

# Real-world experience of fingolimod in patients with multiple sclerosis (MS Fine): An observational study in the UK

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## Abstract

**Background:** Fingolimod is approved for the treatment of highly active relapsing–remitting multiple sclerosis in Europe. There is limited information on its effectiveness and safety in clinical practice within the UK.

**Objective:** To evaluate retrospectively the effectiveness and safety of fingolimod in patients with relapsing–remitting multiple sclerosis who were prescribed fingolimod by UK neurologists within the National Health Service.

**Methods:** This was a multicentre, observational study conducted in the UK. Patients were initiated on fingolimod 0.5 mg 12 months before inclusion in the study. Key efficacy outcomes included annualised relapse rate and the proportion of patients free from relapses, disability progression and clinical and radiological disease activity at 12 months following fingolimod initiation. Resource utilisation and safety outcomes were also assessed.

**Results:** In 12 months of treatment with fingolimod, the mean annualised relapse rate was reduced by 79%, the majority of patients were free from relapses (83.7%). Based on limited data, most patients were free from disability progression and clinical and radiological disease activity. More than 90% of patients continued on fingolimod. Lymphocyte count reductions and liver enzyme increases were observed.

**Conclusion:** Fingolimod was effective in reducing the disease activity in relapsing–remitting multiple sclerosis patients requiring an escalation from first-line therapies who were prescribed fingolimod in clinical practice in the UK.

**Keywords:** Multiple sclerosis, fingolimod, real-world, observational study, relapsing–remitting multiple sclerosis, relapsing multiple sclerosis

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## Introduction

Fingolimod (FTY720<sup>®</sup>, Gilenya, Novartis Pharma AG), a sphingosine 1-phosphate receptor modulator, is approved for the treatment of relapsing forms of multiple sclerosis (MS). Fingolimod improved all four key measures of disease activity (relapses, magnetic resonance imaging activity, disability progression and brain volume loss) versus placebo in two 24-month FREEDOMS<sup>1</sup> and FREEDOMS II<sup>2</sup> trials, and versus interferon (IFN)  $\beta$ -1a in the 12-month TRANSFORMS trial.<sup>3</sup> As of May 2018, more than

255,000 patients have been treated with fingolimod in clinical trials and post-marketing settings, with a cumulative patient exposure exceeding 566,000 patient-years.<sup>4,5</sup>

In the European Union, fingolimod was approved for the treatment of patients with highly active relapsing–remitting MS (RRMS) despite treatment with at least one disease-modifying therapy (DMT) or in patients with severe RRMS.<sup>6</sup> In the UK, the National Institute for Health and Care Excellence

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(NICE) approved fingolimod for the treatment of adult patients with highly active RRMS despite previous treatment with IFN $\beta$  or glatiramer acetate on the National Health Service (NHS) in England and Wales.<sup>7,8</sup>

While the efficacy and safety profiles of fingolimod are established in clinical trials<sup>1–3</sup> and real-world settings,<sup>9–15</sup> limited data are available on the effectiveness and safety of fingolimod in the UK. Clinical experience with fingolimod in daily practice would be helpful for physicians and other healthcare professionals caring for people with MS. The aim of this study is to determine the effectiveness and safety outcomes in patients with RRMS who were treated with fingolimod for 12 months in clinical practice in the UK.

## Methods

### Study design

This study was a multicentre, observational, retrospective review of medical records from 209 patients who were treated with fingolimod 0.5 mg as part of the normal clinical practice at 11 secondary/tertiary care NHS hospitals in the UK (details of recruiting hospitals are provided in the Acknowledgements section). All patients were initiated on fingolimod at least 12 ( $\pm 3$ ) months before their inclusion in the study. The study was discussed orally with the patients and patients provided verbal consent for the analysis of their medical records. The study protocol was reviewed and approved by the local ethics committee.

