Journal of the Neurological Sciences 398 (2019) 163–170

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Real-world durability of relapse rate reduction in patients with multiple sclerosis receiving fingolimod for up to 3 years: a retrospective US claims database analysis

Edward Fox[a], Maria Cecilia Vieira[b], Kristen Johnson[b,*], Miranda Peeples[c], Arielle G. Bensimon[c], James Signorovitch[c], Vivian Herrera[b]

[a] Central Texas Neurology Consultants, 16040 Park Valley Dr., #B-100,Round Rock, TX, USA
[b] Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ, USA
[c] Analysis Group, Inc., 111 Huntington Ave, 14th Floor, Boston, MA, USA

ARTICLE INFO

Keywords:
Fingolimod
Multiple sclerosis
Real-world evidence
Relapse rates
Retrospective
Durability
Effectiveness

ABSTRACT

Objective: To assess real-world durability of reduction in relapse rates among patients with multiple sclerosis (MS) receiving fingolimod therapy over a longer-term period of follow-up.

Methods: Patients with MS who initiated fingolimod were identified from a US claims database (January 1, 2009 to September 30, 2016) and followed for 3 years post-initiation. Annualized relapse rates (ARRs) were calculated during the 1-year pre-initiation period, and during each year over the 3-year follow-up period. Time from fingolimod initiation to discontinuation (≥60-day treatment gap) was also summarized.

Results: Among 1599 fingolimod initiators, 1158 (72%) had continuous fingolimod use up to the start of year 2 and 937 (59%) had continuous fingolimod use up to the start of year 3. The mean baseline ARR during the 1-year pre-initiation period for all initiators was 0.51. After fingolimod initiation, mean ARRs were consistently lower in each year of follow-up: 0.25 (95% CI: 0.22, 0.28) in year 1 for all fingolimod initiators, 0.22 (0.18, 0.25) in year 2 for patients with continuous fingolimod use up to the start of year 2, and 0.23 (0.19, 0.27) in year 3 for patients with continuous fingolimod use up to the start of year 3. Median time on treatment was 33 months for all patients initiating fingolimod.

Conclusions: Patients with MS who received continuous fingolimod therapy experienced a sustained reduction in relapse rates (> 50% vs. baseline) during each year of a 3-year follow-up period.

1. Introduction

Relapsing-remitting multiple sclerosis (RRMS) is the most common form of MS, affecting approximately 80–85% of patients with MS (1,2). Clinical disability can occur as central nervous system damage accumulates from new relapses and incomplete remissions (3,4). The main objectives of MS treatment are to avoid disability from relapses, delay the progression to permanent disability, and manage symptoms (5). Disease-modifying therapies (DMTs) for RRMS can reduce the frequency, severity, and duration of relapses and delay disease progression (6–9). Durable effects of DMTs, as indicated by long-term sustained reductions in relapse rates, can help improve long-term outcomes for patients with MS (10,11).

Fingolimod, a sphingosine 1-phosphate receptor modulator, was the first oral DMT approved by the US Food and Drug Administration (FDA) for relapsing forms of MS (12). Approved in 2010, fingolimod has the longest duration of real-world clinical experience among oral DMTs, and is thus well-suited for studying the durability of longer-term treatment effects. Three pivotal Phase III clinical trials have described the efficacy and safety of fingolimod. The 24-month, double-blind FREEDOMS (N = 1272) and FREEDOMS II (N = 1083) trials each reported that fingolimod 0.5 mg significantly reduced mean annualized relapse rates (ARRs) by approximately half in comparison with placebo (FREEDOMS: 0.18 vs. 0.40, $p < .001$; FREEDOMS II: 0.21 vs. 0.40, $p < .001$) (13,14). The 12-month, double-blind TRANSFORMS trial (N = 1292) reported that fingolimod reduced patients' ARRs by over half in comparison with interferon beta-1a (IFNβ-1a) (0.16 vs. 0.33, $p < .001$) (15). In addition, the recent open-label Phase IV Evaluate Patient OutComes (EPOC) study (N = 1053) demonstrated that patients who switched to fingolimod reported significantly improved treatment

* Corresponding author at: Director, HE&OR, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, USA.
E-mail address: Kristen_m.johnson@novartis.com (K. Johnson).

https://doi.org/10.1016/j.jns.2019.01.036
Received 7 August 2018; Received in revised form 14 January 2019; Accepted 21 January 2019
Available online 22 January 2019
0022-510X/

satisfaction and quality of life outcomes (e.g., reduced depression and fatigue) in comparison with patients who continued with an injectable DMT (16).

