inpatient stays and corticosteroid use were similar in the fingolimod and natalizumab cohorts and were significantly reduced versus the pre-index period ($p < 0.01$) [24]. None of the included studies provided data on direct healthcare costs associated with fingolimod treatment. PROs were investigated in two studies in patients initiating fingolimod [39, 51], including one study of short duration (98 days follow-up) [39], and reported no significant change between baseline, on initiation of fingolimod, and at follow-up for the 9-item Patient Health Questionnaire, the MS Performance Scale test, and EuroQol 5-dimension questionnaire [39, 51]. Finally, 10 studies provided data on treatment pathways for fingolimod [20, 21, 23, 25, 28, 31, 34, 37, 39, 40]. Only a minority of patients in most studies were naïve to treatment before initiating fingolimod [20, 21, 25, 28, 31, 34, 37, 39, 40, 42, 44, 46, 49, 51]. For studies conducted in the EU [23, 28, 34, 40, 42, 44], this likely reflects the EU label for fingolimod [54].

### 4. Discussion

Real-world studies provide valuable insight into diseases, treatment approaches, treatment effectiveness, and patient experience from the clinical practice setting [4, 5]. These studies complement and strengthen the body of evidence from RCTs by providing generalizable RWD from a broad and diverse population of patients who are treated and monitored according to a care-driven approach [4, 5]. Real-world
studies have the additional benefit over RCTs in that they can be used to generate pharmacoeconomic data and data on resource use, which aid real-world decision-making but are not typically assessed in clinical trials [55]. As the body of real-world evidence grows, SRs are a valuable tool to assess the overall benefit profile of an intervention in clinical practice and to evaluate the methodologies being used in real-world studies.

The present SR assessed the published literature on the real-world effectiveness of fingolimod in the treatment of MS and, to the best of our knowledge, it is the only study to have done so. In addition to providing a summary of RWD for fingolimod, this study used fingolimod as a case study to present the range of methodologies being used to evaluate DMTs for MS in the real world, and it also provided insight into the quality of the RWD being generated in these studies. The benefit of reviewing the evidence for fingolimod stems from the fact that it has been extensively investigated in the real world. However, a similar SR approach could be performed as part of real-world studies to investigate other DMTs being used to treat MS in clinical practice. As part of a future study, these RWD could be combined with data from RCTs in network meta-analyses in order to increase the sensitivity of measurements of treatment effect [56].

This SR was based on data from 34 peer-reviewed published papers [20-53]. RWD for several different effectiveness outcomes were available, representing over 7000 patient-years of data. It is likely that data for fingolimod would be available for a much higher number of patient-years if the 134 congress materials identified as meeting the eligibility criteria in this SR were also taken into consideration. However, owing to limited information presented in abstracts and posters, these were not included. The
majority of included published papers were considered to report data of a high–to–medium quality [20-22, 24-29, 31, 32, 34-40, 42-53]. This was because they adhered to many, if not all, of the criteria identified as contributing to well-designed studies that have the potential to generate robust data. These quality assessment criteria included defining eligibility criteria, investigating a representative population using data collected from multiple centers, defining outcomes according to objective criteria, having a study follow-up period that was long enough to assess outcomes accurately (as regarded by the authors of the present study), and using statistical methodology to reduce bias and confounding. For studies identified as being of a low quality, results should be interpreted with caution [23, 30, 33, 41].

Among the single-arm studies that assessed outcomes after initiation of fingolimod therapy, or that compared fingolimod with IFN/GA, most reported improved clinical outcomes with fingolimod treatment [20, 25-27, 35, 42-46, 48-52]. The trends reported in this SR for fingolimod versus IFN/GA are consistent with RCT data for fingolimod versus intramuscular IFN beta-1a [15] and with the results of real-world studies that were published after the search date or were available only as congress materials, and were therefore not included in the SR (but have been discussed here).

Duerr et al. and Alsop et al. reported better outcomes during treatment with fingolimod than with IFN/GA using registry data from propensity score-matched patients [57-59]. Among the included studies comparing fingolimod with natalizumab, the reported trends were contradictory, with studies reporting outcomes with natalizumab to be either better than or similar to those with fingolimod regarding relapses, disability, and persistence/adherence [24, 27, 29, 31, 32, 34, 36-38, 41, 42, 47, 50, 53]. A recent observational study, which was also published after the search date, compared natalizumab and fingolimod and reported that fingolimod and natalizumab had similar effectiveness for relapse and disability outcomes, according
to results from a multicenter, retrospective analysis of adjusted data from propensity score-matched patients [60]. Therefore, the relative effectiveness of fingolimod and natalizumab remains unclear, and further large, long-term studies are required to address this [42].

It is notable that only one study compared outcomes in patients receiving fingolimod and other recently approved DMTs [45]. Lo Re et al. compared fingolimod with first-line DMTs, including oral teriflunomide [45], but owing to the fact that data were presented collectively for all first-line DMTs (IFN/GA/teriflunomide/azathioprine), no conclusions could be made about the comparative effectiveness of fingolimod and teriflunomide [45]. Two posters identified in the SR compared fingolimod with another recently approved oral therapy, dimethyl fumarate, and reported a lower risk of treatment discontinuation with fingolimod but a similar risk of relapse or MRI activity [61, 62]; however, the conclusions that can be made for relapse and MRI outcomes are limited by the short follow-up times (3–6 months) [61, 62].

Among the included studies, most RWD for fingolimod were collected retrospectively, using patient records from national or international MS registries, hospital databases or MS clinics, or administrative/pharmacy claims databases [20-22, 24-27, 30, 31, 33-37, 39, 40, 44-46, 49]. In retrospective studies, data collection and defining of study objectives are independent processes [4]. Retrospective studies are therefore particularly reliant on the quality and type of data available, and missing or incomplete information can compromise the quality and robustness of results [38]. Only a small proportion of the included published papers reported results of prospective studies [28, 32, 38, 42, 48, 50, 52] for which patients would have been identified and data collected after study objectives had been defined. Prospective
Studies are likely to be based on a more complete data set than retrospective studies, and they have the potential to collect and report data that are not routinely recorded in clinical practice [4]. The strengths and limitations of retrospective or prospective study designs and their impact on data quality and data generation should be considered when assessing and interpreting data from real-world studies.

Patients with MS were selected in the included studies using broad selection criteria on the basis of prescribed DMTs; some studies had the additional criterion that patients had experienced disease activity with previous DMTs or had received DMTs of interest for a minimum length of time, or the studies had a minimum follow-up period [21, 22, 25, 27, 29, 31, 35, 38, 41, 43-45, 47, 48]. In studies using administrative/pharmacy claims databases, insured patients with MS were identified on the basis of diagnosis codes or pharmacy claims [20, 27]; while there a possibility of wrongly identifying individuals as being patients with MS, this is likely to be limited in those studies requiring a diagnosis for MS, DMT use and (in some studies) evidence of relapses [24-27]. Inclusive eligibility criteria and large treatment cohorts, particularly when selected from multiple centers, ensure that a range of patients in clinical practice are represented, generating RWD that are more generalizable across the entire MS population than data generated from clinical trials [4]. The diversity of patients and their non-randomized assignment to treatment cohorts in real-world studies can, however, lead to a higher risk of bias and confounding than in RCTs [63]. To account for differences in characteristics between treatment cohorts, some studies used adjustment or propensity score-matching [24, 26, 35, 38, 42, 43, 52, 53, 63], which can allow for treatment effect to be estimated more accurately [63]. Identifying factors that can contribute to bias and confounding and selecting appropriate statistical analytic methodology are therefore important considerations in the design of robust real-world studies that have the potential to generate high-quality
data [5]. It should be noted, however, that these statistical approaches cannot adjust for unknown confounding factors or for covariates that were not recorded in the data source [7].

A challenge of MS research is the difficulty of assessing some aspects of disease progression, such as relapses and disability, which can be difficult to define or to measure accurately and consistently. For example, there is a degree of subjectivity involved in evaluating relapses, with the severity threshold or range of symptoms required for an event to be recognized varying among physicians or patients. Disability can also be difficult to define and measure, and changes in EDSS scores can be influenced, particularly in the short term, by the residual effects of relapses [64]. Results for these ‘soft endpoints’ may therefore not be comparable across studies, or indeed between patients within a study, which can have an impact on the estimated treatment effect. Some of the included studies used standardized criteria to define outcomes or required that outcomes were assessed by accredited individuals, which may address this problem to some degree [29, 34, 37, 40, 42, 43]. In contrast, ‘hard endpoints’ are assessed using objective, stringent criteria (e.g. number of MRI lesions), and are likely to be more comparable across studies.

In studies using administrative/pharmacy claims databases, relapses were evaluated using claims that have been shown to correlate with this event [24-26]. Proxy measures to assess disease activity can lack sensitivity or specificity, and may therefore not give a complete picture of treatment effect. In line with this, the relapse algorithm used in claims databases, which is defined as an inpatient visit with a primary diagnosis code for MS or an outpatient visit with a diagnosis code for MS and corticosteroid use within 7 days of the visit, may detect only relapses that require
hospitalization or corticosteroid treatment, not mild relapses that do not impact on daily activities or require treatment [9]. The relapse algorithm has, however, been validated in several studies, and the trends reported for fingolimod from administrative/pharmacy claims are aligned with those from patient records or MS registry databases [7, 24-26]. Furthermore, in matched analyses, any bias would apply to both treatment arms equally [24]. A limitation of administrative claims database studies is that some disease outcomes (e.g. relapse severity, disability, MRI lesion type) and baseline parameters, which may be confounding factors, cannot be assessed in the data source [7, 24].