### Study population

The study population consisted of patients with RRMS under the care of a UK NHS MS specialist neurology service. Patients were included in the study if they were diagnosed with RRMS, according to the revised McDonald criteria 2010,<sup>16</sup> at least 12 months before fingolimod initiation and were initiated on fingolimod at least 12 months before the date on which they were approached for study participation. Patients were required to be under the care of the participating centre for at least 1 year before fingolimod initiation. All patients were prescribed fingolimod in accordance with NICE and NHS guidelines.<sup>7,8</sup> Patients aged under 18 years at the time of initiation of fingolimod, and those who received fingolimod as part of an interventional study were excluded from this study. In addition, patients who lacked the capacity to provide consent

or were too unwell to be approached for consent were excluded from the study.

Patients were divided into three subgroups based on the use of DMTs prior to fingolimod initiation: those who had received only one DMT, those who had received two or more DMTs, and those who received natalizumab.

### Outcome measures

The primary outcome measure was the proportion of patients free from relapses for 12 months after fingolimod initiation. Key secondary outcome measures included reduction in the annualised relapse rate (ARR); the proportion of patients free from disability progression at 12 months following fingolimod initiation, defined as an increase of one point on the sustained Expanded Disability Status Scale (EDSS) above baseline (or 1.5 EDSS points if the baseline EDSS score was 0); the proportion of patients free from clinical disease activity, defined as absence of relapses and disability progression 12 months after fingolimod initiation; change from baseline in the EDSS scores; the radiological disease activity status at initiation and at 12 months after fingolimod initiation; and time to first relapse if it occurred within 12 months.

Data on variables describing the characteristics of patients who were prescribed fingolimod in clinical practice were obtained during the study. In demographics, data on gender and age were collected. Baseline characteristics included reasons for initiating fingolimod and DMTs used prior to fingolimod, EDSS scores at 12 months prior to and during fingolimod initiation, the change in EDSS scores prior to the start of fingolimod initiation, and the duration of RRMS prior to fingolimod initiation. Resource use was summarised for the period of 12 months prior to and the 12 months following fingolimod initiation by the number and type of hospital visits and the reasons for visits.

Safety was evaluated by change from baseline in absolute lymphocyte counts (ALCs) and liver function tests. Ophthalmic evaluations were performed to assess macular oedema. The proportion of patients receiving fingolimod at 12 months after initiation was also determined.

### Statistical analyses

An overall sample size of 300 patients was considered to provide results of sufficient reliability (confidence interval (CI) of  $\pm 5\%$  around the expected outcome of 80% relapse-free patients).

However, variations in the number and types of patients attending various regional and national specialist services were anticipated. A total of 215 patients were screened and 209 patients were enrolled. Based on overlapping CIs, a sample size of 209 patients was considered valid to obtain the results.

The proportion and two-sided 95% CIs, calculated using Wald's methods, were used to present the primary endpoint. Categorical variables were presented as frequencies and percentages. Mean, standard deviation (SD), median, minimum and maximum were used to present continuous variables. Where data were missing or not available from the original medical record, the affected analyses were conducted using only the results of those patients with available data.

## Results

### *Patient population*

A total of 215 patients consented to participate in the study, and 209 patients were included in the analysis. Six patients did not meet the inclusion criteria and were excluded from the analysis. The mean (SD) age was 42.4 (9.12) years and was similar across the three subgroups; the majority of patients were in the age groups of 31–40 years and 41–55 years. Women were predominant in the patient population (72.2%), with the highest percentage in the natalizumab group (84.8%; Table 1). Prior to fingolimod initiation, 62.2% ( $n = 130$ ) of patients were previously treated with one DMT, 22.0% treated with two or more DMTs ( $n = 46$ ) and 15.8% with natalizumab ( $n = 33$ ). The most frequently used DMTs before fingolimod were subcutaneous IFN $\beta$ -1a (43.1%), followed by intramuscular IFN $\beta$ -1a (33.0%), glatiramer acetate (29.7%) and natalizumab (15.8%). The mean EDSS score of the overall population at baseline was 3.6 at the time of fingolimod initiation and was the highest (4.0) in the subgroup of patients who received natalizumab previously. Patients who received one DMT had the longest mean duration of RRMS (7.5 years; Table 1). In the overall population, patients reported lack of efficacy (77.0%) or intolerance to previous treatment (15.8%) as the primary reason for initiating fingolimod treatment, with a similar trend observed in patients who received one DMT and two or more DMTs. Patients in the natalizumab subgroup reported a lack of efficacy (33.3%) as one of the reasons for switching.