The long-term effects of fingolimod in RRMS have been demonstrated in an extension study of the FREEDOMS trial, which showed that reduction in relapse rates during continuous fingolimod therapy can be sustained for up to 4 years (17). In addition, an extension of the TRANSFORMS clinical trial describing ARRs over up to 4.5 years demonstrated that patients with RRMS who received continuous fingolimod 0.5 mg had significantly lower ARRs than patients who were initially treated with IFNβ-1a and later switched to fingolimod (0.17 vs. 0.27, $p < .001$) (18). That study also reported that, in the latter group, there were significant reductions in disease activity and the rate of brain volume loss following the switch to fingolimod.

However, protocol-driven clinical studies may or may not reflect outcomes achievable in real-world clinical practice. It is therefore important to establish the longer-term durability of fingolimod effectiveness in real-world settings. In the US, earlier claims-based studies have shown reductions in ARRs measured over periods of 1 to 1.5 years following fingolimod initiation (19–21). A 2-year observational study of 249 patients in Spain reported that fingolimod reduced the ARR by 67–85% relative to baseline, with the highest benefit observed in treatment-naïve patients (22). A cohort study in Germany found that, among patients who failed prior injectable DMT, switching to fingolimod (vs. another injectable DMT) was associated with fewer relapses and lower risk of disability progression over a 2-year timeframe based on a propensity score-matched comparison ($N = 99$ in each group) (23); similar results were observed in an international registry of patients with RRMS who switched to fingolimod ($N = 148$) or an injectable DMT ($N = 379$) (24). The ongoing PANGAEA study in Germany is investigating the long-term efficacy and safety of fingolimod in clinical practice, with > 300 patients having completed 5 years of fingolimod treatment as of January 2017; preliminary 5-year results support the efficacy findings of Phase III trials, with mean ARR improving from 1.5 to 0.42 (25).

Therefore, there are few real-world studies to date examining the durability of relapse rate reductions with fingolimod beyond 2 years of follow-up, and no large-scale observational assessments of patients in the US. The present study assessed the extent to which the long-term efficacy profile of fingolimod exhibited in the FREEDOMS and TRANSFORMS extension trials is observable in a real-world US cohort followed for 3 years after fingolimod initiation.

2. Methods

2.1. Data source

This retrospective claims database analysis was conducted using data from Truven Health MarketScan® Commercial Claims and Encounters and the Medicare Supplemental databases (MarketScan) spanning January 1, 2009 to September 30, 2016. The MarketScan databases include individual-level plan enrollment files and medical and pharmacy claims for insured active employees, dependents, early retirees, and Consolidated Omnibus Budget Reconciliation Act continuers, as well as Medicare-eligible retirees with employer-provided Medicare Supplemental plans. The data are obtained from > 130 employers that sponsor private insurance, representing approximately 40 million covered lives annually. All US census regions are represented in the databases. Data were de-identified and complied with the patient requirements of the Health Insurance Portability and Accountability Act. No ethical review was required.

2.2. Sample selection

Patients included in the study were required to have either one inpatient claim or two outpatient claims (dated at least 30 days apart) associated with an MS diagnosis. Diagnoses indicating MS were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 340.xx or, for claims with a service date on or after October 1, 2015, International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code G35. Patients initiating fingolimod were identified as those with at least one prescription filled for fingolimod on or after the MS diagnosis (National Drug Codes [NDC]: 00078060715, 00078060751, and 00078060789). The date of fingolimod initiation was defined as the *index date*. Patients with age at least 18 and < 65 years old at the index date, and continuous health plan enrollment for at least one year prior to (defined as the *baseline period*) and at least 3 years following (defined as the *study period*) the index date were included. All patients meeting these criteria were followed for 3 years after the index date, and were classified into three nested groups based on their duration of continuous fingolimod use: 1) the full cohort of all fingolimod initiators; 2) the subset of patients with continuous fingolimod use during year 1 (i.e., up to the start of year 2); and 3) the further subset of patients with continuous fingolimod use during years 1 and 2 (i.e., up to the start of year 3). Continuous fingolimod use was defined as a sequence of prescription fills free of any ≥60-day gaps between the end of the supply of one prescription fill and the date of the next prescription fill.

2.3. Study measures and statistics

Baseline characteristics were summarized for the three patient cohorts, and included age, gender, geographic region, and type of insurance assessed at the index date, as well as MS symptoms, comorbidities, the Charlson Comorbidity Index (CCI) score (26), prior DMT use, number of relapses, and corresponding ARRs during the 1-year baseline period. Symptoms associated with MS were defined based on the variables reported in a published retrospective study by Boster et al. (2017) (21). Baseline ARRs were calculated as the number of relapses during the baseline period divided by time at risk (in years) during the baseline period; time at risk was equal to either 1 year or, for patients diagnosed with MS < 1 year before the index date, the portion of the 1-year baseline period occurring on or after the first observed MS diagnosis date.