The studies included in this SR generally highlight the diversity of data sources and methodologies being used to investigate MS and the benefit of DMTs in clinical practice. Such diversity, while generating a wealth of RWD, can lead to heterogeneity across studies in the patient populations being assessed (e.g. differences in disease severity due to variations in eligibility criteria or the treatment label in different countries), or in the approaches used to evaluate treatment effectiveness (e.g. differences in outcome definitions or in follow-up times) [5]. Heterogeneity can impact on outcomes and preclude comparison of data across studies, and may account for the general non-uniformity in the RWD presented in this SR. This does not reduce the value of the RWD being generated, which reflect patient and physician behavior and outcomes in the real world. Instead, when assessing RWD, it is important to be aware of the potential sources of variation across studies and their potential impact on outcomes. Furthermore, consistent trends across studies that vary in their methodological approach can provide more confidence in the comparative effectiveness of DMTs.
This SR has identified several key gaps in the evidence base for the effectiveness of fingolimod in the real world, including RWD for combined measures of disease activity (relapses, disability, MRI lesions, and BVL), PROs, and healthcare costs/resource use, which likely reflect a more general deficiency in the field of MS research. As of the cut-off date for this SR, to the best of our knowledge, most studies presented relapse, disability, and MRI data as separate outcomes. Only a small proportion of studies assessed DMTs according to combined measures, although none included BVL in this assessment [29-31, 43, 45-49, 51]. Combined measures of disease activity that assess relapses, disability, MRI lesions, and BVL can indicate the overall effectiveness of DMTs in helping patients achieve no evidence of disease activity (NEDA) status [55]. The limited focus on combined measures of disease activity may reflect the lack of available data for all disease outcomes in RWD sources, or the fact that BVL is not routinely assessed in clinical practice and MRI data are not typically included in real-world databases [3, 55, 65]. Developments in methodology to assess BVL, evolution of databases, and recognition of the value of combined measures to evaluate focal and diffuse damage may increase the use of NEDA assessment in clinical practice [3, 55]. The patient voice is also under-reported in the real world, despite there being several disease-specific PRO instruments for MS [2, 66]. In line with this, only two studies included in this SR assessed PROs, one of which measured outcomes after 3 months of fingolimod treatment [39, 51]. PROs are increasingly recognized as an important measure when assessing treatments, given the impact of patients' perceptions of treatment on their persistence with and adherence to DMTs; these in turn can influence relapse risk, healthcare resource use and quality of life [2, 27]. Finally, only one study reported on healthcare resource use associated with fingolimod compared with natalizumab treatment [24], and none of the included studies reported on direct healthcare costs. These outcomes, which are often not assessed in RCTs, are important for healthcare decision-makers and deserve more attention. An ongoing
German study is investigating PROs and healthcare costs associated with fingolimod, and it is therefore likely that new data will become available to address some of these evidence gaps for fingolimod [67].

5. Conclusions

The present SR provides a comprehensive insight into the RWD available for fingolimod. It also highlights the diversity of methodologies being adopted to improve our understanding of MS and the impact of DMTs in the real world, as well as the challenges of conducting these studies. Although the included studies provide good evidence of the effectiveness of fingolimod in clinical practice, they also emphasize the gaps in the evidence base for this treatment, which likely reflect a more general deficiency in the field of MS research. Future research should address these gaps in the evidence base in order to provide a more balanced and complete view of treatment benefit and disease progression. Furthermore, the challenges associated with researching MS should be accounted for when designing real-world studies, and reliable methodology should be used in order to generate robust results. Finally, the heterogeneity that is intrinsic to real-world studies, which can impact on outcomes, should be considered when assessing RWD and comparing DMTs in clinical practice, both within and across studies. SRs, as performed for fingolimod in the present study, should be part of the standard protocol when assessing the benefit profile of treatments in the real-world studies.

6. Disclosures

Competing interests

TZ has received speaking honoraria and travel expenses for scientific meetings and has been a steering committee member of clinical trials or participated in advisory
boards of clinical trials with Almirall, Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis and Teva Pharmaceuticals. JM is a paid employee of Novartis Pharma AG. CA-MC and CRM are paid employees of Oxford PharmaGenesis, which was paid by Novartis Pharma AG.

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**Author contributions**

All authors were involved in the design of the study. CRM was responsible for the first draft of the protocol, which was critically reviewed, further developed and approved by all authors. CA-MC and CRM performed the literature search, collected and extracted the data, and performed the quality assessment of included published papers. CA-MC drafted all stages the manuscript. All authors contributed to data interpretation, critically reviewed all manuscript versions and approved the final version.

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Table and Figure

Fig. 1. PRISMA diagram of included and excluded studies. Searches were conducted on 4 March 2016. Data were extracted only from the 34 published papers.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Table 1. Eligibility criteria used in the assessment of studies.

| Inclusion                                                                 | Exclusion                                      |
|---------------------------------------------------------------------------|-----------------------------------------------|
| **Population**                                                            | **Exclusion**                                 |
| • Adult human patients with multiple sclerosis                             | • Animal/in vitro studies                     |
| • Pediatric patients                                                       | • Pediatric patients                          |
| **Interventions**                                                         | **Interventions**                             |
| • Fingolimod/Gilenya/FTY720                                               | • Studies not including fingolimod           |
| **Study design**                                                          | **Study design**                              |
| • Observational or non-randomized interventional studies                  | • General reviews                             |
| • Cross-sectional surveys                                                 | • Systematic reviews and meta-analyses (tagged so bibliographies could be interrogated) |
| • Cohort studies                                                          | • RCTs including phase 1, 2, and 3           |
| • Case-control studies                                                    | • Case series reports                         |
| • Before and after studies                                                | • Case reports                                |
| • Pharmacy/claims databases                                               | • Editorials, commentaries, and letters       |
| • Pharmaceutical company databases                                        | • Pre-clinical and phase 1 studies            |
| • Electronic registers or electronic medical/health records               | • Pilot data                                  |
| • Insurance/administrative claims database studies                        | • Prognostic studies                          |
| • Registry studies                                                        | • Pharmacodynamic studies                     |
| • Questionnaires                                                          | • Pooled or post hoc analyses and secondary analyses of previously reported data |
| • Prospective/retrospective studies                                       | • Economic evaluations                        |
| • Longitudinal/follow-up studies                                          |                                               |
| • Consensus group reports (Delphi panel)                                  |                                               |
| **Outcomes**                                                              | **Outcomes**                                  |
| • Relapse rate                                                            | • Cost-effectiveness                          |
| • Disability progression/improvement                                      | • Indirect costs                              |
| • MRI outcomes (including brain volume loss)                              |                                               |
| • Persistence                                                             |                                               |
| • Discontinuation                                                         |                                               |
| • Adherence                                                               |                                               |
| • Healthcare costs                                                        |                                               |
| • Healthcare resource use                                                 |                                               |
| • Treatment patterns                                                      |                                               |
| • Patient-reported outcomes                                               |                                               |
| **Publication**                                                           | **Publication**                               |
| • English language                                                       | • Non-English language                        |

MRI = magnetic resonance imaging; RCT = randomized controlled trial.
Appendix A

**Fig. A1.** Number of real-world studies, categorized by country from which data were collected. Studies included in the international category used real-world data generated in more than one country.
Fig. A2. Characteristics of A) fingolimod single-arm studies; B) fingolimod versus IFN/GA studies; C) fingolimod versus natalizumab studies. Studies that present data for more than one treatment are presented separately in each graph. aDoes not include seven studies for which the type of observational study was not specified and which contained insufficient methodological information to categorize them as being retrospective or prospective.
**Table A.1.** Electronic search strings used in database searches.

**Embase**

| #  | Searches                                                                 |
|----|--------------------------------------------------------------------------|
| 1  | fingolimod.mp. or exp fingolimod/                                        |
| 2  | gilenya.mp.                                                              |
| 3  | FTY720.mp.                                                               |
| 4  | 1 or 2 or 3                                                              |
| 5  | multiple sclerosis.mp. or exp multiple sclerosis/                         |
| 6  | 4 and 5                                                                  |
| 7  | (registry or register$).mp.                                              |
| 8  | (real world or RWE).mp.                                                  |
| 9  | observational.mp.                                                        |
| 10 | exp Observational Study/                                                 |
| 11 | exp Prospective Studies/                                                 |
| 12 | exp Longitudinal Studies/ or longitudinal.mp.                            |
| 13 | exp Retrospective Studies/                                               |
| 14 | patient record.mp. or exp Medical Records/                               |
| 15 | (electronic health record$ or EHR).mp.                                  |
| 16 | (electronic medical record$ or EMR).mp.                                 |
| 17 | (dataset$ or data set$).mp.                                              |
| 18 | database.mp.                                                             |
| 19 | (administrat* adj3 claim).mp.                                            |
| 20 | clinical practice.mp. or exp clinical practice/                          |
| 21 | Non-interventional.mp.                                                   |
| 22 | Real-life.mp.                                                            |
| 23 | 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 |
| 24 | 6 and 23                                                                 |
Medline