### *Fingolimod exposure*

The median duration of fingolimod exposure in the overall population was 360 days, with 14.8% of the study population being exposed to fingolimod for more than 360 days. The median duration of exposure was comparable between the subgroups of patients who received one and two or more DMTs (362 vs. 369 days), whereas it was 301 days in patients who received natalizumab before fingolimod.

### *Effectiveness outcomes*

Overall, 159 patients (83.7%) were free from relapses for 12 months after fingolimod initiation. This proportion was the highest in the subgroup of patients who had received one DMT (88.0%) followed by those who received two or more DMTs (78.6%) and natalizumab (74.2%) before fingolimod (Figure 1). The mean ARR (SD) in the overall population decreased significantly from 1.52 (0.76) before fingolimod initiation to 0.32 (0.74) at 12 months after fingolimod initiation, representing a reduction of 79.0% ( $P < 0.0001$ ). The reduction in the ARR was significant in all subgroups of patients, with the highest reduction observed in patients who received one DMT (86.1%,  $P < 0.0001$ ) followed by those who received two or more DMTs (75.7%,  $P < 0.0001$ ) and natalizumab (41.2%,  $P = 0.0309$ ; Figure 2).

At 12 months following fingolimod initiation, 91.3% (21/23) of patients in the overall population were free from disability progression. In subgroups of patients who received two or more DMTs or natalizumab, all patients (3/3, each group) were free from disability progression. Of the patients who received one DMT, 88.2% (15/17) were free from disability progression (Table 2).

After fingolimod initiation, 81.8% (18/22) of the overall population was free from clinical disease activity. This proportion was the highest in the subgroup of patients who received one DMT before fingolimod (87.5%, 14/16); in the subgroups of patients who received two or more DMTs and those who received natalizumab, 66.7% (2/3, each group) were free from clinical disease activity (Table 2).

Of 93 patients in whom radiological activity was assessed, 66.7% of patients were free from radiological activity. In patients with radiological activity, 22.6% reported new/enlarging T2 lesions and 9.7% showed gadolinium-enhancing T1 lesions

**Table 1.** Demographics and baseline characteristics of all patients enrolled in the study by previous treatment received