Relapses were identified using a validated published algorithm that has been previously used in claims database analyses for MS (19,20,27,28). The algorithm identified relapses by the presence of either: an outpatient claim with diagnosis of MS followed by a claim for an oral or intravenous corticosteroid or corticotropin within seven days of the outpatient claim; *or* an inpatient claim with diagnosis of MS with or without use of a corticosteroid or corticotropin within seven days. Multiple relapses within a 30-day window were treated as a single relapse event, and the first available service date was considered the relapse date. A patient's first MS diagnosis was identified as a relapse event if it met the qualifications of the relapse algorithm described above (i.e., if the diagnosis was associated with an inpatient claim, or was accompanied by a corticosteroid or corticotropin claim within 7 days).

To assess the durability of relapse rate reductions following fingolimod initiation, ARRs and corresponding means and 95% CIs were calculated during each year of the 3-year follow-up period for the three patient cohorts: 1) the ARR during the first year after fingolimod initiation among all fingolimod initiators; 2) the ARR during the second year after fingolimod initiation among the subset of patients with continuous fingolimod use up to the start of year 2; and 3) the ARR during the third year after fingolimod initiation among the further subset of patients with continuous fingolimod use up to the start of year 3. Under this approach, patients who discontinued fingolimod treatment in a given year of follow-up were nevertheless included in the calculation of ARR for that year. The rationale was to avoid overstating the effectiveness of fingolimod by excluding patients who may have discontinued due to intolerance or breakthrough disease activity. As a

Table 1
Patient selection.

Selection criteria	Number of patients
At least one inpatient claim with an associated diagnosis of MS or at least two outpatient claims (dated at least 30 days apart) with an associated diagnosis of MS	216,297
First observed prescription fill for fingolimod (index date) occurring on or after the first MS diagnosis	9312
At least 18 and < 65 years of age on the index date	9129
At least 1 year of continuous health plan enrollment prior to the index date	6322
At least 3 years of continuous health plan enrollment following the index date	1599

Notes: MS—Multiple sclerosis.

sensitivity analysis, an on-treatment approach was also tested in which the ARR in each year of follow-up was calculated only among patients with continuous fingolimod use throughout the entire year.

Time from initiation to discontinuation of fingolimod was described for the 3-year study period among all fingolimod initiators using Kaplan-Meier analysis (29). Treatment discontinuation was defined by the presence of a ≥ 60-day gap in prescription supply, consistent with the definition used in several prior observational studies (30–32).

3. Results

3.1. Patient selection

Among the 216,297 patients who had one inpatient claim or two outpatient claims (dated at least 30 days apart) associated with an MS diagnosis, a total of 9312 filled at least one prescription for fingolimod after MS diagnosis. A total of 1599 adult fingolimod initiators met all criteria for inclusion in the study, including requirements for a total of 4 years of continuous health plan enrollment (Table 1).

Of the 1599 fingolimod initiators identified at the start of year 1, 1158 (72.4%) had continuous fingolimod use up to the start of year 2 and 937 (58.6%) had continuous fingolimod use up to the start of year 3 (Fig. 1: Patient cohorts).

3.2. Baseline characteristics

Baseline characteristics were similar across the three patient cohorts (Table 2). The average age was 46 years and a majority of the patients (76–77%) were female. Across patient cohorts, the most common MS symptoms were disorders of the optic nerve and visual pathways (22–24%), followed by fatigue/malaise (20–21%). The most common physical comorbidities were hypertension (20–21%) and hyperlipidemia (20%), followed by urinary tract infection (16–17%). The most common mental health comorbidity was depression (15–16%).

Mean baseline ARRs were similar across patient cohorts and ranged from 0.48 to 0.51 relapses per patient-year. In the three months prior to index date, mean ARRs ranged from 0.58 to 0.62. During the 1-year baseline period prior to initiation of fingolimod, 28–30% of patients did not have a prescription fill for a DMT. Across the patient cohorts, 30–33% of patients received interferon beta-1a or beta-1b, 21% of patients received glatiramer acetate, and 12–13% received natalizumab at some point during the baseline period; these proportions were not mutually exclusive and some patients had prescription fills for multiple DMTs within the baseline period.

