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Original article

Long-term real-world evidence for sustained clinical benefits of fingolimod following switch from natalizumab

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ABSTRACT

Background: The risk of progressive multifocal leukoencephalopathy limits the duration over which patients can receive natalizumab before requiring a switch to other therapies such as fingolimod. To date, no studies have assessed the long-term real-world effectiveness and safety of fingolimod following a switch from natalizumab. We aimed to investigate the benefit–risk profile of fingolimod over 48 months in patients switching from natalizumab, and the impact of washout duration after natalizumab discontinuation on outcomes during fingolimod treatment.

Methods: This analysis used data from PANGAEA, an ongoing German multicenter, prospective, non-interventional, observational study. In total, 3912 patients were included: 530 had switched from natalizumab (natalizumab subpopulation), and a reference population of 3382 had switched from other treatments or were treatment-naïve (non-natalizumab subpopulation). The natalizumab subpopulation was stratified by washout duration (30–89 days, 90–149 days, and ≥ 150 days) prior to fingolimod initiation.

Results: In the natalizumab subpopulation over 48 months of fingolimod treatment, 58.2% (n = 227/390) of patients remained on fingolimod. Over this period, mean annualized relapse rates (ARRs) and proportions of patients who relapsed were similar across washout durations, and ranged from 0.455 (95% confidence interval [CI]: 0.363–0.571) to 0.546 (95% CI: 0.446–0.669) and 54.1% (n = 92/170) to 60.2% (n = 127/211), respectively. Overall, 17.1% (n = 36/211) had 6-month confirmed disability worsening. In the non-natalizumab subpopulation, ARR was 0.300, 40.9% (n = 1325/3237) of patients relapsed, and a similar proportion to the natalizumab subpopulation had 6-month disability worsening (16.6% [n = 232/1394]). In both subpopulations, the safety profile of fingolimod was consistent with that observed in randomized controlled trials.

Conclusions: In patients discontinuing natalizumab, fingolimod has a favorable benefit–risk profile over 48 months. These findings also suggest using a short washout following natalizumab discontinuation, consistent with guidelines and current clinical practice in Germany.

Abbreviations: AE, adverse event; ARR, annualized relapse rate; CI, confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; EU, European Union; JCV, John Cunningham virus; MRI, magnetic resonance imaging; MS, multiple sclerosis; PANGAEA, Post Authorization Non-interventional German sAfety study of GilEnyA; PML, progressive multifocal leukoencephalopathy; RCT, randomized controlled trial; SAE, serious adverse event; SD, standard deviation; SmPC, Summary of Product Characteristics

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1. Introduction

Fingolimod, a sphingosine 1-phosphate receptor modulator, is an oral disease-modifying therapy (DMT) (Mehling et al., 2011). In the European Union (EU), fingolimod is indicated as a switch therapy for patients with multiple sclerosis (MS) experiencing high disease activity on their current DMT, or as a first-line DMT for patients with rapidly evolving severe MS (Gilenya, 2018). Natalizumab, a selective adhesion molecule inhibitor, is an infusible DMT that has a similar EU indication to that of fingolimod (Tysabri, 2018). Treatment with fingolimod or natalizumab is associated with a risk of developing progressive multifocal leukoencephalopathy (PML) in patients with the John Cunningham virus (JCV; indicated by the presence of JCV antibodies) (Berger, 2017). However, this risk is significantly lower in patients receiving fingolimod than in those receiving natalizumab (Berger, 2017). Furthermore, for natalizumab, the risk of PML can be stratified based on treatment duration and circulating JCV antibody levels (JCV index); patients with a JCV index exceeding 1.5 are at particular risk of PML (European Medicines Agency, 2018).

The Summary of Product Characteristics (SmPC) for natalizumab, but not fingolimod, recommends that its benefit–risk profile be reassessed after 2 years of therapy (Tysabri, 2018). This limits the duration over which patients can receive natalizumab before they need to switch to alternative DMTs such as fingolimod (Havla et al., 2013a; Kramer et al., 2017). The long half-life of natalizumab means a washout period is recommended following its discontinuation and before switching to alternative DMTs (Havla et al., 2013a; Sehr et al., 2016). In patients switching to fingolimod from natalizumab, the washout duration needs to be long enough to avoid potential additive effects of these two drugs on immune cell trafficking, but not so long as to increase the risk of disease reactivation (Havla et al., 2013a; Kornek, 2015). The SmPC for fingolimod recommends a washout of at least 8–12 weeks (Gilenya, 2018), whereas recent German guidelines recommend a washout of 6–8 weeks. In clinical practice, physicians prefer a shorter washout duration to avoid disease reactivation (Kompetenznetz Multiple Sklerose, 2018).

Randomized controlled trials (RCTs) and real-world studies have demonstrated that fingolimod controls disease activity following natalizumab discontinuation (Capobianco et al., 2015; Jokubaitis et al., 2014; Kappos et al., 2015; Leurs et al., 2017; Lo Re et al., 2015; Prosperini et al., 2015). However, studies have also reported that disease activity returns in a proportion of patients during fingolimod treatment (Giovannoni and Naismith, 2014). The extent of disease reactivation following natalizumab discontinuation is associated with the washout duration and disease activity before and during natalizumab treatment (Cohen et al., 2014; Comi et al., 2015; Hoepner et al., 2014; Jokubaitis et al., 2014; Kappos et al., 2015); these studies have typically been conducted in small populations, and outcomes were observed over limited follow-up periods (4–18.7 months) (Comi et al., 2015; Hoepner et al., 2014). Larger, long-term studies in representative populations are thus needed to assess the effects of fingolimod in patients switching from natalizumab.

The large 5-year Post Authorization Non-interventional German sAfety study of GilEnyA (PANGAEA) was designed to assess fingolimod according to its use in routine clinical practice, using systematically collected real-world data (Ziemssen et al., 2015b, 2018). Here, we used data from PANGAEA to assess the long-term effectiveness and safety of fingolimod for up to 48 months in patients switching from natalizumab compared with patients switching from other DMTs or initiating fingolimod first line.