| Characteristic   | Previous treatment received        |                                     |                              |                         |
|--|------------------------------------|-------------------------------------|------------------------------|-------------------------|
|  | 1 first-line DMT<br><i>N</i> = 130 | ≥2 First-line DMTs<br><i>N</i> = 46 | Natalizumab<br><i>N</i> = 33 | Total<br><i>N</i> = 209 |
| Age, years   |                                    |                                     |                              |                         |
| Mean (SD)  | 42.8 (9.0)                         | 42.4 (8.9)                          | 41.0 (10.0)                  | 42.4 (9.1)              |
| Median (min–max)   | 43.0 (18.0–67.0)                   | 43.0 (25.0–59.0)                    | 41.0 (24.0–63.0)             | 43.0 (18.0–67.0)        |
| Age group, years, <i>n</i> (%)                             |                                    |                                     |                              |                         |
| 18–30  | 11 (8.5)                           | 4 (8.7)                             | 4 (12.1)                     | 19 (9.1)                |
| 31–40  | 41 (31.5)                          | 14 (30.4)                           | 11 (33.3)                    | 66 (31.6)               |
| 41–55  | 67 (51.5)                          | 26 (56.5)                           | 15 (45.5)                    | 108 (51.7)              |
| >55  | 11 (8.5)                           | 2 (4.3)                             | 3 (9.1)                      | 16 (7.7)                |
| Female/male, <i>n</i> (%)                                  | 89 (68.5)/41 (31.5)                | 34 (73.9)/12 (26.1)                 | 28 (84.8)/5 (15.2)           | 151 (72.2)/58 (27.8)    |
| Duration of RRMS, years                                    |                                    |                                     |                              |                         |
| <i>n</i>   |                                    |                                     |                              |                         |
| Mean (SD)  | 111 7.5 (5.29)                     | 41 6.9 (4.16)                       | 31 6.5 (4.58)                | 183 7.2 (4.93)          |
| EDSS score at 12 months prior to fingolimod initiation     |                                    |                                     |                              |                         |
| <i>n</i>   | 52                                 | 20                                  | 13                           | 85                      |
| Mean (SD)  | 3.7 (1.36)                         | 3.5 (1.70)                          | 3.8 (1.73)                   | 3.6 (1.49)              |
| Median (min–max)   | 3.5 (1.0–6.5)                      | 3.3 (1.0–6.5)                       | 3.5 (1.0–6.5)                | 3.5 (1.0–6.5)           |
| EDSS score at the time of fingolimod initiation            |                                    |                                     |                              |                         |
| <i>n</i>   | 34                                 | 9                                   | 3                            | 46                      |
| Mean (SD)  | 3.7 (1.41)                         | 3.3 (1.86)                          | 4.0 (1.32)                   | 3.6 (1.48)              |
| Median (min–max)   | 3.5 (1.0–6.0)                      | 3.5 (1.0–6.5)                       | 4.5 (2.5–5.0)                | 3.5 (1.0–6.5)           |
| Change in EDSS score at the start of fingolimod initiation |                                    |                                     |                              |                         |
| <i>n</i>   | 21                                 | 3                                   | 1                            | 25                      |
| Mean (SD)  | 0.4 (1.53)                         | 0.0 (1.00)                          | 0 (0.0)                      | 0.3 (1.43)              |
| Median (min–max)   | 0.0 (–2.5 to 4.0)                  | 0.0 (–1.0 to 1.0)                   | 0.0 (0.0 to 0.0)             | 0.0 (–2.5 to 4.0)       |
| Previous use of DMTs, <i>n</i> (%)                         |                                    |                                     |                              |                         |
| IFNβ-1b (Extavia)  | 3 (2.3)                            | 1 (2.2)                             | 0 (0.0)                      | 4 (1.9)                 |
| IFNβ-1a (Avonex)   | 33 (25.4)                          | 30 (65.2)                           | 6 (18.2)                     | 69 (33.0)               |
| IFNβ-1b (Betaferon)  | 11 (8.5)                           | 9 (19.6)                            | 1 (3.0)                      | 21 (10.0)               |
| IFNβ-1a (Rebif)  | 55 (42.3)                          | 27 (58.7)                           | 8 (24.2)                     | 90 (43.1)               |
| Glatiramer acetate (Copaxone)                              | 26 (20.0)                          | 29 (63.0)                           | 7 (21.2)                     | 62 (29.7)               |
| Natalizumab  | 0 (0.0)                            | 0 (0.0)                             | 33 (100.0)                   | 33 (15.8)               |
| Other  | 2 (1.5)                            | 7 (15.2)                            | 1 (3.0)                      | 10 (4.8)                |

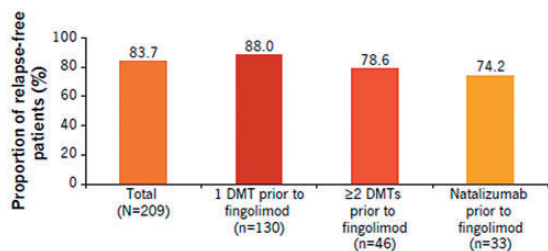
DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; IFN: interferon; RRMS: relapsing–emitting multiple sclerosis; SD: standard deviation.

(Table 2). A higher proportion of patients (17/21; 81.0%) in the subgroup who received two or more DMTs were free from radiological activity, followed by subgroups who received one DMT (37/57; 64.9%) or natalizumab (8/15; 53.3%).