# Searches
1 fingolimod.mp.
2 Gilenya.mp.
3 FTY720.mp.
4 1 or 2 or 3
5 multiple sclerosis.mp. or exp multiple sclerosis/
6 exp Multiple Sclerosis, Relapsing--Remitting/
7 5 or 6
8 4 and 7
9 (registry or register$).mp.
10 exp Registries/
11 (real world or RWE).mp.
12 observational.mp.
13 exp Observational Study/
14 exp Longitudinal Studies/ or longitudinal.mp.
15 exp Retrospective Studies/
16 patient record.mp. or exp Medical Records/
17 (electronic health record$ or EHR).mp.
18 (electronic medical record$ or EMR).mp.
19 (dataset$ or data set$).mp.
20 database.mp.
21 (administrat* adj3 claim).mp.
22 clinical practice.mp.
23 Non-interventional.mp.
24 Real-life.mp.
25 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 8 and 25
Cochrane Library

# Searches
1 fingolimod.mp.
2 Gilenya.mp.
3 FTY720.mp.
4 1 or 2 or 3
5 multiple sclerosis.mp. or exp multiple sclerosis/
6 exp Multiple Sclerosis, Relapsing--Remitting/
7 5 or 6
8 4 and 7
9 (registry or register$).mp.
10 exp Registries/
11 (real world or RWE).mp.
12 observational.mp.
13 exp Observational Study/
14 exp Longitudinal Studies/ or longitudinal.mp.
15 exp Retrospective Studies/
16 patient record.mp. or exp Medical Records/
17 (electronic health record$ or EHR).mp.
18 (electronic medical record$ or EMR).mp.
19 (dataset$ or data set$).mp.
20 database.mp.
21 (administrat* adj3 claim).mp.
22 clinical practice.mp.
23 Non-interventional.mp.
24 Real-life.mp.
25 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26 8 and 25
Table A.2. Key outcomes of interest.

| Relapse rate          |                                                                 |
|-----------------------|------------------------------------------------------------------|
| ARR (over a time interval) | Proportion of patients with/without a relapse                  |
| Time to first relapse or inflammatory event | |

| Disability progression and improvement |                                                                 |
|----------------------------------------|------------------------------------------------------------------|
| Proportion of patients with/without disability progression/improvement (3-month and 6-month) based on EDSS score | |
| Change from baseline (to a set time point) in EDSS score | |
| Time to 3-month or 6-month confirmed disability progression/improvement | |

| Magnetic resonance imaging outcomes |                                                                 |
|------------------------------------|------------------------------------------------------------------|
| Mean number of T2-weighted lesion outcomes | |
| Mean number of gadolinium-enhancing T1-weighted lesions | |
| Percentage change in brain volume | |

| Persistence/discontinuation |                                                                 |
|-----------------------------|------------------------------------------------------------------|
| Proportion of patients who discontinued study or treatment (and reasons) | |
| Proportion of patients persistent with treatment | |
| Time to treatment discontinuation | |
| Number of persistent days | |

| Adherence |                                                                 |
|-----------|------------------------------------------------------------------|
| Proportion of patients who were adherent/non-adherent to study treatment | |
| Time to treatment non-adherence | |

| Healthcare costs |                                                                 |
|------------------|------------------------------------------------------------------|
| Medication costs | Hospital costs and length of stay                               |
| Physician visits and medical tests | |
| Nursing costs | Cost estimates for adverse events | |

| Healthcare resource use |                                                                 |
|-------------------------|------------------------------------------------------------------|
| Proportion of patients with resource use (inpatient stays, emergency department visits, etc.) | |
| Days’ supply of medication | |

| Treatment patterns |                                                                 |
|--------------------|------------------------------------------------------------------|

| Patient-reported outcomes |                                                                 |
|---------------------------|------------------------------------------------------------------|
| General HRQoL             | Disease-specific HRQoL                                           |
| Functional status         | Cognitive functioning                                            |
| Fatigue status            |                                                                  |

ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life.
Table A.3. Overview of study characteristics of included studies.

| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|-------------|------------------------|------------|----------------|---------------------|
| Agashivala et al., 2013 [20] USA | Retrospective analysis of pharmacy claims data in patients initiating DMTs | Medco Health Solutions administrative claims database covering over 60 million lives in the USA | IFN/GA | Fingolimod, N = 248 IFN, N = 936 GA, N = 707 | 12 months |
| Al-Hashel et al., 2014 [21] Kuwait | Retrospective analysis of registry data in patients with RRMS initiating fingolimod | National MS Registry in Kuwait using data from three major hospitals | Baseline | Fingolimod, N = 175 | 21.7 months (mean treatment duration) |
| Alroughani et al., 2014 [22] Kuwait | Retrospective analysis of registry data in patients with RRMS initiating fingolimod | Three MS registries in Kuwait | Baseline | Fingolimod, N = 76 | 18.5 months (mean treatment duration) |
| Baldi et al., 2014 [23] Italy | Observational study of clinical/MRI records in patients with RRMS switching from natalizumab/IFN/GA/other to fingolimod | Six MS centers in Northern Italy | Baseline therapy (IFN/GA/natalizumab/other) | Fingolimod, N = 127 (previous therapy: IFN/GA, n = 68 [IFN, n = 51; GA, n = 17]; natalizumab, n = 39; other, n = 4; no treatment for ≥ 1 year, n = 16) | 10 months (mean) |
| Barbin et al., 2016 [42] France | Retrospective analysis of prospectively collected data from patients with RRMS initiating either fingolimod or natalizumab | Twenty-seven French university hospitals involved in the Observatoire of MS. Data were extracted from the European Database for MS software (EDMUS) | Natalizumab | Fingolimod, N = 303 Natalizumab, N = 326 | 12 and 24 months |
| Bergvall et al., 2013 [25] USA | Retrospective analysis of administrative claims data in patients with MS and a history of relapses | US PharMetrics Plus administrative claims database covering over 87 million lives | IFN/GA (also considered as separate treatment cohorts) | Fingolimod, N = 128 IFN/GA, N = 397 (IFN, n = 200; GA, n = 197) | 18 months (mean) |
| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|--------------|------------------------|------------|----------------|-------------------|
| Bergvall et al., 2014 [26] USA | Retrospective analysis of administrative claims data in patients with MS switching from IFN to fingolimod or GA | US PharMetrics Plus administrative claims database covering over 87 million lives | GA | Propensity score-matched cohorts Fingolimod, N = 132 GA, N = 132 | 12 months |
| Bergvall et al., 2014 [24] USA | Retrospective analysis of administrative claims data in patients switching from previous DMTs to fingolimod or natalizumab | US PharMetrics Plus administrative claims database covering over 87 million lives | Natalizumab | Propensity score-matched cohorts Fingolimod, N = 185 Natalizumab, N = 185 | 12 months |
| Bergvall et al., 2014 [27] USA | Retrospective analysis of administrative claims data in patients receiving fingolimod, IFN, GA, or natalizumab | US PharMetrics Plus administrative claims database covering over 87 million lives | IFN, GA, natalizumab | Fingolimod, N = 889 GA, N = 1233 IFN, N = 1341 Natalizumab, N = 287 | 12 months |
| Bianco et al., 2015 [28] Italy | Prospective observational analysis of patients with RRMS receiving fingolimod | MS center of the Catholic University of Rome | Baseline (no exposure or prior exposure to natalizumab) | N = 71 (prior natalizumab exposure, n = 26; no prior natalizumab exposure, n = 45) | 21.8 months (mean) |
| Braune et al., 2016 [43] Germany | Observational cohort study of health data routinely collected patient data in those with RRMS switching from an injectable therapy to fingolimod or another injectable therapy owing to treatment failure on the previous DMT | Outpatient neurology practices in Germany that are part of the NeuroTransData network | IFN/GA | Propensity score-matched cohorts Fingolimod, N = 99 IFN/GA, N = 99 | 833.5 days in the fingolimod cohort; 1242.3 days in the IFN/GA cohort (mean) |
| Braune et al., 2013 [29] Germany | Observational analysis of patient data in patients with RRMS switching to fingolimod or natalizumab owing to failure of first-line therapy | Clinics within the NeuroTransConcept network in Germany | Natalizumab | Fingolimod, N = 190 Natalizumab, N = 237 | 12 months |
| Capobianco et al., 2015 [30] Italy | Retrospective analysis of patients with RRMS switching to another therapy or receiving no therapy after discontinuing natalizumab | Regional MS center in Italy | Immunomodulatory or other first-line therapy, no therapy | Fingolimod, N = 35 (immunomodulatory/other first-line therapy, n = 19; no therapy, n = 24) | 1–12 months |
| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|-------------|------------------------|------------|---------------|-------------------|
| Carruthers et al., 2014 [31] USA | Retrospective analysis of patients with RRMS initiating either fingolimod or natalizumab depending on JCV serology | Oracle database at Partners MS Center, Harvard, USA | N = 36 | Natalizumab, N = 69 | 18 months (mean) |
| Cohen et al., 2014 [32] France | Prospective, multicenter study of data collected as part of the ENIGM study in patients with MS switching from natalizumab to fingolimod | 36 tertiary MS referral centers in France | Washout period after natalizumab discontinuation | N = 333 | 6 months |
| Correia et al., 2016 [44] Portugal | Retrospective study of data from patients with RRMS receiving fingolimod for at least 6 months | Neurology department at a Portuguese university hospital | Baseline in patients who failed first-line DMT (IFN/GA), failed immunosuppressive treatments, switched from natalizumab as a second-line treatment or were treatment- naïve | Fingolimod, N = 104 (previous treatment: first-line DMT, n = 56; second-line natalizumab, n = 41; treatment-naïve, n = 7) | 21.4 months (mean treatment duration) |
| Fragoso et al., 2014 [33] Brazil | Retrospective analysis of patients with MS after their initial dose of fingolimod | MS units in Brazil | Baseline | N = 180 | Minimum follow-up 6 hours, maximum not reported |
| Frisell et al., 2016 [53] Sweden | Analysis of patients enrolled in the Immunomodulation and MS Epidemiology Study (IMSE) who initiated treatment with natalizumab or fingolimod | Swedish MS register, although participation is voluntary, overall coverage is estimated to be 80% | Natalizumab | Fingolimod, N = 876; Natalizumab, N = 640 | 12 months |
| Gajofatto et al., 2014 [34] Italy | Retrospective analysis of patients with RRMS receiving fingolimod or natalizumab | Italian health authority registries for fingolimod and natalizumab, and chart data from two neurology units at the university hospital in Italy | Natalizumab | Fingolimod, N = 30; Natalizumab, N = 57 | 25 months (mean) |
| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|-------------|------------------------|------------|---------------|-------------------|
| He et al., 2015 [35] international | Retrospective analysis of patients with MS switching from IFN/GA to another IFN/GA preparation or fingolimod | MSBase international patient registry (as of April 2016, contains data from 71 countries and > 30,000 patients with MS) [68] | IFN/GA | Propensity score-matched cohorts | 13.1 months (median) |
| Hersh et al., 2015 [51] USA | Analysis of electronic medical records of patients who were prescribed fingolimod at the Mellen Center. Most patients had RRMS and had received at least one other DMT | Electronic medical records of patients at the Mellen Center | Patients continuing with fingolimod vs those discontinuing fingolimod | Whole cohort, N = 306 (with follow-up data) (remained on fingolimod, n = 230; discontinued fingolimod, n = 76) | 12 months |
| Hoepner et al., 2014 [36] Germany | Retrospective analysis of patients with RRMS switching from natalizumab to fingolimod | Three university-based tertiary referral MS centers in Germany | Baseline after natalizumab discontinuation | N = 33 | 81.1 weeks (mean) |
| Iaffaldano et al., 2015 [52] Italy | Observational, prospectively acquired cohort study | Longitudinal data from 45 Italian MS centers that are part of the iMedWeb registry | IFN/GA in patients discontinuing natalizumab (after at least 6 infusions) | Propensity score-matched cohorts | Not defined |
| Jokubaitis et al., 2014 [37] international | Retrospective analysis of patients with MS initiating fingolimod | MSBase international patient registry (as of April 2016, contains data from 71 countries and > 30,000 patients with MS) [68] | Baseline when patients switched from natalizumab or IFN/GA or were treatment-naïve | N = 536 (natalizumab, n = 89; IFN/GA, n = 350; treatment-naïve, n = 97) | 10 months (median) |
| Kalincik et al., 2015 [38] international | Observational, prospective study of patients with RRMS switching to natalizumab or fingolimod after experiencing recent disease activity on injectable DMTs | MSBase international patient registry (as of April 2016, contains data from 71 countries and > 30,000 patients with MS) [68] | Natalizumab | Propensity score-matched cohorts | 12 months (mean) |
| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|-------------|------------------------|------------|---------------|---------------------|
| Lo Re et al., 2015 [45] Italy | Study of patients with RRMS who initiated other treatment, restarted natalizumab, or were untreated after discontinuing natalizumab | Electronic databases and clinical records from two Italian MS referral centers (Orbassano and Palermo) | First-line therapies (IFN-beta/GA/teriflunomide, azathioprine), restarted natalizumab, rituximab, immunosuppressive agents (cyclophosphamide, mitoxantrone), AHSCT or no therapy | Therapy-free, $N = 37$  
Natalizumab, $N = 9$  
Fingolimod, $N = 57$  
First-line therapies, $N = 16$  
Immunosuppressive treatment, $N = 4$  
Rituximab, $N = 7$  
AHSCT, $N = 2$ | 12 months |
| Ontaneda et al., 2012 [39] USA | Retrospective analysis of patients with MS initiating fingolimod | Electronic medical records from an academic MS center in the USA | Baseline | Patients with follow-up data, $N = 307$  
(natalizumab, $n = 36$; IFN/GA, $n = 271$) | 3.2 months (mean) |
| Ramseier et al., 2015 [40] Switzerland | Retrospective, observational analysis of patients with RRMS initiating fingolimod | One hospital-based MS center and two private practices in Switzerland | Baseline | $N = 136$ | 6.8 months (mean) |
| Rasenack et al., 2016 [46] Switzerland | Retrospective, non-randomized, open-label, observational study in patients with RRMS who initiated fingolimod treatment | Patient records from one MS center | Baseline | $N = 105$ | 12 months |
| Sempere et al., 2013 [41] Spain | Observational study of patients with RRMS who switched from natalizumab to fingolimod if JCV positive or remained on natalizumab if JCV negative | University hospital MS unit in Spain | Natalizumab | Fingolimod, $N = 8$  
Natalizumab, $N = 9$ | Fingolimod, 9 months (mean); natalizumab, 13 months (mean) |
| Totaro et al., 2015 [47] Italy | Study of patients with RRMS who initiated fingolimod or natalizumab | Four MS centers throughout Central and Southern Italy | Natalizumab | Fingolimod, $N = 194$  
Natalizumab, $N = 197$ | 12 months |
| Author, year, country | Study design | Source of patient data | Comparator | Size of cohort | Length of follow-up |
|-----------------------|-------------|------------------------|------------|---------------|---------------------|
| Totaro et al., 2015 [48] Italy | Prospective, observational, multicenter study of patients with RRMS initiating fingolimod treatment | Three MS centers throughout Central and Southern Italy | Baseline | $N = 142$ | 1–33 months (mean treatment duration: 14.95 months) |
| Warrender-Sparkes et al., 2015 [50] international | Prospective, observational study of patients with CIS, RRMS, or SPMS who initiated immunomodulatory treatment | MSBASIS (sub-study of the MSBase registry) | IFN-beta, GA, natalizumab | Fingolimod, $N = 45$ IFN-beta 1a IM, $N = 812$ IFN-beta 1a SC, $N = 792$ IFN-beta 1b, $N = 520$ GA, $N = 403$ Natalizumab, $N = 68$ | 4.8 years (median follow-up period) |
| Yamout et al., 2015 [49] Lebanon | Observational, retrospective review of chart data from a prospectively followed cohort of patients with RRMS initiating fingolimod treatment | MS center at the American University of Beirut Medical Center | Baseline | $N = 122$ ($n = 110$ available for efficacy analysis [received fingolimod for ≥ 6 months]) | 19.2 months (mean duration of fingolimod treatment) |

$^a$ Azathioprine, mitoxantrone, cyclophosphamide.

$^b$ IFN-beta, GA, azathioprine, or entered pregnancy status.

AHSC = autologous hematopoietic stem cell transplant; CIS = clinically isolated disease; DMT = disease-modifying therapy; ENIGM = Enquête Nationale sur l’Introduction du Fingolimod en Relais au Natalizumab; GA = glatiramer acetate; IFN = interferon; IM, intramuscular; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing–remitting multiple sclerosis; SC, subcutaneous; SPMS = secondary progressive MS.
Table A.4. Quality assessment of included published papers.

| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|--------------|------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **High-quality studies** | | | | | | | |
| Agashivala et al., 2013 [20] | Yes | Yes | No (differences in age, % female, % naïve to DMT between groups) | Yes | Yes | Yes | Yes, only for adjusted time to discontinuation (risk) |
| Barbin et al., 2016 [42] | Yes | Yes | No (differences in baseline EDSS score, number of relapses in the preceding year, MRI outcomes) | Yes | Yes | Yes | Yes; multivariate logistic regression and propensity score weighting |
| Bergvall et al., 2013 [25] | Yes | Yes | No (differences in previous use of non-index DMTs or dalfampridine, symptoms affecting ≥ 10% of patients, pre-index relapses and healthcare costs) | Yes | Yes | Yes | Yes; adjusted risk of relapse and the impact of individual variables on the number of relapses per year was also assessed |
| Bergvall et al., 2014 [26] | Yes | Yes | Yes | Yes | Yes | Yes | Yes, propensity score-matching and sensitivity analyses for some measures |
| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|-------------|---------------------------------------------|-----------------------------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------|-----------------------------------------------|
| Bergvall et al., 2014 [24] | Yes | Yes | Yes, with the exception of clinical global impression scale scores | Yes | Yes | Yes | Yes, propensity score matching |
| Bergvall et al., 2014 [27] | Yes | Yes | No (differences in median age, previous use of non-index DMT, previous use of dalfampridine, symptoms and comorbidities affecting ≥ 10% of patients, pre-index relapses and healthcare costs) | Yes | Yes | Yes | Yes, adjusted for baseline differences The impact of individual variables on the risk of discontinuation or non-adherence was also assessed |
| Braune et al., 2016 [43] | Yes | Yes | Yes, with the exception of follow-up time, which was significantly longer in the IFN/GA cohort | Yes | Yes, with the exception of differences in follow-up time | Yes | Yes, propensity score matching |
| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|-------------|---------------------------------------------|------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Braune et al., 2013 [29] | Yes (exclusion criteria not defined) | Yes | No (difference in EDSS score, relapses, but ARR did not differ significantly) | Yes, but relapses were not defined | Yes | Yes | Yes, adjusted linear regression analyses to assess correlation between baseline variables and outcomes Propensity score-matching also performed |
| He et al., 2015 [35] | Yes | Yes | Yes | Yes | Yes | Yes | Yes, propensity score-matching; potential bias from unknown confounders acknowledged |
| Iaffaldano et al, 2015 [52] | Yes | Yes | Yes | Yes | Yes | Unclear, length of follow-up not defined. For relapse analysis, 890.7 patient-years analyzed | Yes, propensity score matching |
| Jokubaitis et al., 2014 [37] | Yes | Yes | No (fingolimod stratified by pre-fingolimod treatment) | Yes | Yes, but follow-up time was not the same between cohorts | Yes | Yes, ARR adjusted for baseline covariates |
| Kalincik et al., 2015 [38] | Yes | Yes | Yes | Yes | Yes | Yes | Yes, propensity score-matching and sensitivity analysis (adjustment) |