2. Methods

2.1. PANGAEA study design and patient population

PANGAEA is an ongoing German multicenter, prospective, non-interventional, observational long-term study. Further details on study design and patient population have been reported previously (Ziemssen et al., 2015b). Recruitment has been completed, and observations were ongoing at the time of the data cutoff (October 2018). Patients who had a diagnosis of relapsing–remitting MS, had been prescribed fingolimod 0.5 mg by their physician, as part of routine clinical practice, and had provided written consent were included in the study. There were no exclusion criteria, except the contraindications in the SmPC for fingolimod (Ziemssen et al., 2015b).

The study was conducted in accordance with the Declaration of Helsinki. The leading ethics committee for the study was the Ethics Committee of the Technical University Dresden, which is registered at the Office for Human Research Protections under the numbers IRB00001473 and IORG0001076. Written informed consent was obtained from all participants to document their data before inclusion in the study. Independent monitoring was performed during the study, including extensive question-and-answer sessions with the centers.

For the present analysis, patients were assigned to either the natalizumab or non-natalizumab subpopulation. For inclusion in the natalizumab subpopulation, patients were required to have switched to fingolimod from natalizumab after a defined washout period (further details are provided in the footnote to Fig. 1). Patients who met the study criteria but who were treatment-naïve or did not receive natalizumab prior to switching to fingolimod were included in the non-natalizumab subpopulation, which served as a reference population.

2.2. Data collection and study outcomes

Baseline characteristics were assessed by the treating neurologist during interviews or medical examinations. Clinical outcomes were assessed by the treating neurologist at each visit during months 0–48. Outcomes assessed included time to therapy discontinuation, annualized relapse rates (ARRs), and the proportions of patients with 6-month confirmed disability worsening, 6-month confirmed disability improvement, or stable disability (assessed using Expanded Disability Status Scale [EDSS] scores). For relapse and disability outcomes, patients in the natalizumab subpopulation were additionally stratified according to the duration of washout (30–89 days, 90–149 days, and ≥ 150 days). For safety outcomes, adverse events (AEs) and serious AEs (SAEs) were assessed by their treating neurologist at each visit and classified using the Medical Dictionary for Regulatory Activities.

2.3. Statistical analyses

Data for categorical variables are presented as the number of cases and the proportion of cases in each category. For continuous variables, data are summarized using the mean, 95% confidence interval (CI), median, and standard deviation (SD). For proportions of patients, 95% CIs were calculated using the exact (Clopper–Pearson) method. Time to therapy discontinuation was estimated using a Kaplan–Meier approach. ARR and associated 95% CIs were analyzed using a negative binomial distribution model and logarithm of time on study as an offset variable. Patients for whom MS was a cause of death were considered to have confirmed disability worsening regardless of baseline EDSS score or change in EDSS score. If patient data were missing or if patients were lost to follow-up, data were taken into consideration up to the point of discontinuation.

3. Results

3.1. Study population and baseline characteristics

In total, 530 patients were included in the natalizumab subpopulation and 3382 in the non-natalizumab subpopulation (Fig. 1). Overall, 199/534 (37.3%) and 1318/3403 (38.7%) patients were followed up for the entire 48-month follow-up period in the natalizumab