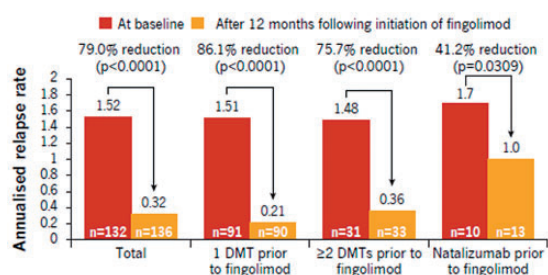
The mean EDSS scores at baseline and 12 months after fingolimod initiation were available for 23

patients. The mean EDSS scores from baseline decreased in patients who received one DMT before fingolimod but remained unchanged in the other subgroups (Table 2).

The mean time to first relapse was 154 days in the overall population. It was shortest (143.4 days) in the subgroup that received one DMT, compared with



**Figure 1.** Proportion of patients free from relapses for 12 months after fingolimod initiation. DMT: disease-modifying therapy.



**Figure 2.** Annualised relapse rates by prior DMT received. DMT: disease-modifying therapy.

those who received two or more DMTs (167.3 days) or natalizumab (157.6 days) prior to fingolimod initiation.

### Adherence to fingolimod

At the end of the 12 months after fingolimod initiation, approximately 91.9% of patients from the overall population were continuing on fingolimod. In all three subgroups, over 90% of patients were receiving fingolimod 12 months after treatment initiation (one DMT 90%; two or more DMTs 96%; natalizumab 94%). The reasons for fingolimod discontinuation included lack of efficacy ( $n=1$ ), abnormal lymphocyte count ( $n=1$ ), abnormal liver function tests ( $n=1$ ), abnormal cardiac monitoring results ( $n=1$ ) and other ( $n=3$ ).

### Resource utilisation

The use of NHS resources before and after 12 months of fingolimod initiation is presented in Table 3. Outpatient visits were predominant both before fingolimod initiation (97.1%) and after 12 months of fingolimod treatment (95.2%), with the most common reason for a visit being for neurology services. Day care admissions increased from 3.8% to 60.8% within 12 months of fingolimod treatment.

### Safety outcomes

Following fingolimod initiation, the mean (SD) of the lymphocyte count decreased from 1.9 (0.96) at baseline to 0.8 (2.35) after 12 months. The decrease in the count was more prominent in patients who received natalizumab before fingolimod initiation (2.3 (1.23) at baseline vs. 0.5 (0.24) after 12 months following fingolimod initiation). No cases of opportunistic infections, including progressive multifocal leukoencephalopathy or cryptococcal meningitis, were observed.

After 12 months following fingolimod initiation, the mean (SD) values of the liver enzymes increased relative to baseline in all of the subgroups. The subgroup of patients who received natalizumab prior to fingolimod showed the lowest mean changes from baseline for all of the liver enzymes that were analysed.

Ophthalmic evaluations were conducted in 72.2% of the overall population after fingolimod initiation and no cases of macular oedema were reported during the observation period.

Changes from baseline in ALCs and liver enzymes are presented in Supplementary Table 1. The subgroup of patients who received prior natalizumab treatment showed the greatest mean change in ALCs and the lowest mean changes for all of the liver enzymes analysed.

### Discussion

We retrospectively reviewed the medical records of 209 patients who received fingolimod for 12 months as part of clinical practice in the UK. These patients were older (mean age 42 vs. 39 years) with higher EDSS scores (3.6 vs. 3.0) compared to the patient population from PANGAEA, a large prospective, non-interventional 5-year-long term study from Germany.<sup>16</sup> Prior to fingolimod initiation, more than 75% of patients received one DMT including natalizumab and 22% received two or more DMTs, suggesting that in the UK fingolimod may be prescribed immediately after the first-line treatment has failed. The most frequently used previous DMT was subcutaneous IFN $\beta$ -1a, and lack of efficacy was the main reason for initiating fingolimod. The results of this study are in line with the known efficacy and safety profiles of fingolimod in patients with RRMS.<sup>1-3</sup> In addition, patients in the subgroup with one DMT had better clinical outcomes compared with the two other subgroups, thus further strengthening the evidence of the effectiveness of