3.3. Relapse rates by year

During each year of the study period, ARRs were consistently lower than baseline ARRs for each the three patient cohorts with continuous fingolimod use: 0.25 relapses per patient-year (95% CI: 0.22, 0.28) in year 1 among all fingolimod initiators (N = 1599), 0.22 (95% CI: 0.18, 0.25) in year 2 for the subset of patients with continuous fingolimod use up to the start of year 2 (N = 1158), and 0.23 (95% CI: 0.19, 0.27) in year 3 for the further subset of patients with continuous fingolimod use up to the start of year 3 (N = 937) (Fig. 2). These represent a 51%, 54%, and 53% reduction of relapse rates from each patient cohort's mean baseline ARR, respectively.

Larger relapse rate reductions were estimated in the sensitivity analysis among patients with continuous fingolimod use throughout each year of follow-up (**Fig. S1, Supplemental Material**). The mean ARR (in terms of relapses per patient-year) was: 0.19 (95% CI: 0.16, 0.21) in year 1 among patients with continuous fingolimod use through the end of year 1 (N = 1158); 0.18 (95% CI: 0.15, 22) in year 2 among those with continuous fingolimod use through the end of year 2 (N = 937); and similarly 0.18 (95% CI: 0.15, 22) in year 3 among those with continuous fingolimod use through the end of year 3 (N = 755). Corresponding reductions in the ARR relative to baseline in each of these cohorts were 61%, 62%, and 61%, respectively.

3.4. Time on treatment

Among all fingolimod initiators, median time to discontinuation

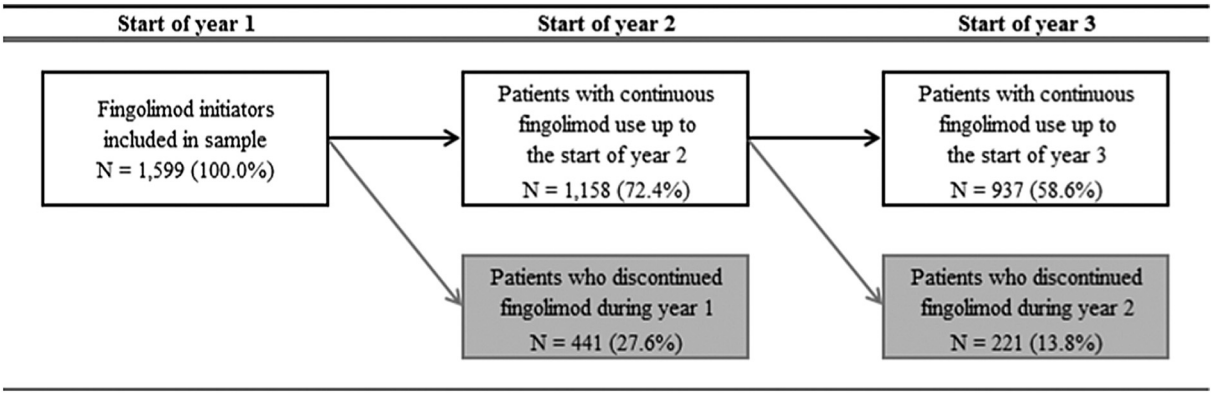

Fig. 1. Patient cohorts.
The three groups of patients shown in white boxes were included in the primary analyses of relapse rates.

Table 2
Patient baseline characteristics.