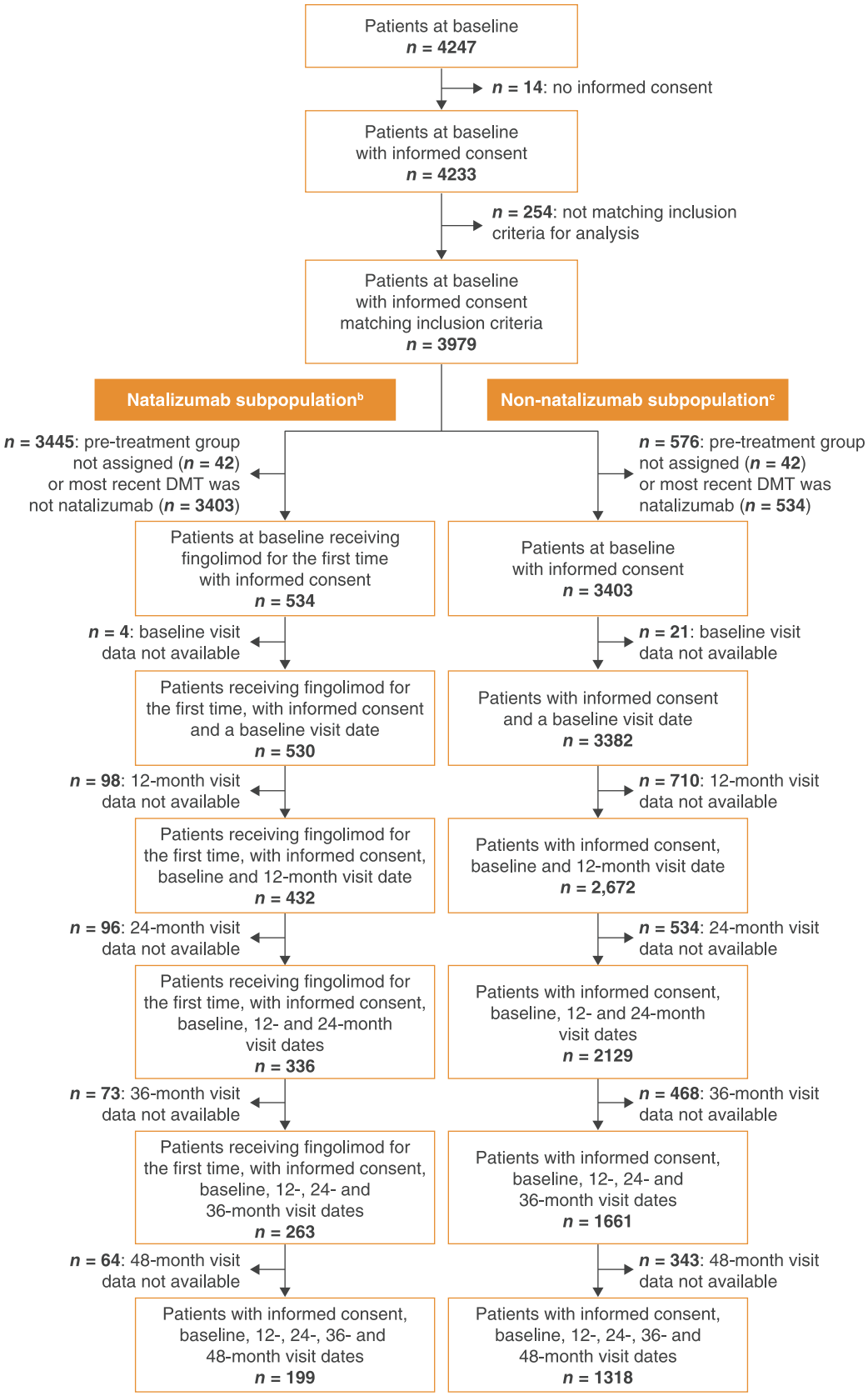

Fig. 1. Patient flow chart[a].

[a] Patients were recruited from neurological centers and practices across Germany between April 2011 and December 2013, with the observational period expected to continue until December 2018 (Ziemssen et al., 2015b).

[b] For inclusion in the natalizumab subpopulation, patients were required to have switched to fingolimod from natalizumab after a defined washout period. Patients were excluded from this subpopulation if their previous DMT was not natalizumab, if they had no follow-up data during fingolimod treatment, if the duration of natalizumab washout was 30 days or less or more than 3 years, if they received fingolimod in more than one of the 13 clinical pre-studies prior to enrolment, or if they received fingolimod in only one clinical study but had a treatment gap of more than 30 days between the pre-study and PANGAEA.

[c] Patients who met the study criteria but who were treatment naïve or did not receive natalizumab prior to switching to fingolimod were included in the non-natalizumab subpopulation, which served as a reference population.

DMT, disease-modifying therapy.

subpopulation and non-natalizumab subpopulation, respectively. Baseline demographic and clinical characteristics were generally similar between these subpopulations (Table 1). However, median baseline EDSS scores were numerically higher in the natalizumab subpopulation than in the non-natalizumab subpopulation (median [interquartile range]: 3.5 [2.0–5.0] versus 2.5 [1.5–4.0]), and disease duration was numerically longer (mean ± SD: 10.7 ± 6.3 years versus 7.8 ± 6.1 years). The mean duration of natalizumab treatment

in the natalizumab subpopulation was (mean ± SD) 1078 ± 626 days, and a large proportion of patients were JCV positive (72.6%, n = 385/530).

3.2. Natalizumab washout duration

Mean washout duration between the last natalizumab infusion and fingolimod initiation was (mean ± SD) 170 ± 175 days (Table 1). A total of 170 patients (32.1%) had a washout duration of 30–89 days, 211 patients (39.8%) had a washout duration of 90–149 days, and 149 patients (28.1%) had a washout duration of ≥ 150 days. When patients were stratified according to the presence (101 patients [19.1%]) or absence (429 patients [80.9%]) of a relapse during the washout period, those who experienced a relapse had a longer duration of washout than those who did not experience a relapse (mean ± SD: 242 ± 245 days versus 153 ± 149 days).

3.3. Effectiveness outcomes during fingolimod treatment

The rate of fingolimod discontinuation after 48 months was numerically higher in the natalizumab subpopulation (41.8% [n = 163/390]) than in the non-natalizumab subpopulation (32.9% [n = 778/2365]), which trended toward significance (p = 0.051; Fig. 2). The proportion of patients discontinuing fingolimod was highest during the first 12 months in both the natalizumab (13.5% [95% CI: 10.6–16.8], n = 67/496) and non-natalizumab (9.8% [95% CI: 8.8–11.0], n = 292/2969) subpopulations. When reasons for study termination were provided, 20.3% (n = 51/251) and 13.1% (n = 200/1529) of reasons in the natalizumab and non-natalizumab subpopulations, respectively, were related to physician-reported lack of effectiveness (relapses, EDSS score worsening, magnetic resonance imaging [MRI] activity, progression to secondary progressive MS).

Compared with 12 months prior to study start, the mean ARR and proportion of patients who relapsed declined during 48 months of fingolimod treatment in both subpopulations. At month 48 in the natalizumab subpopulation, after washout durations of 30–89, 90–149, and ≥ 150 days, the mean ARRs were 0.455 (95% CI: 0.363–0.571), 0.546 (95% CI: 0.446–0.669), and 0.486 (95% CI: 0.382–0.619), respectively (Fig. 3A). The proportions of patients who relapsed were 54.1% (95% CI: 46.3–61.8, n = 92/170), 60.2% (95% CI: 53.2–66.9, n = 127/211), and 53.7% (95% CI: 45.4–61.9, n = 80/149), respectively (Fig. 3B). At month 48, reductions in the non-natalizumab subpopulation were more pronounced, with an overall mean ARR of 0.300 (95% CI: 0.282–0.319; Fig. 3A) and 40.9% who relapsed (95% CI: 39.2–42.7, n = 1325/3237; Fig. 3B).