**Table 2.** Secondary efficacy outcomes by previous treatment received.

| Outcome  | Previous treatment received    |                                 |                       | Total<br>N = 209 |
|--|--------------------------------|---------------------------------|-----------------------|------------------|
|  | 1 first-line<br>DMT<br>N = 130 | ≥2 First-line<br>DMTs<br>N = 46 | Natalizumab<br>N = 33 |                  |
| Proportion of patients free from disability progression    |                                |                                 |                       |                  |
| N'   | 17                             | 3                               | 3                     | 23               |
| n (%)  | 15 (88.2)                      | 3 (100.0)                       | 3 (100.0)             | 21 (91.3)        |
| Proportion of patients free from clinical disease activity |                                |                                 |                       |                  |
| N'   | 16                             | 3                               | 3                     | 22               |
| n (%)  | 14 (87.5)                      | 2 (66.7)                        | 2 (66.7)              | 18 (81.8)        |
| Change from baseline in EDSS score                         |                                |                                 |                       |                  |
| N'   | 17                             | 3                               | 3                     | 23               |
| Mean (SD)  | -0.35 (0.86)                   | 0.00 (0.00)                     | 0.00 (0.00)           | -0.26 (0.75)     |
| Radiological disease activity                              |                                |                                 |                       |                  |
| Status at fingolimod initiation, n (%)                     |                                |                                 |                       |                  |
| Not known  | 12 (9.2)                       | 10 (21.7)                       | 0 (0.0)               | 22 (10.5)        |
| Radiological activity assessed <sup>a</sup>                | 78 (60.0)                      | 26 (56.5)                       | 29 (87.9)             | 133 (63.6)       |
| Free from radiological activity                            | 20 (25.6)                      | 10 (38.5)                       | 18 (62.1)             | 48 (36.1)        |
| Radiological disease activity present                      | 58 (74.4)                      | 16 (61.5)                       | 11 (37.9)             | 85 (63.9)        |
| New/enlarged T2-weighted lesions                           | 44 (56.4)                      | 12 (46.2)                       | 6 (20.7)              | 62 (46.6)        |
| Evidence of contrast-enhancing lesions on T1-weighted MRI  | 14 (17.9)                      | 6 (23.1)                        | 4 (13.8)              | 24 (18.0)        |
| Status at 12 months following fingolimod initiation, n (%) |                                |                                 |                       |                  |
| Not known  | 4 (3.1)                        | 3 (6.5)                         | 0 (0.0)               | 7 (3.3)          |
| Radiological activity assessed <sup>a</sup>                | 57 (43.8)                      | 21 (45.7)                       | 15 (45.5)             | 93 (44.5)        |
| Free from radiological activity                            | 37 (64.9)                      | 17 (81.0)                       | 8 (53.3)              | 62 (66.7)        |
| Radiological disease activity present                      | 20 (35.1)                      | 4 (19.0)                        | 7 (46.7)              | 31 (33.3)        |
| New/enlarged T2-weighted lesions                           | 13 (22.8)                      | 3 (14.3)                        | 5 (33.3)              | 21 (22.6)        |
| Evidence of contrast-enhancing lesions on T1-weighted MRI  | 5 (8.8)                        | 2 (9.5)                         | 2 (13.3)              | 9 (9.7)          |
| Time to first relapse, days                                |                                |                                 |                       |                  |
| n  | 14                             | 9                               | 8                     | 31               |
| Mean (SD)  | 143.4 (107.7)                  | 167.3 (126.8)                   | 157.6 (170.5)         | 154.0 (127.3)    |

<sup>a</sup>Percentages calculated based on the number of patients who had radiological activity assessed.

N' is the number of patients with available data

DMT: disease-modifying therapy; EDSS, Expanded Disability Status Scale; SD: standard deviation.

fingolimod on clinical outcomes after the failure of first-line treatment.