Baseline characteristics[a]	Fingolimod initiators included in sample	The subset of patients with continuous fingolimod use up to the start of year[b]	The further subset of patients with continuous fingolimod use up to the start of year [3]
	(*N* = 1599)	**(*N* = 1158)**	**(N = 937)**
Demographics at index date			
Age (years), mean ± SD	45.5 ± 9.5	45.5 ± 9.3	45.7 ± 9.0
Female, n (%)	1228 (76.8%)	880 (76.0%)	720 (76.8%)
Geographic region, n (%)			
Northeast	290 (18.1%)	219 (18.9%)	172 (18.4%)
North central	391 (24.5%)	276 (23.8%)	224 (23.9%)
South	671 (42.0%)	496 (42.8%)	403 (43.0%)
West	247 (15.4%)	167 (14.4%)	138 (14.7%)
Insurance type, n (%)			
Health maintenance organization (HMO)	191 (11.9%)	137 (11.8%)	105 (11.2%)
Preferred provider organization (PPO)	963 (60.2%)	703 (60.7%)	560 (59.8%)
Other insurance plan type[b]	445 (27.8%)	318 (27.5%)	272 (29.0%)
Index year, n (%)			
2010	75 (4.7%)	54 (4.7%)	45 (4.8%)
2011	832 (52.0%)	584 (50.4%)	474 (50.6%)
2012	476 (29.8%)	360 (31.1%)	284 (30.3%)
2013	216 (13.5%)	160 (13.8%)	134 (14.3%)
MS symptoms during baseline period, n %			
Demyelinating disease of CNS, unspecified	102 (6.4%)	77 (6.6%)	61 (6.5%)
Disorders of optic nerve and visual pathways	355 (22.2%)	275 (23.7%)	222 (23.7%)
General symptoms: dizziness and giddiness	110 (6.9%)	72 (6.2%)	61 (6.5%)
General symptoms: fatigue/malaise	342 (21.4%)	236 (20.4%)	189 (20.2%)
Neurogenic bladder NOS	100 (6.3%)	66 (5.7%)	50 (5.3%)
Other causes of myelitis	7 (0.4%)	5 (0.4%)	4 (0.4%)
Other disorders of soft tissues: neuralgia, neuritis, and radiculitis, unspecified	31 (1.9%)	20 (1.7%)	18 (1.9%)
Comorbidities during baseline period			
CCI, mean ± SD	0.40 ± 0.83	0.38 ± 0.83	0.37 ± 0.81
Physical comorbidities, n (%)			
Chronic pain	25 (1.6%)	16 (1.4%)	12 (1.3%)
Diabetes	84 (5.3%)	59 (5.1%)	50 (5.3%)
Hyperlipidemia	313 (19.6%)	235 (20.3%)	186 (19.9%)
Hypertension	325 (20.3%)	231 (19.9%)	193 (20.6%)
Irritable bowel syndrome	17 (1.1%)	11 (0.9%)	8 (0.9%)
Osteoarthritis	76 (4.8%)	55 (4.7%)	41 (4.4%)
Osteoporosis	53 (3.3%)	35 (3.0%)	28 (3.0%)
Rheumatoid arthritis	15 (0.9%)	12 (1.0%)	12 (1.3%)
Thyroid disease	172 (10.8%)	118 (10.2%)	97 (10.4%)
Urinary tract infection	273 (17.1%)	188 (16.2%)	153 (16.3%)
Mental comorbidities, n (%)			
Anxiety	155 (9.7%)	94 (8.1%)	66 (7.0%)
Depression	248 (15.5%)	174 (15.0%)	140 (14.9%)
Relapses during baseline period			
ARR, mean ± SD	0.51 ± 1.12	0.48 ± 1.13	0.49 ± 1.17
Number of relapses, mean ± SD	0.40 ± 0.72	0.37 ± 0.68	0.37 ± 0.68
0	1118 (69.9%)	833 (71.9%)	669 (71.4%)
1	361 (22.6%)	246 (21.2%)	206 (22.0%)
2	82 (5.1%)	54 (4.7%)	44 (4.7%)
3	32 (2.0%)	23 (2.0%)	16 (1.7%)
≥4	6 (0.4%)	2 (0.2%)	2 (0.2%)
Relapses during 3 months prior to index date			
ARR, mean ± SD	0.62 ± 1.63	0.58 ± 1.57	0.60 ± 1.62
Number of relapses, mean ± SD	0.15 ± 0.37	0.14 ± 0.35	0.14 ± 0.36
0	1376 (86.1%)	1004 (86.7%)	808 (86.2%)
1	212 (13.3%)	151 (13.0%)	126 (13.4%)
≥2	11 (0.7%)	3 (0.3%)	3 (0.3%)
DMTs during baseline period, n (%)			
Number of DMTs used, mean ± SD	0.74 ± 0.53	0.76 ± 0.51	0.76 ± 0.52
0	483 (30.2%)	327 (28.2%)	262 (28.0%)
1	1046 (65.4%)	788 (68.0%)	638 (68.1%)
2	69 (4.3%)	42 (3.6%)	36 (3.8%)
≥3	1 (< 0.1%)	1 (< 0.1%)	1 (0.1%)
DMTs at any time during baseline period, n (%)			
Glatiramer acetate	340 (21.3%)	247 (21.3%)	198 (21.1%)
Interferon beta-1a	475 (29.7%)	361 (31.2%)	306 (32.7%)
Interferon beta-1b	153 (9.6%)	111 (9.6%)	93 (9.9%)
Mitoxantrone	3 (0.2%)	2 (0.2%)	2 (0.2%)
Natalizumab	214 (13.4%)	153 (13.2%)	114 (12.2%)
Rituximab	1 (< 0.1%)	1 (< 0.1%)	–

(*continued on next page*)

Table 2 (*continued*)