When relapse outcomes during fingolimod treatment were stratified into 6-month follow-up periods, the mean ARRs during the first 6 months in the natalizumab subpopulation were reduced versus the 12 months prior to study start to 0.703 (95% CI: 0.537–0.919), 0.725 (95% CI: 0.571–0.920), and 0.707 (95% CI: 0.531–0.940) following washout durations of 30–89, 90–149, and ≥ 150 days, respectively. The mean ARR in the non-natalizumab subpopulation was lower (0.390 [95% CI: 0.358–0.426]; Fig. 3A). Mean ARRs decreased in the natalizumab subpopulation during the 6–12-month follow-up period to 0.496 (95%

Table 1
Baseline characteristics.

Characteristics	Natalizumab subpopulation (N = 530)			Non-natalizumab subpopulation (N = 3382)
	Patients with relapse(s) during washout period (n = 101)	Patients without relapse(s) during washout period (n = 429)	Overall population (N = 530)	
Age, years				
Mean (SD)	40.1 (10.1)	39.4 (9.4)	39.5 (9.5)	39.4 (9.5)
Median	40.4	39.6	39.7	39.9
Female, *n* (%)	69 (68.3)	315 (73.4)	384 (72.5)	2420 (71.6)
Duration of MS[a], years, mean (SD)	11.0 (6.6)	10.7 (6.2)	10.7 (6.3)	7.8 (6.4)
No. of relapses within 12 months before study start, mean (SD)	1.8 (1.2)	1.3 (1.1)	1.5 (1.2)	1.7 (1.1)
EDSS score at baseline, median (IQR)	4.0 (2.5–5.5)	3.5 (2.0–4.5)	3.5 (2.0–5.0)	2.5 (1.5–4.0)
Duration of pre-treatment with natalizumab, days, mean (SD)			1078.4 (625.7)	NE
Duration of washout, days, mean (SD)	241.6 (245.1)	152.6 (148.8)	169.6 (174.6)	NE
No. of T2 lesions, *n* (%)				
0	7 (6.9)	14 (3.3)	21 (4.0)	179 (5.3)
1–9	4 (4.0)	35 (8.2)	39 (7.4)	394 (11.6)
> 9	86 (85.1)	369 (86.0)	455 (85.8)	2606 (77.1)
Missing	4 (4.0)	11 (2.6)	15 (2.8)	203 (6.0)
No. of Gd^+ lesions, *n* (%)				
0	62 (61.4)	313 (73.0)	375 (70.8)	1920 (56.8)
1–9	23 (22.8)	57 (13.3)	80 (15.1)	920 (27.2)
> 9	11 (10.9)	42 (9.8)	53 (10.0)	313 (9.3)
Missing	5 (5.0)	17 (4.0)	22 (4.2)	229 (6.8)
Previous MS DMTs, *n* (%)				
No previous DMT	0 (0.0)	0 (0.0)	0 (0.0)	251 (7.4)
Interferons	0 (0.0)	0 (0.0)	0 (0.0)	1986 (58.7)
Glatiramer acetate	0 (0.0)	0 (0.0)	0 (0.0)	947 (28.0)
Fingolimod	0 (0.0)	0 (0.0)	0 (0.0)	23 (0.7)
Natalizumab	101 (100.0)	429 (100.0)	530 (100.0)	0 (0.0)
Azathioprine/mitoxantrone	0 (0.0)	0 (0.0)	0 (0.0)	85 (2.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	90 (2.7)
JCV antibody status[b], *n* (%)				
Negative	11 (10.9)	56 (13.1)	67 (12.6)	0 (0.0)
Positive	68 (67.3)	317 (73.9)	385 (72.6)	0 (0.0)
Not done	21 (20.8)	56 (13.1)	77 (14.5)	1 (0.0)
Missing	1 (1.0)	0 (0.0)	1 (0.2)	3381 (100.0)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; Gd, gadolinium; IQR, interquartile range JCV, John Cunningham virus; MS, multiple sclerosis; NE, not evaluable; SD, standard deviation.

[a] Time from diagnosis to baseline visit.

[b] Not assessed in the non-natalizumab subpopulation.