Overall, 83.7% of patients were relapse free 12 months after fingolimod initiation, with 88.0% relapse free in the subgroup of patients who received one DMT. These results are consistent with those of the TRANSFORMS trial, in which approximately 80% of participants were relapse free after 12 months of fingolimod treatment.<sup>3</sup> These results are also consistent with published reports from other real-world studies: in PANGAEA, 69–76% of patients were free from relapses during the first

4 years.<sup>17</sup> In a retrospective review of 175 patients with RRMS from the Kuwait National MS Registry, the proportion of patients who were free from relapses increased from 33% to 86% post-fingolimod treatment.<sup>9</sup> In another study with 317 patients who started on fingolimod, 87% of the patients were relapse free at 12 months after fingolimod initiation.<sup>10</sup> Approximately 80% of patients were relapse free in another observational study from the Middle East.<sup>18</sup>

In line with the primary outcome, the mean ARR decreased from 1.52 to 0.32 at 12 months after

**Table 3.** Resource utilisation before and after fingolimod initiation.

| Outcome                             | Previous treatment received    |                                 |                       | Total<br>N = 209 |
|-------------------------------------|--------------------------------|---------------------------------|-----------------------|------------------|
|                                     | 1 first-line<br>DMT<br>N = 130 | ≥2 First-line<br>DMTs<br>N = 46 | Natalizumab<br>N = 33 |                  |
| <i>Before fingolimod initiation</i> |                                |                                 |                       |                  |
| Type of visit, n (%)                |                                |                                 |                       |                  |
| Outpatient visit                    | 124 (95.4)                     | 46 (100.0)                      | 33 (100.0)            | 203 (97.1)       |
| Day care admission                  | 4 (3.1)                        | 0 (0.0)                         | 4 (12.1)              | 8 (3.8)          |
| Accident and emergency              | 1 (0.8)                        | 0 (0.0)                         | 0 (0.0)               | 1 (0.5)          |
| Reason for visit, n (%)             |                                |                                 |                       |                  |
| Neurology outpatient                | 118 (90.8)                     | 45 (97.8)                       | 33 (100.0)            | 196 (93.8)       |
| Physiotherapy                       | 6 (4.6)                        | 5 (10.9)                        | 0 (0.0)               | 11 (5.3)         |
| Occupational therapy                | 2 (1.5)                        | 1 (2.2)                         | 0 (0.0)               | 3 (1.4)          |
| Incontinence management             | 6 (4.6)                        | 2 (4.3)                         | 0 (0.0)               | 8 (3.8)          |
| Other                               | 81 (62.3)                      | 31 (67.4)                       | 24 (72.7)             | 136 (65.1)       |
| <i>After fingolimod initiation</i>  |                                |                                 |                       |                  |
| Type of visit, n (%)                |                                |                                 |                       |                  |
| Outpatient visit                    | 124 (95.4)                     | 43 (93.5)                       | 32 (97.0)             | 199 (95.2)       |
| Day care admission                  | 71 (54.6)                      | 26 (56.5)                       | 30 (90.9)             | 127 (60.8)       |
| Accident and emergency              | 4 (3.1)                        | 3 (6.5)                         | 4 (12.1)              | 11 (5.3)         |
| Reason for visit, n (%)             |                                |                                 |                       |                  |
| Neurology outpatient                | 119 (91.5)                     | 43 (93.5)                       | 32 (97.0)             | 194 (92.8)       |
| Physiotherapy                       | 6 (4.6)                        | 4 (8.7)                         | 1 (3.0)               | 11 (5.3)         |
| Occupational therapy                | 0 (0.0)                        | 1 (2.2)                         | 0 (0.0)               | 1 (0.5)          |
| Incontinence management             | 4 (3.1)                        | 0 (0.0)                         | 1 (3.0)               | 5 (2.4)          |
| Other                               | 53 (40.8)                      | 16 (34.8)                       | 22 (66.7)             | 91 (43.5)        |

DMT: disease-modifying therapy.

fingolimod initiation in the overall population. The ARR observed in this study aligns with that of the FREEDOMS<sup>1</sup> and TRANSFORMS<sup>3</sup> trials, and the PANGAEA real-world study.<sup>17</sup> The reduction in the ARR was high in the subgroup of patients who received one DMT before fingolimod.