Baseline characteristics[a]	Fingolimod initiators included in sample	The subset of patients with continuous fingolimod use up to the start of year[b]	The further subset of patients with continuous fingolimod use up to the start of year [3]
	(*N* = 1599)	**(*N* = 1158)**	**(N = 937)**
Teriflunomide	1 (< 0.1%)	–	–
No DMT used	483 (30.2%)	327 (28.2%)	262 (28.0%)
Most recent DMT prior to index date, n (%)			
Glatiramer acetate	320 (20.0%)	234 (20.2%)	188 (20.1%)
Interferon beta-1a	450 (28.1%)	346 (29.9%)	291 (31.1%)
Interferon beta-1b	144 (9.0%)	105 (9.1%)	87 (9.3%)
Mitoxantrone	3 (0.2%)	2 (0.2%)	2 (0.2%)
Natalizumab	198 (12.4%)	143 (12.3%)	107 (11.4%)
Rituximab	1 (< 0.1%)	1 (< 0.1%)	–
Teriflunomide	–	–	–
No DMT used	483 (30.2%)	327 (28.2%)	262 (28.0%)

Abbreviations: ARR—Annualized relapse rate, CCI—Charlson Comorbidity Index, CNS—Central nervous system, DMT—Disease-modifying therapy, HMO—Health maintenance organization, MS—Multiple sclerosis, N—Number, NOS—Not otherwise specified, PPO—Preferred provider organization, SD—Standard deviation.

[a] Baseline characteristics were assessed in the 1-year prior to the index date.

[b] Other plan types include: comprehensive, basic/major medical, exclusive provider organization, point-of-service, consumer-driven, and high deductible health plans.

was 33 months. At the end of year 1, 72% (*N* = 1158) of patients remained on treatment with fingolimod, and by the end of 1.5 years, 65% (*N* = 1046) of patients continued treatment. By the end of years 2 and 3, 59% (*N* = 937) and 47% (*N* = 755) of patients, respectively, had remained on fingolimod (Fig. 3).

4. Discussion

This retrospective claims database study found that patients with MS who received fingolimod therapy experienced a durable and sustained reduction in relapse rates over a 3-year period. While mean ARRs ranged from 0.48 to 0.51 relapses per patient-year prior to fingolimod initiation, these rates were reduced during the 3 years following fingolimod initiation to 0.25, 0.22, and 0.23 among groups with 0, 1, or 2 prior years of fingolimod use, respectively. This finding represents a durable reduction in relapse rates by > 50%.

Two previous smaller claims database analyses by Bergvall et al. reported relapse rates for patients receiving continuous fingolimod therapy over shorter timeframes (19,20). Bergvall et al. (2013) studied patients with at least one relapse prior to fingolimod initiation and reported an unadjusted ARR of 0.50 during 1.5-years of fingolimod use (19). This estimate is higher than the relapse rates observed in the present study, potentially because Bergvall et al. (2013) required a history of relapse prior to fingolimod initiation, while the present study did not impose this requirement. Bergvall et al. (2014) studied patients switching from interferon to fingolimod and reported an ARR of 0.46 over 1 year before the switch followed by 0.19 over 1 year of fingolimod use, a lower post-index ARR than in the present study (20). While Bergvall et al. (2014) excluded patients who discontinued fingolimod from the calculation of ARRs, the present study adopted a real-world intention-to-treat perspective by including all patients with continuous use up to the year of interest, regardless of whether the patients continued or discontinued fingolimod over the observation year. For example, the ARR for year 1 among all fingolimod initiators was calculated among all patients who initiated fingolimod, including those who discontinued fingolimod during year 1. This approach was expected to inflate ARRs and produce more conservative estimates of relapse rate reduction associated with fingolimod. The sensitivity analysis among patients with continuous fingolimod use throughout each year of follow-up confirmed that ARRs were lower on average among patients with continuous fingolimod use than those who discontinued treatment mid-year.

Observational studies with longer follow-up periods are lacking in the literature, although a 5-year prospective, multi-center study of the efficacy and safety of fingolimod in Germany (PANGAEA) has reported interim results, with the mean ARR improving from 1.5 at baseline to