Medium-quality studies
| Author, year                  | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|------------------------------|-----------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------|---------------------------------------------|-----------------------------------------------|------------------------------------------------|
| Al-Hashel et al., 2014 [21]  | Yes                                           | Yes                                                                      | NA (fingolimod cohort only)               | Yes                                            | NA                                          | Yes                                           | No, but the effects of some variables on response to fingolimod were considered for the risk of relapse and MRI activity |
| Alroughani et al., 2014 [22] | Yes                                           | Yes                                                                      | NA (fingolimod cohort only)               | Yes                                            | NA                                          | Yes                                           | No, but possibility of bias acknowledged |
| Bianco et al., 2015 [28]     | Yes                                           | Yes                                                                      | NA (fingolimod cohort only)               | Yes                                            | NA                                          | Yes                                           | No, but the impact of some variables on ARR in the fingolimod cohort were considered; outcomes were also assessed in patient cohorts stratified by previous exposure to natalizumab |
| Carruthers et al., 2014 [31] | Yes                                           | No                                                                       | Yes, but fingolimod cohort was JCV positive and natalizumab cohort was JCV negative | Yes                                            | Yes                                          | Yes                                           | Yes, adjusted potential confounding variables for time to next relapse or time to next relapse/MRI |
| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|--------------|---------------------------------------------|---------------------------------------------------------------|--------------------------------------------|-------------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------------------------------------------|
| Cohen et al., 2014 [32] | Yes | Yes | NA (fingolimod cohort only) | Not described in the published paper | NA | Yes | No, but statistical analyses assessed variables correlated with a relapse during fingolimod treatment |
| Correia et al., 2016 [44] | Yes | No | NA (fingolimod cohort only) | Yes | NA | Yes | No |
| Frisell et al., 2016 [53] | Yes | Yes | No (differences in age, % male, MS Severity Score, Symbol Digit Modalities Test and MS Impact Scale) | Not defined | Not described | Yes | Yes, covariate-adjusted drug survival sensitivity analysis |
| Gajofatto et al., 2014 [34] | Yes | No | No (relapses, EDSS) | Yes | Yes, but states in Discussion that MRI protocol was not standardized | Yes | Yes, risk of relapse and MRI outcomes adjusted for baseline factors |
| Hersh et al., 2015 [51] | No | No | NA (for fingolimod cohort only); for remained vs discontinued fingolimod cohorts baseline characteristics not described | Yes | Yes | Yes | No |
| Hoepner et al., 2014 [36] | Yes | No | NA (fingolimod cohort only) | Not defined | NA | Yes | No, but predictors of relapse activity assessed |
| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|--------------|-----------------------------------------------|-----------------------------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Lo Re et al., 2015 [45] | Yes                                           | No                                                             | Not described                            | Yes                                           | Yes                                           | Yes                                           | No                                           |
| Ontaneda et al., 2012 [39] | Yes                                           | Yes                                                           | NA (fingolimod cohort only)              | Yes                                           | NA                                           | No                                           | No                                           |
| Ramseier et al., 2015 [40] | Yes                                           | Yes                                                           | NA (fingolimod cohort only)              | NA                                           | NA                                           | Yes                                           | No, but only persistence was assessed as an effectiveness outcome |
| Rasenack et al., 2016 [46] | Yes                                           | No                                                             | NA (fingolimod cohort only)              | Yes                                           | Yes                                           | Yes                                           | No                                           |
| Totaro et al., 2015 [47] | Yes                                           | No                                                             | NA (fingolimod cohort only)              | Yes                                           | Yes                                           | Yes                                           | No                                           |
| Totaro et al., 2015 [48] | Yes                                           | No                                                             | NA (fingolimod cohort only)              | NA                                           | No, for some patients                         | Yes                                           | No                                           |
| Warrender-Sparkes et al., 2015 [50] | Yes                                           | No                                                             | NA (fingolimod cohort only)              | Yes                                           | Yes                                           | Yes                                           | No                                           |
| Yamout et al., 2015 [49] | Yes                                           | No                                                             | NA (fingolimod cohort only)              | Yes                                           | NA                                           | Yes                                           | No                                           |

**Low-quality studies**

| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|--------------|-----------------------------------------------|-----------------------------------------------------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Baldi et al., 2014 [23] | No (exclusion not defined)                   | Yes                                                           | NA (for fingolimod only cohort); no when stratified according to DMT in the pre-fingolimod period | Not defined                                  | Not defined                                  | Yes                                           | No, but the effect of some variables was considered on the risk of relapse and MRI activity Possibility of bias was acknowledged |

**Notes:**

- **Yes** indicates the criteria were satisfied.
- **No** indicates the criteria were not satisfied.
- **Not described** indicates the criteria were not described in the study.
- **Not defined** indicates the criteria were not defined in the study.
- **NA** indicates the criteria were not applicable or not available.
| Author, year | Were the inclusion/exclusion criteria defined? | Was the study based on a representative sample from a relevant population? | Were treatment cohorts similar at baseline? | Were outcomes assessed using objective criteria? | Were cohorts assessed in an equivalent manner? | Was follow-up long enough to assess outcomes? | Were sources of bias/confounding accounted for? |
|-------------|---------------------------------------------|-------------------------------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Capobianco et al., 2015 [30] | Yes | No | Yes, as stated in published paper but no data are presented | Not described | Not described | Unclear; follow-up specified as being between 1 and 12 months | No |
| Fragoso et al., 2014 [33] | No | Yes | NA (fingolimod cohort only) | Not described in the published paper | NA | Unclear; follow-up not specified | No, but only persistence assessed as an effectiveness outcome |
| Sempere et al., 2013 [41] | Yes | No | No | Yes | No, different follow-up time in cohorts | Yes | No |

ARR = annualized relapse rate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; JCV = John Cunningham virus; MRI = magnetic resonance imaging; NA = not applicable.
Table A.5. Summary of relapse outcomes.