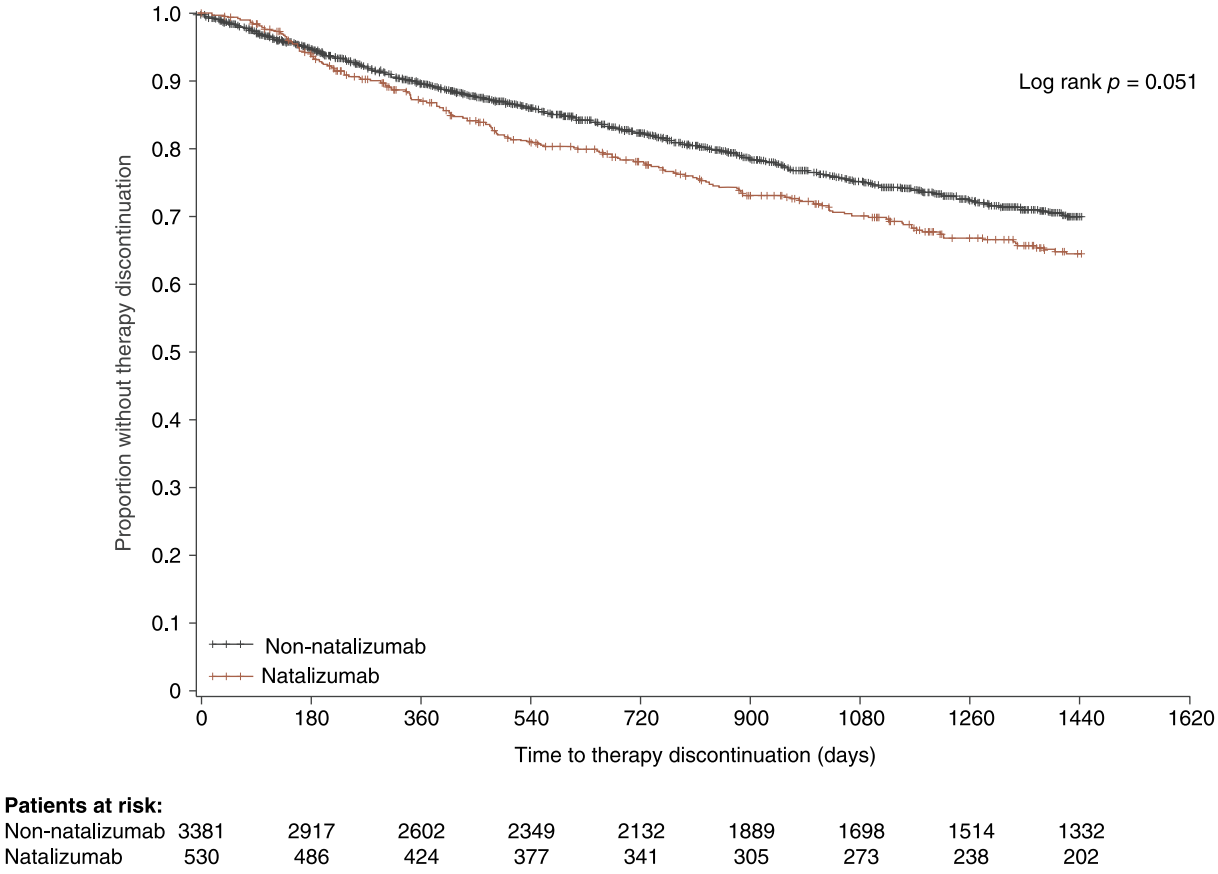

Fig. 2. Kaplan–Meier curve of time to fingolimod discontinuation.

CI: 0.359–0.686), 0.455 (95% CI: 0.334–0.620), and 0.501 (95% CI: 0.354–0.709), respectively, which were similar to the ARR in the non-natalizumab subpopulation in this period (0.338 [95% CI: 0.306–0.373]; Fig. 3A). A higher proportion in the natalizumab subpopulation (27.7% [95% CI: 21.1–35.0], n = 47/170; 29.9% [95% CI: 23.8–36.5], n = 63/211; and 26.2% [95% CI: 19.3–34.0], n = 39/149) than in the non-natalizumab subpopulation (15.6% [95% CI: 14.4–16.9], n = 506/3237) relapsed in the first 6 months (Fig. 3B). The proportions who relapsed in the natalizumab subpopulation decreased in the 6–12-month follow-up period to 19.9% (95% CI: 13.9–27.0, n = 31/156), 20.6% (95% CI: 15.1–27.1, n = 39/189), and 22.1% (95% CI: 15.4–30.0, n = 30/136), respectively, and to 13.8% (95% CI: 12.5–15.1, n = 397/2884) in the non-natalizumab subpopulation (Fig. 3B). During the remaining follow-up periods, the mean ARRs (Fig. 3A) and the proportions of patients who relapsed (Fig. 3B) continued to numerically decrease over time, reaching a plateau during month 36–42 up to month 48 in both subpopulations.

During 48 months of fingolimod treatment, the proportions of patients with 6-month confirmed disability worsening were 17.1% (95% CI: 12.2–22.8, n = 36/211) and 16.6% (95% CI: 14.7–18.7, n = 232/1394) in the natalizumab and non-natalizumab subpopulations, respectively (Fig. 4A). The corresponding proportions with confirmed disability improvement were 14.2% (95% CI: 9.8–19.7, n = 30/211) and 20.2% (95% CI: 18.1–22.4, n = 281/1394), respectively (Fig. 4A). The corresponding proportions with stable disability were 63.0% (95% CI: 56.1–69.6, n = 133/211) and 66.4% (95% CI: 63.9–68.9, n = 926/1394), respectively. When patients in the natalizumab subpopulation were stratified according to washout duration, similar proportions across the washout durations had 6-month confirmed disability worsening, 6-month confirmed disability improvement (Fig. 4B for both), or stable disability (data not shown).

When the 48 months of fingolimod treatment were stratified into 12-month follow-up periods, the proportions of patients in the natalizumab subpopulation with 6-month confirmed disability worsening were 5.1% (95% CI: 3.2–7.6, n = 22/432), 9.8% (95% CI: 6.9–13.5, n = 33/336), 12.2% (95% CI: 8.5–16.7, n = 32/263), and 12.6% (95% CI: 8.3–18.0, n = 25/199) during months 0–12, 12–24, 24–36, and 36–48, respectively (Fig. 4A). A numerically lower proportion in the non-natalizumab subpopulation had 6-month confirmed disability worsening in each 12-month period: 3.0% (95% CI: 2.4–3.8, n = 81/2672), 7.1% (95% CI: 6.1–8.3, n = 152/2129), 9.6% (95% CI: 8.2–11.1, n = 159/1661), and 13.0% (95% CI: 11.2–14.9, n = 171/1318), respectively (Fig. 4A). Similar trends were observed for the proportions of patients with 6-month confirmed disability improvement (Fig. 4A) and stable disability (data not shown).

3.4. Safety outcomes during fingolimod treatment

The proportions of patients reporting AEs were similar between the natalizumab and non-natalizumab subpopulations during each 12-month follow-up period. In the natalizumab subpopulation, AEs were experienced by 18.3% (n = 97/530), 16.4% (n = 71/432), 18.6% (n = 65/350), and 16.5% (n = 46/279) of patients, respectively; the corresponding proportions for SAEs were 4.3% (n = 23/530), 2.3% (n = 10/432), 3.1% (n = 11/350), and 3.9% (n = 11/279), during months 0–12, 12–24, 24–36, and 36–48, respectively. In the non-natalizumab subpopulation, AEs were experienced by 20.3% (n = 686/3382), 18.4% (n = 492/2672), 18.0% (n = 391/2177), and 17.9% (n = 308/1721) of patients, respectively. The corresponding proportions of patients with SAEs were 3.4% (n = 116/3382), 3.6% (n = 97/2672), 3.4% (n = 73/2177), and 3.3% (n = 57/1721), respectively. Regarding PML as an SAE of special interest in the present analysis, no cases were reported in the natalizumab subpopulation, whereas one case was reported in the non-natalizumab subpopulation: a 49-year-old