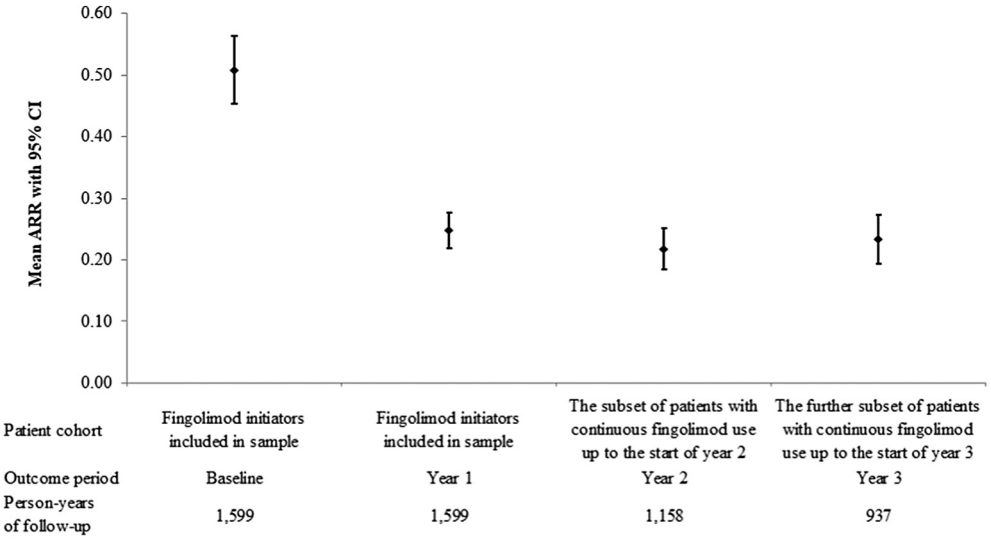

Fig. 2. ARRs of patient cohorts with continuous fingolimod use.
The study period mean ARRs (95% CI) of patients with continuous fingolimod use. Abbreviations: ARR—Annualized relapse rate, CI—Confidence interval. The baseline ARRs for the subset of patients with continuous fingolimod use up to the start of year 2 was 0.48 (95% CI: 0.41, 0.54) and the further subset of patients with continuous fingolimod use up to the start of year 3 was 0.49 (95% CI: 0.41, 0.56).

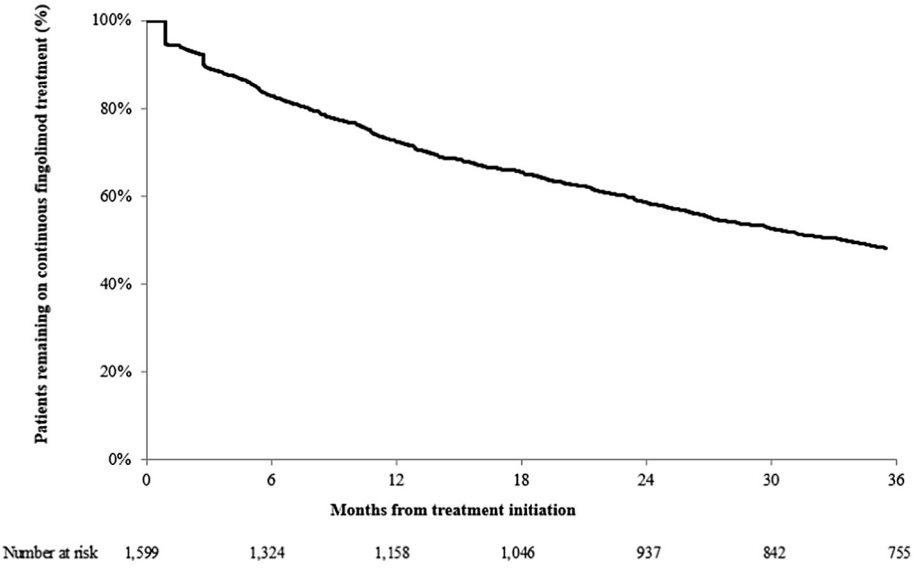

Fig. 3. Time on continuous fingolimod treatment.
The Kaplan-Meier curve of patients who remained on fingolimod therapy during the 3-year study period. Discontinuation was defined as a ≥ 60-day gap in supply of fingolimod.

0.42 (a 72% reduction) (25). The PANGAEA study had a higher baseline ARR (1.5) than the present study (0.51), as well as a higher ARR during follow-up (0.42 vs. 0.22–0.25, respectively), which may reflect differences in patient locality (Germany vs. US) or disease severity, or differences in the identification of MS relapses.

The findings of this study are consistent with and lend real-world support to the results of the FREEDOMS extension trial, which reported relapse rates for patients from the original FREEDOMS trial who continued to receive fingolimod for an additional 2 years (4 years total) (13,17). Respective ARRs assessed for months 0–24 (original trial) and 24–48 (extension trial) were 0.21 and 0.18 for continuous fingolimod users who received the label-recommended dose of 0.5 mg once-daily, indicating sustained efficacy of fingolimod in patients with MS for up to four years. The numerical differences in ARRs between the trial and current real-world study could be explained by differences between the study settings. In addition, the trial used direct clinical assessments such as the Expanded Disability Status Score (EDSS) to define relapses, whereas this study used an indirect, claims-based algorithm. The present results are also consistent with the TRANSFORMS extension trial describing ARRs (over up to 4.5 years) of patients receiving continuous fingolimod 0.5 mg vs. those who switched to fingolimod from IFNβ-1a (18). Patients who received continuous fingolimod had ARRs that were significantly lower than patients who switched from IFNβ-1a (0.17 vs. 0.27), with a 35% lower risk of relapse, and those who switched experienced lower disease activity on fingolimod vs. IFNβ-1a (ARR 0.20 vs. 0.40, respectively).