The mean change in EDSS score from baseline decreased slightly in the 23 patients analysed in the overall population and in the subgroup of patients who received one DMT (17 patients). A total of 21/23 patients analysed from the overall population were free from disability progression in the 12 months after fingolimod initiation. Similar to the relapse outcomes, 15/17 patients in the subgroup who received one DMT were free from disability progression. Similarly, 81.8% of patients from the overall population were free from clinical disease activity at 12 months after fingolimod initiation, with the highest proportion of patients from the subgroup who received one DMT (14/16 patients). These results were consistent with outcomes from

the PANGAEA study, in which approximately 60–73% of patients were free from clinical disease activity in each year up to 4 years.<sup>17</sup>

Consistent with the pharmacodynamic properties of fingolimod,<sup>1–3</sup> a reduction in the lymphocyte count was observed in patients from all three subgroups; the total mean change in the lymphocyte count from baseline was –1.4. There were no cases of opportunistic infections; no progressive multifocal leukoencephalopathy infections were observed in those patients who switched to fingolimod from natalizumab due to a high viral load. No cases of macular oedema were reported in this study, a known adverse event with fingolimod treatment that was reported in 0.3% of cases with fingolimod 0.5 mg in clinical trials.<sup>19</sup>

Resource utilisation in terms of outpatient visits to neurology specialists was predominant before and after fingolimod initiation and remained unchanged. However, day care admissions increased largely in

the 12 months after fingolimod initiation. This is because, as a standard practice in UK, most centres admit patients during the first dose of administration to evaluate cardiac safety. In general, a reduction in healthcare resource utilisation and non-prescription medical costs were reported with the initiation of different DMTs such as fingolimod, dimethyl fumarate, IFN, glatiramer acetate and teriflunomide.<sup>20</sup>

Approximately 92% of patients continued on fingolimod after 12 months of treatment initiation; the highest proportion was in patients who received two or more DMTs, with the highest mean duration of exposure being 368.4 days. These rates are in line with the real-world data from PANGAEA in which 11–15% of patients discontinued fingolimod in the second and third year after fingolimod initiation.<sup>20,21</sup>

#### *Limitations and generalisability*

There are a few limitations to our study as a result of its observational and retrospective design. Data were collected only from those patients who provided their consent for participation and, hence, patients who were too unwell to provide consent may have been underrepresented. Thus the results might have overestimated the proportion of disease-free patients at 12 months. Patient data were collected from the investigating centres only and not from the referring hospitals or general practitioners, which may have led to missing information pertaining to treatment and relapses.

The data for change from baseline in EDSS scores post-fingolimod treatment were available in only 23 patients, which may have impacted the other outcomes, including the proportion of patients free from clinical and radiological disease activity. In the majority of the clinics, it is not regular practice to assess the EDSS score at regular intervals, which might have led to the lack of availability of EDSS data. This may also be due to the dearth of neurologists (one neurologist per 115,000 population) and adult neurological services in the UK. Moreover, the services provided outside regional centres often focus on diagnosis only, with little provision for long-term support, which is required for a disease such as MS.<sup>22,23</sup>

Because of its nature as a retrospective study, the evaluation of outcomes was completely dependent on the quality and completeness of the information in the medical records. The lack of a control group might have introduced bias because the outcomes were compared with baseline data rather than with an independent control group. The number of

patients who were available for evaluation of disability progression and EDSS score was small. This large amount of missing data on clinical outcomes may limit the generalisability of the data to the overall UK population.

#### **Conclusions**

This study provides real-world evidence of 12 months of fingolimod treatment in clinical practice in the UK. Fingolimod has been shown to be effective in patients who had a failure of first-line treatment, especially in those previously treated with one DMT, with an adherence to treatment of 90% or higher 12 months after initiation. Fingolimod treatment improved clinical outcomes such as relapse rates, disability progression, clinical disease activity and radiological activity. The effectiveness and safety results observed in this population were consistent with those from pivotal trials and other real-world studies.

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#### **Conflict of Interests**

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