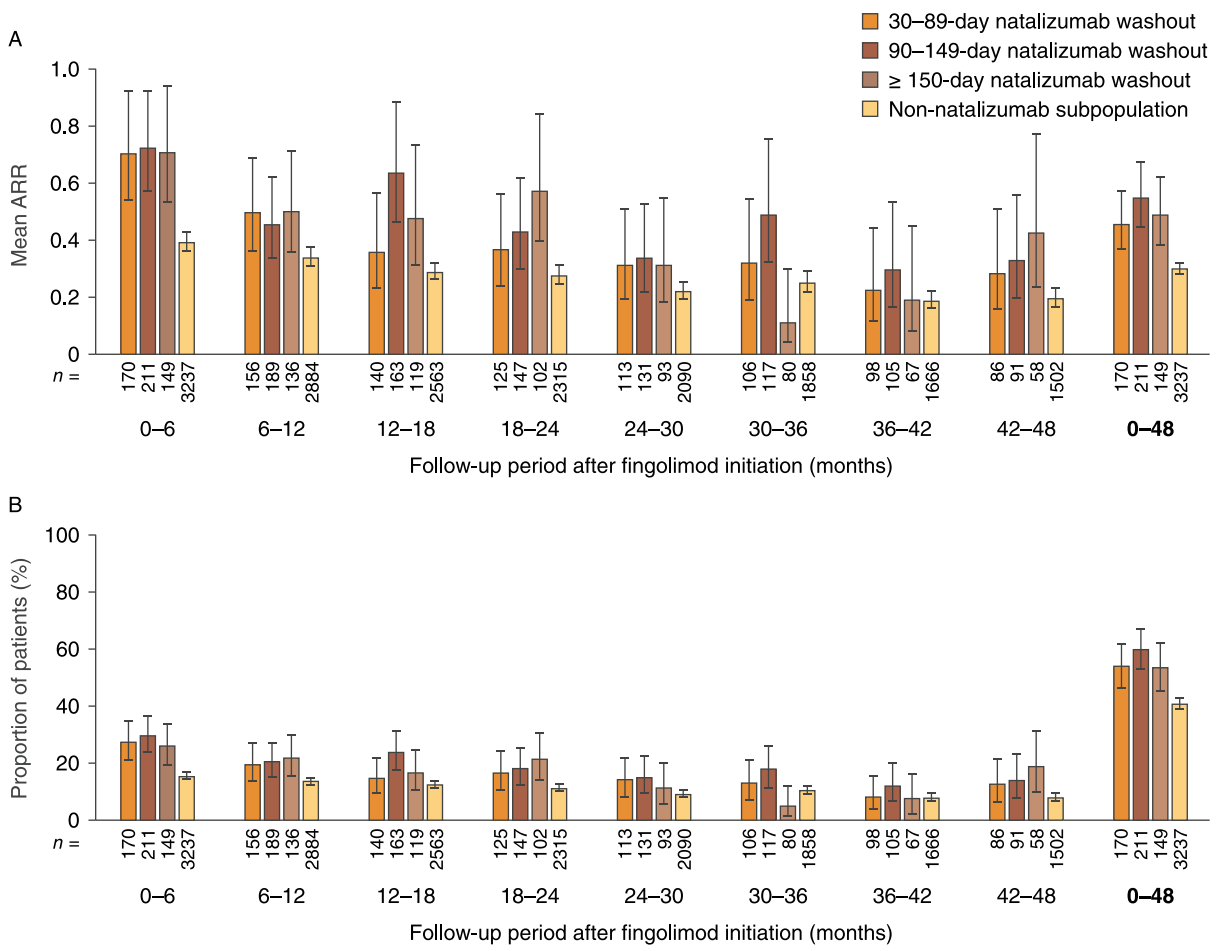

Fig. 3. Relapse[a] outcomes during treatment with fingolimod: (A) ARR and (B) proportion of patients with relapse(s) during 48 months of fingolimod treatment, stratified according to duration of washout between natalizumab discontinuation and fingolimod initiation.

[a] Relapses were assessed in accordance with the clinical judgment of physicians, and details of the duration and severity of the relapse as well as the need for hospitalization and/or treatment with steroids were captured. Relapses were not included in this analysis if they occurred within 30 days of a previous relapse that had already been included.

The number of patients included in each 6-month follow-up period for the natalizumab subpopulation was as follows. 0–6 (and 0–48) months: n = 530; 6–12: n = 481; 12–18: n = 422; 18–24: n = 374; 24–30: n = 337; 30–36: n = 303; 36–42: n = 270; 42–48: n = 235.

The number of patients included in each 6-month follow-up period for the non-natalizumab subpopulation was as follows. 0–6 (and 0–48) months: n = 3237; 6–12: n = 2884; 12–18: n = 2563; 18–24: n = 2315; 24–30: n = 2090; 30–36: n = 1858; 36–42: n = 1666; 42–48: n = 1502.

Error bars show 95% CIs.

ARR, annualized relapse rate; CI, confidence interval; n, number of patients.

patient was diagnosed with PML after 4 years and 3 months of treatment with fingolimod. The patient was asymptomatic, and no treatment was initiated. As of April 2015, JCV was no longer detectable.

4. Discussion

Using data from the non-interventional study PANGAEA, this analysis highlights the favorable benefit–risk profile of fingolimod over 48 months in patients switching from natalizumab. The effectiveness of fingolimod in improving relapse and disability outcomes was apparent early during fingolimod treatment, and was sustained over the observation period. This is consistent with findings in the overall PANGAEA study population (Ziemssen et al., 2019). This study contributes to the growing body of real-world evidence for fingolimod as an effective switch therapy and, to the best of our knowledge, is the first study to present long-term data on the safety and effectiveness of fingolimod in a large population in clinical practice who have discontinued natalizumab. Indeed, the study population included here is larger than those included in two recent long-term studies assessing outcomes following a switch to fingolimod from natalizumab (Diem et al., 2018; Guger et al., 2019).