The persistence findings of fingolimod therapy are in line with those reported by Bergvall et al. in 2013 and 2014 with shorter follow-up periods (year 1: 72% versus 72%; year 1.5: 65% versus 57%) and show for the first time a 3-year persistence rate of 47% in a real-world setting (19,20). These results are also reflective of recent evidence suggesting that the efficacy, safety profile, and oral administration route of fingolimod, compared with injection/infusion-based DMTs, significantly increases patients' persistence on treatment, which can lead to improved clinical outcomes (20,30). In a US claims-based study by Agashivala et al. (2013), for example, 1-year persistence was only 46–56% for injectable DMTs compared with 69% for fingolimod among patients naïve to prior DMTs (30). Reasons for treatment discontinuation were not examined in the present study but represent an important area for further research, given that continuous DMT use can promote sustained reduction of relapse rates and help delay progression of disability (10,11). Prior studies have found that non-persistence to DMTs may result from breakthrough disease or disability progression, cognitive impairment, depression, tolerability or safety issues, and high out-of-pocket drug costs; injection burden is another major barrier to persistence that is specific to intravenous and injectable DMTs (33–36).

5. Limitations

This study is subject to limitations inherent to claims database analyses. First, insurance claims databases are susceptible to coding errors and data omissions. Second, because there are no specific medical codes to directly identify relapses, relapses were instead identified using a validated published algorithm based on a combination of different proxies (19,20,27,28). The algorithm could result in false-negative identification of relapses (e.g., if a relapse was untreated or only treated with an MS-associated outpatient claim without receipt of an acute MS therapy), or false-positive identification in other instances (e.g., due to pseudo-relapses). Nevertheless, because the claims-based algorithm was consistently applied in both the baseline and study periods, this limitation would be unlikely to account for the observed relapse rate reductions. Third, certain clinical factors that are indicative of disease activity or risk of disability progression (e.g., EDSS score, magnetic resonance imaging [MRI] of brain lesions) were unavailable in the claims database, and thus could not be described at baseline or examined as additional endpoints in this study. Reasons for treatment discontinuation were also not directly reported in claims. Fourth, the data include only commercially-insured patients or those with commercial insurance supplementing Medicare, and may not be generalizable to other patient populations, such as patients who are uninsured or insured by Medicaid or traditional Medicare plans. The real-world effectiveness of MS therapies may be sensitive to population-specific characteristics such as socioeconomic status, which is likely to be higher on average in the study sample than in the general US population. Despite this limitation, the databases were expected to be informative given that the majority of individuals in the US (56% overall and 61% among the insured as of 2017) have coverage through an employer-sponsored health plan (37). Moreover, the claims-based algorithm used to identify relapses in this study has only been validated in a commercial plan setting (28).

6. Conclusion

In this retrospective analysis of a US commercial claims database, patients with MS receiving fingolimod therapy experienced a sustained and durable reduction in relapse rates (> 50%) during the 3-year study period compared to baseline. These findings are consistent with results of the FREEDOMS and TRANSFORMS extension trials and provide evidence of the longer-term effectiveness of fingolimod in a real-world setting.

Acknowledgements

The authors thank Monica Macheca. Manuscript drafts were prepared by the authors with editorial assistance from a professional medical writer, Shelley Batts, PhD, an employee of Analysis Group, Inc., which received funding for this research and for medical writing from Novartis.

Author contributions and role of funding source

Funding for this research was provided by Novartis Pharmaceuticals Corporation. The study sponsor was involved in all stages of the study research and manuscript preparation. All authors participated in the design of the study and contributed to the manuscript development. All authors vouch for the accuracy and completeness of the data reported and the adherence of the study to the protocol, and all authors approved this version of the manuscript for publication.

Disclosures

K.J. and V.H. are employees of Novartis and own stock and/or stock options. M.C.V. was an employee of Novartis at the time of the study and manuscript development. M.P., A.G.B., and J.S. are employees of Analysis Group Inc., which received consultancy fees from Novartis. E.F. has received compensation as an advisor, consultant, or member of the speakers' bureau for Acorda, Bayer, Biogen, EMD Serono, Genentech, Genzyme, Novartis, Roche, Sanofi, and Teva, and has received research support from Acorda, Bayer, Biogen, Chugai, EMD Serono, Genzyme, Novartis, Opexa, Roche, Teva, and TG Therapeutics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.01.036.

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