| Author, year | Comparator | Definition of relapse | Relapse outcomes | Length of follow-up |
|--------------|------------|-----------------------|------------------|---------------------|
| Al-Hashel et al., 2014 [21] | Baseline | Occurrence, recurrence, or worsening of symptoms of neurological dysfunction lasting more than 24 hours and usually ending with a partial or complete remission | Proportion relapse-free: baseline, 32.6%; follow-up, 86.3% ($p < 0.001$) | 21.7 months (mean treatment duration) |
| Alroughani et al., 2014 [22] | Baseline | New or recurrent neurological symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurological signs | Proportion relapse-free: baseline, 13.2%; at last follow-up, 77.6% ($p < 0.0001$) | 18.5 months (mean treatment duration) |
| Baldi et al., 2014 [23] | Baseline therapy (natalizumab/IFN/GA/other) | Not defined | Previous treatment with natalizumab associated with an increased risk for relapse 30.7% patients receiving fingolimod had a relapse at follow-up | 10 months (mean) |
| Barbin et al., 2016 [42] | Natalizumab (and baseline) | New or recurrent exacerbation of neurological symptoms without fever that lasted for at least 24 hours | Proportion with at least one relapse in matched cohorts Fingolimod: baseline, 76.9%; year 1, 27.1% ($p < 0.0001$); year 2, 37.9% ($p < 0.0001$) Proportion with a relapse, fingolimod vs natalizumab Unadjusted: similar in the fingolimod and natalizumab cohorts at year 1 ($p = NS$) and year 2 ($p = NS$) Adjusted (multivariate logistics regression): higher activity in the fingolimod vs natalizumab cohort at year 1 ($p = 0.0314$) and year 2 ($p = 0.0419$) Adjusted (propensity score weighting): higher activity in the fingolimod vs natalizumab cohort at year 1 ($p = 0.0092$) and year 2 ($p = 0.0059$) | 1 year and 2 years |
| Author, year          | Comparator         | Definition of relapse                                                                 | Relapse outcomes                                                                 | Length of follow-up |
|----------------------|-------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------|
| Bergvall et al.,     | IFN/GA (also      | Algorithm using diagnosis codes and claims that has been shown to correlate with the occurrence of clinical relapses | Proportion experiencing relapses: fingolimod, 31.3%; IFN/GA, 34.0% (p = NS)     | 18 months           |
| 2013 [25]            | considered as     |                                                                                      | ARR: fingolimod, 0.50; IFN/GA, 0.55; 50% reduction in ARR for fingolimod vs IFN/GA (p = 0.0006) |                     |
|                      | separate treatment cohorts) |                                                                                      | 52% reduced probability of having a relapse with fingolimod vs IFN/GA (OR, 0.48; 95% CI 0.28–0.84; p = 0.0097) |                     |
|                      |                   |                                                                                      | 52% reduced probability of having a relapse with fingolimod vs IFN/GA (OR, 0.48; 95% CI 0.28–0.84; p = 0.0097) |                     |
|                      |                   |                                                                                      | ARR: fingolimod, 0.19; GA, 0.51; 62% fewer relapses per year with fingolimod vs GA (p = 0.0013) | 12 months           |
|                      |                   |                                                                                      | 59% lower probability of experiencing relapse with fingolimod vs GA (p = 0.0091) |                     |
|                      |                   |                                                                                      | Longer time to first relapse with fingolimod (360 days) vs GA (274 days) |                     |
|                     | GA                | Algorithm using diagnosis codes and claims that have been shown to correlate with the occurrence of clinical relapses | Proportion relapse-free: fingolimod, 68.1%; natalizumab, 68.6% (p = NS) | 12 months           |
|                      | Natalizumab       | Algorithm using diagnosis codes and claims that have been shown to correlate with the occurrence of clinical relapses | Proportion relapse-free: fingolimod, 68.1%; natalizumab, 68.6% (p = NS) | 12 months           |
|                      | Baseline (no or   | Clinical examination and assessment of EDSS score                                    | 42.2% of patients in the fingolimod cohort had relapses                           | 21.8 months (mean)  |
|                      | prior exposure to natalizumab) |                                                                                      | ARR during fingolimod treatment: all patients, 0.66; patients exposed to natalizumab, 1.15; patients not exposed to natalizumab, 0.38 |                     |
| Bianco et al.,       | IFN/GA            | Not defined                                                                          | ARR: fingolimod, 0.21; IFN/GA, 0.33 (p = 0.0178); relapse rate ratio: 0.63       |                     |
| 2015 [28]            |                   |                                                                                      | 1.7-fold higher probability of having a relapse in the IFN/GA vs fingolimod cohort (p = 0.028) |                     |
|                      |                   |                                                                                      | Time to first relapse significantly longer in the fingolimod vs IFN/GA cohort (p = 0.026) |                     |
|                      |                   |                                                                                      | Fingolimod, 833.5 days; IFN/GA, 1242.3 days (mean) |                     |
|                      | Natalizumab       | Not defined                                                                          | Mean number of relapses at 12 months: fingolimod, 0.1; natalizumab, 0.06         | 12 months           |
|                      |                   |                                                                                      | Proportion relapse free: fingolimod, 75.79%; natalizumab, 71.73% (p = NS) |                     |
| Author, year, Comparator | Definition of relapse | Relapse outcomes | Length of follow-up |
|--------------------------|----------------------|------------------|--------------------|
| Capobianco et al., 2015 [30] | Immunomodulatory or other first-line therapy, no therapy | Clinical disease activity recurrence | Proportion with clinical relapses: fingolimod, 31.4%; other therapies, 41.8% | 1–12 months |
| Carruthers et al., 2014 [31] | Natalizumab | New neurological symptoms consistent with a demyelinating event, lasting more than 24 hours in the absence of fever or infection | 2.2-fold longer time to first relapse with natalizumab (HR, 2.20; 95% CI 0.87–5.55; p = NS) | 18 months (mean) |
| Cohen et al., 2014 [32] | Washout period after natalizumab discontinuation | Not defined | Proportion relapsing: washout period, 27%; fingolimod, 20% | 6 months |
| Correia et al., 2016 [44] | Baseline in patients who failed first-line DMT, switched from natalizumab, or were treatment-naive | Occurrence, recurrence, or worsening of symptoms of neurological dysfunction lasting more than 24 hours and usually ending with a partial or complete remission | ARR: 51.9% decrease in ARR from baseline (0.5 vs 1.04; p < 0.001) \[\text{Switching from first-line DMT: baseline, 1.43; fingolimod, 0.45 (p < 0.001)}\] \[\text{Switching from second-line natalizumab: baseline, 0.64; fingolimod, 0.41 (p = NS)}\] \[\text{Treatment-naïve: baseline, 1.57; fingolimod, 0.08 (p = 0.027)}\] | 21.4 months (mean treatment duration) |
| Gajofatto et al., 2014 [34] | Natalizumab | Subjective report of new neurological disturbances suggestive of demyelination backed up by objective findings and lasting at least 24 hours in the absence of infection of other conditions associated with an increase of body temperature | ARR: fingolimod, 0.3; natalizumab, 0.1 (p = NS) \[\text{67% reduced risk of relapse in the natalizumab vs fingolimod cohort (HR, 0.33; 95% CI 0.11–1.03; p = 0.056)}\] \[\text{Shorter time to first relapse in the natalizumab vs fingolimod cohort (p = 0.08)}\] | 25 months (mean) |
| He et al., 2015 [35] | IFN/GA | New symptoms or exacerbation of existing symptoms persisting for at least 24 hours in the absence of concurrent illness or fever and occurring at least 30 days after a previous relapse | ARR: fingolimod, 0.31; IFN/GA, 0.42 (p = 0.009) \[\text{26% lower risk of relapse with fingolimod vs IFN/GA cohort (HR, 0.74; 95% CI 0.56–0.98; p = 0.04)}\] | 13.1 months (median) |
| Hersh et al., 2015 [51] | Patients continuing with fingolimod vs those discontinuing fingolimod | New or worsening symptoms attributable to MS that lasted for at least 24 hours | Proportion relapse-free: whole cohort, 87.3%; remained on fingolimod cohort, 90.9%; discontinued fingolimod cohort, 76.3% | 12 months |
| Hoepner et al., 2014 [36] | Baseline after natalizumab discontinuation | Confirmed clinical deterioration of at least 24 hours’ duration; MRI to confirm relapse if necessary | Proportion relapsing: natalizumab discontinuation, 61%; fingolimod treatment, 48% | 81.1 weeks (mean) |
| Author, year | Comparator | Definition of relapse | Relapse outcomes | Length of follow-up |
|-------------|------------|----------------------|------------------|--------------------|
| Iaffaldano et al., 2015 [52] | IFN/GA in patients discontinuing natalizumab | Not defined | Propensity-score matched cohorts 48% reduction in risk of relapse in the fingolimod vs the IFN/GA cohort (IRR, 0.52; \( p < 0.0003 \)) Significantly lower probability of first relapse after treatment switch in the fingolimod vs IFN/GA cohort (\( p = 0.028 \)) | 890.7 person-years |
| Jokubaitis et al., 2014 [37] | Baseline when patients switched from natalizumab or IFN/GA or were treatment-naïve | New symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse | ARR: natalizumab to fingolimod group, 0.38; natalizumab pre-switch, 0.26 (\( p = 0.002 \)) Marked decrease in relapse rates after switching from IFN/GA to fingolimod | 10 months (median) |
| Kalincik et al., 2015 [38] | Natalizumab | New symptoms or exacerbation of existing symptoms persisting for at least 24 hours, in the absence of concurrent illness or fever, and occurring at least 30 days after a previous relapse Confirmation by EDSS not required | ARR: fingolimod, 0.40; natalizumab, 0.20 50% lower risk of relapse with natalizumab vs fingolimod (\( p = 0.002 \)) | 12 months (mean) |
| Lo Re et al., 2015 [45] | Therapy-free | Not defined | Compared with the therapy-free cohort, the risk of relapse was lower in patients receiving fingolimod (HR = 0.45) or restarting natalizumab (HR = 0.29) than in those receiving first-line therapies (HR = 1.6) | 12 months |
| Rasenack et al., 2016 [46] | Baseline | Standardized neurological examination using relapse assessment | Median ARR: baseline, 0.5; fingolimod, 0.0 (\( p < 0.005 \)) | 12 months |
| Sempere et al., 2013 [41] | Natalizumab | A neurological disturbance that was similar to the type observed in MS and lasted a minimum of 24 hours without a fever or an infection | 63% had clinical relapse on switch to fingolimod | Fingolimod, 9 months (mean) Natalizumab, 13 months (mean) |
| Totalaro et al., 2015 [47] | Natalizumab | Not defined | Cumulative proportion of patients free from clinical relapse: fingolimod, 81.3%; natalizumab, 82.5% (\( p = NS \)) ARR (baseline, 6 months, 12 months): fingolimod, 1.06, 0.3 (\( p < 0.001 \)), 0.23 (\( p < 0.001 \)) | 12 months |
**Table 1: Relapse Outcomes and Follow-up Length**

| Author, year | Comparator | Definition of relapse | Relapse outcomes | Length of follow-up |
|--------------|------------|-----------------------|------------------|---------------------|
| Totaro et al., 2015 [48] | Baseline | Clinical relapse | Proportion free from clinical relapse, 88.1\% ARR: baseline, 1.14; 6 months, 0.14; 1 year, 0.11; 2 years, 0.09 (\( p < 0.0001 \)) | 1–33 months |
| Yamout et al., 2015 [49] | Baseline | Occurrence of new, or worsening of previously stable, neurological symptoms suggestive of demyelination and supported by objective findings on physical examination, lasting at least 24 hours in the absence of infection or fever | ARR: pre-treatment, 1.16; post-treatment, 0.29 75\% relative risk reduction of ARR (\( p < 0.0001 \)) Proportion remaining relapse-free: pre-treatment, 21\%; post-treatment, 77.3\% (\( p < 0.0001 \)) | 19.2 months (mean treatment duration) |

*Other: interferon beta, glatiramer acetate, azathioprine or entered pregnancy status.