In the present analysis, outcomes in the natalizumab subpopulation were compared to those of patients who had switched to fingolimod from DMTs other than natalizumab or initiated fingolimod first line (non-natalizumab subpopulation). Baseline characteristics were generally similar between the natalizumab and non-natalizumab subpopulations. However, patients in the natalizumab subpopulation had higher levels of disability and longer disease duration, suggesting that they had more advanced disease than those in the non-natalizumab subpopulation.

In order to improve clinical outcomes and achieve treatment goals, it is important that DMTs are associated with high levels of prolonged persistence (Trojano et al., 2017; Ziemssen et al., 2015a, 2016). In the present analysis, annual treatment discontinuation rates were generally low over the entire 48-month follow-up period: approximately 40% of patients in the natalizumab subpopulation discontinued fingolimod versus approximately 30% of patients in the non-natalizumab subpopulation. The difference between the subpopulations may reflect the fact that the baseline disease burden was higher in the natalizumab subpopulation than in the non-natalizumab subpopulation. In comparison, there are concerns about continued use of natalizumab for

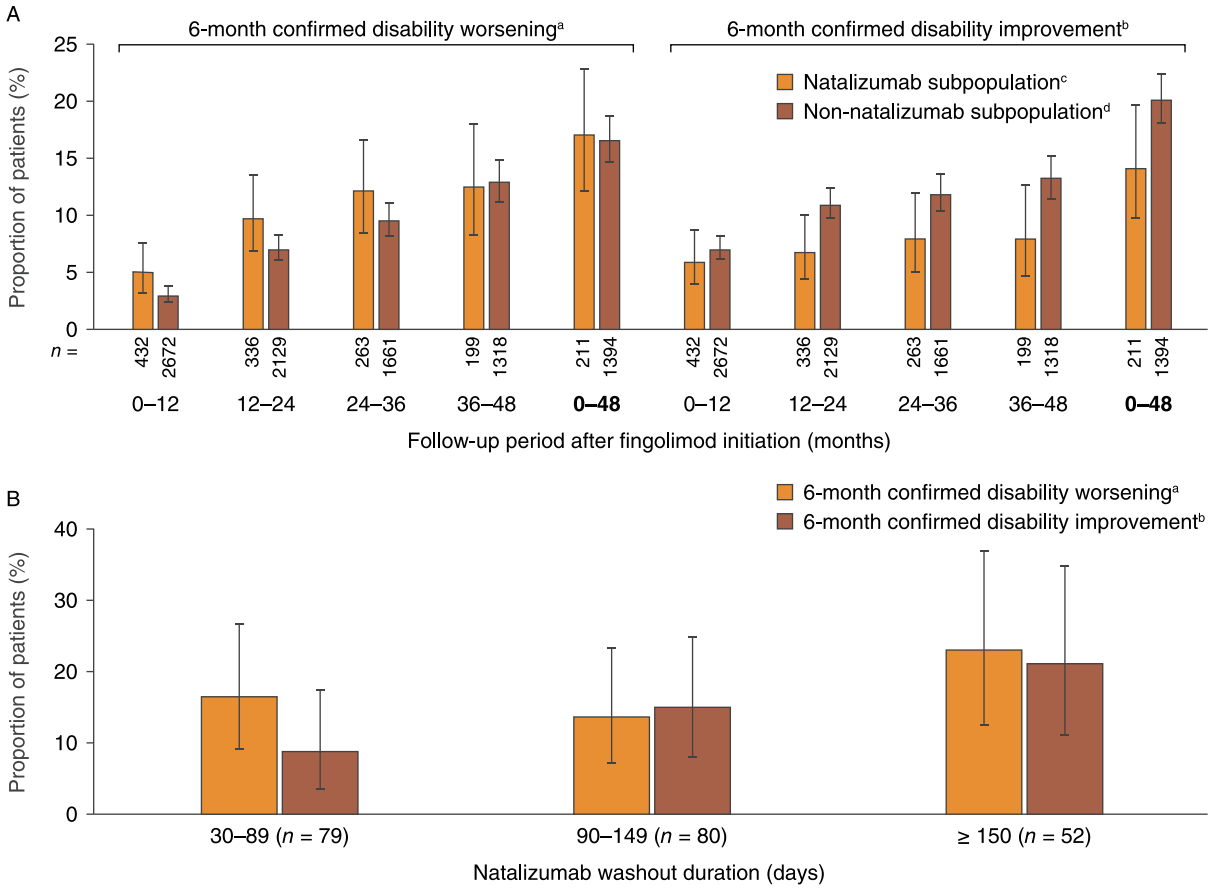

Fig. 4. Disability outcomes during treatment with fingolimod: (A) proportion of patients with 6-month confirmed disability worsening or 6-month confirmed disability improvement during 48 months of fingolimod in the natalizumab subpopulation and non-natalizumab subpopulations, and (B) in the natalizumab subpopulation following stratification based on the duration of washout following natalizumab discontinuation.

[a] Confirmed disability worsening was assessed in accordance with the increases in EDSS score from baseline, with confirmation of the increase in disability made at a visit in the absence of a relapse: a 1.5-point increase from a baseline EDSS score of 0; a 1-point increase from baseline EDSS scores of 1–5.0; and a 0.5-point increase in baseline EDSS scores of 5.5 or more. Patients for whom MS was a cause of death were considered to have confirmed disability worsening irrespective of baseline EDSS score or change in EDSS score.