ARR = annualized relapse rate; CI = confidence interval; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; HR = hazard ratio; IRR, incidence rate ratio; MRI = magnetic resonance imaging; NS = not significant; OR = odds ratio.
Table A.6. Summary of disability outcomes.

| Author, year | Comparator | Disability outcomes | Length of follow-up |
|--------------|------------|---------------------|---------------------|
| Al-Hashel et al., 2014 [21] | Baseline | Mean EDSS score: baseline, 2.60 ± 1.44; fingolimod, 2.26 ± 1.49 (p = 0.03) | 21.7 months (mean treatment duration) |
| Alroughani et al., 2014 [22] | Baseline | Mean EDSS score: baseline, 2.93 ± 1.52; fingolimod, 1.95 ± 1.17 (p < 0.0001) | 18.5 months (mean treatment duration) |
| Baldi et al., 2014 [23] | Natalizumab/IFN/GA | Mean EDSS score unchanged: IFN/GA to fingolimod: unchanged Natalizumab to fingolimod: unchanged | 10 months (mean) |
| Barbin et al., 2016 [42] | Natalizumab (and baseline) | EDSS score: Fingolimod: baseline to year 1, 2.4 to 2.2 (p = 0.0228); baseline to year 2, 2.4 to 2.2 (p = NS) | 1 year and 2 years |
|                          |            | Proportion with disability progression, fingolimod vs natalizumab: Similar in the fingolimod and natalizumab cohorts at year 1 (p = NS) and year 2 (p = NS) in unadjusted and adjusted analysis (multivariate logistics regression and propensity score weighting) |           |
| Bianco et al., 2015 [28] | Baseline | Mean EDSS score: All groups, 2.46 ± 1.96 vs 2.30 ± 1.80 Exposed to natalizumab, 3.37 ± 1.98 vs 3.00 ± 1.60 Not exposed to natalizumab, 1.98 ± 1.80 vs 1.90 ± 1.70 Patients exposed to natalizumab had a significantly higher mean EDSS score after fingolimod treatment than the non-exposed patients (p = 0.005) | 21.8 months (mean) |
| Braune et al., 2016 [43] | IFN/GA | Proportion with disability progression: fingolimod, 15.1%; IFN/GA, 31.0% (p = 0.0231) Similar risk and time to EDSS progression in the fingolimod and IFN/GA cohorts (p = NS) | Fingolimod, 833.5 days; IFN/GA, 1242.3 days (mean) |
| Braune et al., 2013 [29] | Natalizumab | Proportion of patients with unchanged EDSS score: Fingolimod, 53.16%; natalizumab, 51.48% Improved EDSS score: fingolimod, 27.37%; natalizumab, 27.85% | 12 months |
| Author, year          | Comparator                                                                 | Disability outcomes                                                                                                                                                                                                 | Length of follow-up         |
|----------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Capobianco et al., 2015 [30] | Switch from natalizumab to fingolimod vs other therapy/no therapy          | No difference in mean EDSS score                                                                                                                                                                                   | 1–12 months                 |
| Correia et al., 2016 [44] | Baseline in patients who failed first-line DMT, switched from natalizumab or were treatment-naïve | Median EDSS score 20.0% decrease in EDSS from baseline (2.5 vs 2.0; \( p = \text{NS} \)) Switching from first-line DMT: baseline, 2.5; fingolimod, 2.0 \( (p = 0.015) \) Switching from second-line natalizumab: baseline, 2.5; fingolimod, 2.0 \( (p = \text{NS}) \) | 21.4 months (mean treatment duration) |
| Gajofatto et al., 2014 [34] | Natalizumab                                                                | No difference in mean EDSS score                                                                                                                                                                                   | 25 months (mean)            |
| He et al., 2015 [35] | IFN/GA                                                                     | 47% lower risk of disability progression with fingolimod vs IFN/GA (HR, 0.53; 95% CI 0.31–0.91; \( p = 0.02 \))                                                                                                                                                       | 13.1 months (median)        |
| Hoeper et al., 2014 [36] | Natalizumab switched to fingolimod                                          | EDSS score: fingolimod, 3.3; natalizumab, 3.0                                                                                                                                                                     | 81.1 weeks (mean)           |
| Iaffaldano et al., 2015 [52] | IFN/GA in patients discontinuing natalizumab                              | Proportion of patients with 3-month confirmed increase in EDSS of ≥ 1 point: fingolimod, 11.4%; IFN/GA, 22.5% \( (p = \text{NS}) \)                                                                                                                                  | Not defined                 |
| Kalincik et al., 2015 [38] | IFN or GA switched to fingolimod or natalizumab                            | No difference in proportion of patients free from 6-month sustained disability progression \( (p = 0.3) \) Proportion of patients with 6-month disability regression at 24 months: fingolimod, 11%; natalizumab, 20% \( (HR, 2.8, 95\% \text{CI}, 1.7–4.6; \ p < 0.001) \) | 12 months (mean)            |
| Rasenack et al., 2016 [46] | Baseline                                                                  | Proportion with stable/0.5-point improvement in EDSS score: baseline, 58.1%; fingolimod, 82.7%; \( p < 0.01 \)                                                                                                                                                       | 12 months                   |
| Sempere et al., 2013 [41] | Natalizumab                                                                | EDSS score: fingolimod, worsened in 3/8 patients; natalizumab, stable in 9/8 patients                                                                                                                                             | Fingolimod, 9 months (mean) |
| Totaro et al., 2015 [47] | Natalizumab                                                                | Proportion free from EDSS progression: fingolimod, 89.6%; natalizumab, 93.5% \( (p = \text{NS}) \)                                                                                                                                                        | 12 months                   |
| Totaro et al., 2015 [48] | Baseline                                                                  | Cumulative proportion free from confirmed EDSS progression: 69.0% Mean EDSS score: baseline, 2.7 ± 1.1; 18 months, 2.5 ± 1.1 \( (p = \text{NS}) \)                                                                 | 1–33 months                 |
| Author, year | Comparator | Disability outcomes | Length of follow-up |
|--------------|------------|---------------------|---------------------|
| Yamout et al., 2015 [49] | Baseline | Proportion remaining free from disability progression (at least 0.5-point increase in EDSS sustained for at least 3 months) at last visit: 80% | 19.2 months (mean treatment duration) |

Mean EDSS score: baseline, 2.3 ± 1.5; last visit, 1.9 ± 1.7 ($p = 0.001$)

CI = confidence interval; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon; NS = not significant.
Table A.7. Summary of MRI outcomes.

| Author, year         | Comparator                  | MRI outcomes                                                                 | Length of follow-up          |
|----------------------|-----------------------------|------------------------------------------------------------------------------|------------------------------|
| Al-Hashel et al., 2014 [21] | Baseline                    | Proportion with MRI activity at last follow-up: baseline, 77.7%; fingolimod, 18.3% (p < 0.001) | 21.7 months (mean treatment duration) |
| Alroughani et al., 2014 [22] | Baseline                    | Proportion with MRI activity at last follow-up: baseline, 77.6%; fingolimod, 17.1% (p < 0.0001) | 18.5 months (mean treatment duration) |
| Baldi et al., 2014 [23]   | Natalizumab/IFN/GA to fingolimod | Entire cohort Proportion with active MRI: baseline, 65.4%; fingolimod, 45.1% Proportion with Gd+ lesions: baseline, 31.5%; fingolimod, 16.9% IFN/GA to fingolimod cohort Proportion with active MRI: baseline, 72.0%; fingolimod, 41.0% Proportion with Gd+ lesions: baseline, 37.0%; fingolimod, 9.0% Natalizumab to fingolimod cohort Proportion with active MRI: baseline, 46.0%; fingolimod, 54.2% Proportion with Gd+ lesions: baseline, 18.0%; fingolimod, 33.3% | 10 months (mean) |
| Barbin et al., 2016 [42]   | Natalizumab (and baseline)  | Proportion with at least one Gd+ lesion Fingolimod: baseline to year 1, 42.0% to 21.0% (p = 0.0002); maintained over 2 years, 43.9% to 19.3% (p = 0.0001) Proportion with at least one Gd+ lesion, fingolimod vs natalizumab Higher activity in the fingolimod than the natalizumab cohort in unadjusted (year 1, p = 0.0007; year 2, p = 0.0130) and adjusted analysis (multivariate logistic regression: year 1, p = 0.0001; year 2, p = 0.0045; propensity score weighted: year 1, p < 0.0001; year 2, p = 0.0025) Proportion with at least one new T2 lesion, fingolimod vs natalizumab Higher activity in the fingolimod than the natalizumab cohort in unadjusted (year 1, p = 0.0115; year 2, p = 0.0341) and adjusted analysis (multivariate logistic regression: year 1, p = 0.0024; year 2, p = 0.0068; propensity score weighted: year 1, p < 0.0001; year 2, p = 0.0010) | 1 year and 2 years |
| Bianco et al., 2015 [28]  | Baseline                    | No significant difference between groups on MRI outcomes: no active T1 lesions, 78.9%; no new T2 lesions, 60.8% | 21.8 months (mean) |
| Author, year          | Comparator                                                                 | MRI outcomes                                                                                                                                                                                                 | Length of follow-up |
|-----------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| Gajofatto et al., 2014 [34] | Natalizumab                                                               | No significant difference between groups on MRI outcomes  
Proportion with new T2 lesions: fingolimod, 20%; natalizumab, 21%  | 25 months (mean) |
| Hersh et al., 2015 [51]      | Patients continuing with fingolimod vs those discontinuing fingolimod   | Proportion Gd+ lesion-free: whole cohort, 92.2%; remained on fingolimod cohort, 93.9%; discontinued fingolimod, 86.8% | 12 months |
| Lo Re et al., 2015 [45]       | First-line therapies (IFN/GA/teriflunomide, azathioprine), restarted natalizumab, rituximab, immunosuppressive agents (cyclophosphamide, mitoxantrone), AHSCT or no therapy | Proportion with radiological reactivation (new T2/FLAIR lesions and/or Gd+ lesions): therapy-free, 51.4%; restarted natalizumab, 0%; fingolimod, 23.6%; first-line therapies, 28.6%; immunosuppressive treatment, 33.3%; rituximab, 0%; AHSCT, 0% | 12 months |
| Rasenack et al., 2016 [46]    | Baseline                                                                  | Mean number of new/enlarged T2 lesions per scan: baseline, 1.02; fingolimod, 1.07 ($p = NS$)  
Mean number of Gd+ lesions: baseline, 0.26; fingolimod, 0.15 ($p = NS$)  | 12 months |
| Sempere et al., 2013 [41]     | Natalizumab                                                               | Proportion with MRI activity: fingolimod, 75%; natalizumab, 0%  | Fingolimod, 9 months (mean)  
Natalizumab, 13 months (mean)  |
| Totaro et al., 2015 [47]      | Natalizumab                                                               | Proportion free from MRI lesions: fingolimod, 70.0%; natalizumab, 87.5% ($p < 0.001$)  | 12 months |
| Totaro et al., 2015 [48]      | Baseline                                                                  | Cumulative proportion free from new/enlarged T2 lesions: 68.5%  
Cumulative proportion free from new Gd+ lesions: 81.7%  | 1–33 months (mean follow-up: 14.95 months) |
| Yamout et al., 2015 [49]      | Baseline                                                                  | Proportion with no new/enlarged T2 or Gd+ lesions during fingolimod therapy: 66.3%  
Proportion of patients with evidence of Gd+ lesions during fingolimod therapy: 17%  | 19.2 months (mean treatment duration) |

AHSCT, autologous hematopoietic stem cell transplant; GA = glatiramer acetate; Gd+ = gadolinium-enhancing; FLAIR = fluid-attenuated inversion recovery; IFN = interferon; MRI = magnetic resonance imaging.
Table A.8. Summary of persistence/adherence outcomes.

| Author, year | Comparator | Persistence/adherence outcomes reported | Length of follow-up |
|--------------|------------|----------------------------------------|---------------------|
| Agashivala et al., 2013 [20] | IFN or GA | Highest PDC and MPR scores with fingolimod in treatment-naïve and treatment-experienced patients | 12 months |
|                |            | Mean PDC scores: fingolimod, 0.80–0.83; IFN, 0.61–0.72; GA, 0.72–0.73 |                      |
|                |            | Mean MPR scores: fingolimod, 0.90–0.92; IFN, 0.82–0.88; GA, 0.89 |                      |
|                |            | Proportion persistent (< 60 days) with treatment: fingolimod, 68.8–74.3%; IFN, 42.9–55.3%; GA, 56.3–62.6% (p < 0.05 vs fingolimod for all) |                      |
|                |            | 1.5–2.8-fold lower risk of discontinuation in the fingolimod vs IFN/GA cohort (p < 0.05) |                      |
| Al-Hashel et al., 2014 [21] | Baseline | Proportion discontinuing fingolimod, 11.4% | 21.7 months (mean treatment duration) |
| Alroughani et al., 2014 [22] | Baseline | Proportion discontinuing fingolimod, 5.3% | 18.5 months (mean treatment duration) |
| Bergvall et al., 2013 [25] | IFN/GA | Proportion of patients persistent with treatment: fingolimod, 57.0%; IFN/GA, 45.1% (p = 0.0187) | 540 days |
| Bergvall et al., 2014 [26] | IFN to fingolimod or GA | Proportion persistent with treatment: fingolimod, 73.5%; GA, 62.9% (p = NS) | 12 months |
| Bergvall et al., 2014 [24] | IFN/GA to fingolimod or natalizumab | Proportion persistent with treatment: fingolimod, 71.9%; natalizumab, 76.2% | 12 months |
| Bergvall et al., 2014 [27] | GA or IFN or natalizumab | Proportion discontinuing treatment: fingolimod, 27.9%; GA, 39.5%; IFN, 43.7%; natalizumab, 39.5% | 12 months |
|                |            | 1.5–2.0-fold higher risk of discontinuing IFN/GA/natalizumab vs fingolimod (p < 0.0005) |                      |
|                |            | 1.9–2.3-fold higher risk of non-adherence (MPR < 80%) for IFN/GA/natalizumab vs fingolimod (p < 0.05) |                      |
|                |            | 1.4–1.8-fold higher risk of non-adherence (PDC < 80%) for IFN/GA/natalizumab vs fingolimod (p < 0.01 for IFN/GA; NS for natalizumab) |                      |
| Author, year | Comparator | Persistence/adherence outcomes reported | Length of follow-up |
|-------------|------------|----------------------------------------|----------------------|
| Bianco et al., 2015 [28] | Baseline | Proportion discontinuing fingolimod, 23.9% | 21.8 months (mean) |
| Braune et al., 2016 [43] | IFN/GA | Proportion persistent: fingolimod, 82.8%; IFN/GA, 47.5% (p < 0.0001)  
Proportion discontinuing: fingolimod, 12.1%; IFN/GA, 36.4% (p < 0.0001)  
Proportion switching to another therapy: fingolimod, 5.1%; IFN/GA, 16.2% (p < 0.0111)  
1.8-fold higher risk of medication discontinuation in the fingolimod vs IFN/GA cohort (p < 0.0001)  
Significantly longer time to treatment discontinuation in the fingolimod vs IFN/GA cohort (p < 0.0001) | Fingolimod, 833.5 days; IFN/GA, 1242.3 days (mean) |
| Carruthers et al., 2014 [31] | Natalizumab | Proportion discontinuing treatment: fingolimod, 22.2%; natalizumab, 36.2% | 18 months (mean) |
| Cohen et al., 2014 [32] | Washout period after natalizumab discontinuation | Proportion discontinuing fingolimod, 3.0% | 6 months |
| Correia et al., 2016 [44] | Baseline in patients who failed first-line DMT, switched from natalizumab or were treatment-naïve | Proportion discontinuing fingolimod, 10.6% | 21.4 months (mean treatment duration) |
| Fragoso et al., 2014 [33] | Baseline | Proportion discontinuing fingolimod, 99.4% | Not reported |
| Frisell et al., 2016 [53] | Natalizumab | Proportion on drug: fingolimod: 80%; natalizumab, 87% | 12 months |
| Gajofatto et al., 2014 [34] | Natalizumab | Proportion discontinuing treatment: fingolimod, 26.7%; natalizumab, 52.6% | 25 months (mean) |
| He et al., 2015 [35] | IFN/GA | Proportion discontinuing treatment at 24 months: fingolimod, 17.5%; IFN/GA, 26.8% (p = 0.04) | 13.1 months (median) |
| Hersh et al., 2015 [51] | Patients continuing with fingolimod vs those discontinuing fingolimod | Proportion discontinuing treatment fingolimod, 24.8% | 12 months |
| Kalincik et al., 2014 [38] | Natalizumab | Proportion discontinuing treatment: fingolimod, 31%; natalizumab, 27% (p = 0.9) | 24 months |
| Ontaneda et al., 2012 [39] | Baseline | Proportion discontinuing fingolimod, 9.5% | 3.2 months (mean) |
| Author, year                  | Comparator              | Persistence/adherence outcomes reported                                                                 | Length of follow-up |
|----------------------------|-------------------------|----------------------------------------------------------------------------------------------------------|---------------------|
| Ramseier et al., 2015 [40]  | Baseline                | Proportion remaining on fingolimod, 96%                                                                 | 6.8 months (mean)   |
| Rasenack et al., 2016 [46]  | Baseline                | Proportion stopping fingolimod: 6%                                                                      | 12 months           |
| Totaro et al., 2015 [48]    | Baseline                | Proportion stopping therapy: 9.1%                                                                      | 1–33 months         |
| Warrender-Sparkes et al.,   | IFN, GA, natalizumab    | Proportion discontinuing treatment after 1 year: fingolimod, 10.5%; GA, 22.6%; IFN-beta 1a IM, 18.9%; IFN-beta 1a SC, 19.7%; IFN-beta 1b, 21.0%; 21.2% natalizumab | 12 months           |
| Yamout et al., 2015 [49]    | Baseline                | Proportion permanently discontinuing fingolimod: 28.7%                                                | 19.2 months (mean treatment duration) |

DMT = disease-modifying therapy; GA = glatiramer acetate; IFN = interferon; IM = intramuscular; MPR = medication possession ratio, NS = not significant; PDC = proportion of days covered; SC = subcutaneous.