[b] Confirmed disability improvement was assessed in accordance with the decrease in EDSS score from baseline, with confirmation of the decrease in disability made at a visit in the absence of a relapse: a decrease of at least 1 point regardless of baseline EDSS scores.

[c] The number of patients included in each 12-month follow-up period for the natalizumab subpopulation was as follows. 0–12 months: n = 432; 12–24: n = 336; 24–36: n = 263; 36–48: n = 199; 0–48: n = 211.

[d] The number of patients included in each 12-month follow-up period for the non-natalizumab subpopulation was as follows. 0–12 months: n = 2672; 12–24: n = 2129; 24–36: n = 1661; 36–48: n = 1318; 0–48: n = 1394.

Error bars show 95% CIs.

CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; n, number of patients.

longer than 24 months (Kramer et al., 2017; Tysabri, 2018); in line with this, studies have demonstrated that over 50% of patients discontinued natalizumab after 24 months because of the risk of PML (Clerico et al., 2014; Salhofer-Polanyi et al., 2014). A key determinant of the risk of PML is JCV status, and in the present study, more than two-thirds of patients in the natalizumab subpopulation were JCV positive.

In the natalizumab subpopulation, after 48 months of fingolimod treatment, the mean ARRs were reduced from baseline, and at least 40% of patients were relapse-free. These observations are consistent with other studies in which ARRs ranged from 0.20 (Leurs et al., 2017) to 0.97 (Comi et al., 2015), and relapses were experienced by 11.5% (Leurs et al., 2017) to 50.0% (Havla et al., 2013b) of patients switching from natalizumab to fingolimod. When data in the natalizumab subpopulation were stratified into 6-month periods, the effectiveness of fingolimod in improving disease outcomes was apparent within 6 months of initiating treatment, which suggests that control of disease activity can be experienced soon after switching to fingolimod from natalizumab. Trends in the non-natalizumab subpopulation were consistent with those in the natalizumab subpopulation; with the effects of fingolimod on reducing relapse, outcomes were more apparent in the non-natalizumab subpopulation. This difference between the groups may reflect the higher disease burden at baseline or an accumulation of disease activity during the washout period in the natalizumab subpopulation.

Freedom from confirmed disability worsening has been shown to be associated with reduced levels of neurodegeneration and, consequently, reduced physical and cognitive impairment (Zivadinov et al., 2016). In the present analysis, the proportions of patients with 6-month confirmed disability worsening at the end of the 48-month follow-up period were similar between the natalizumab and non-natalizumab subpopulations. When disability outcomes were stratified into 12-month periods, there was no significant difference over time in the proportion of patients with disability worsening. Similar trends were observed for the proportions of patients with improved or stable disability. These data indicate that fingolimod has a sustained effect on disability outcomes in patients who have switched from natalizumab, an effect that is

consistent in patients who have switched from other DMTs or initiated fingolimod first line.

Following natalizumab discontinuation, a key clinical consideration is how best to manage the transition to fingolimod treatment (Havla et al., 2013a), particularly the optimal washout duration. In the present analysis, there was no significant difference in relapse or disability outcomes during fingolimod treatment across the washout periods. This contrasts with the reports of previous RCTs and real-world studies (Jokubaitis et al., 2014; Kappos et al., 2015; Leurs et al., 2017), including the TOFINGO study, which concluded that patients with a washout duration of 16 weeks were at greater risk of MRI and clinical disease reactivation during fingolimod treatment than those with a washout duration of 8 or 12 weeks (Kappos et al., 2015). The difference between our results and those previously reported by Kappos and colleagues may reflect the greater sensitivity of the TOFINGO study, during which MRI outcomes and relapses were assessed at more frequent intervals than in the current study (Kappos et al., 2015). Nevertheless, the results of the present analysis also suggest using a shorter washout duration because the mean duration of washout was longer in patients who relapsed prior to fingolimod initiation than in patients who did not relapse.

In the present study, safety data were systematically assessed. There were no new safety signals relating to the potential additive effects of fingolimod and natalizumab during each 12-month follow-up period over 48 months. AEs or SAEs were experienced by similar proportions of patients in the natalizumab and non-natalizumab subpopulations. The overall frequency and nature of AEs were consistent with those observed during the pivotal fingolimod RCTs and real-world studies (Butzkueven et al., 2017; Calabresi et al., 2014; Cohen et al., 2010; Guarnera et al., 2017; Izquierdo et al., 2017; Kappos et al., 2010; Laroni et al., 2017). Of note, no cases of PML were reported in the natalizumab subpopulation, despite more than two-thirds of patients being JCV positive.

The strengths of the present analysis are that it provides documentation of relapse and disability outcomes as well as safety outcomes in patients switching to fingolimod from natalizumab over a long period of 48 months. Importantly, patients in PANGAEA received fingolimod in accordance with the SmPC and routine clinical practice. Furthermore, this study reports outcomes observed over a longer duration, and includes data from a larger number of patients than many previous studies. As an observational study, PANGAEA was subject to some inherent limitations relating to visit frequency and standardization of data collection. A limitation of the present analysis is that the data only describe outcomes during fingolimod treatment, and therefore do not provide any insight into the comparative effectiveness of fingolimod versus natalizumab or other therapies.

In conclusion, this subgroup analysis from PANGAEA highlights that fingolimod exhibits a favorable benefit–risk profile over 48 months following a switch from natalizumab that is consistent with its benefit–risk profile, following a switch from other DMTs or in patients initiating fingolimod first line. In addition, no new safety signals were observed, and the likelihood of relapses between natalizumab discontinuation and fingolimod initiation increased with longer washout durations. Our data therefore favor the recommendation by German guidelines of a washout interval of 6–8 weeks, bearing in mind the limitations of a *post hoc* analysis.

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Statement on data sharing

Owing to the confidential and proprietary nature of the data, Novartis will not be in a position to make the primary underlying research materials, including data, available.

CRediT authorship contribution statement

Tjalf Ziemssen: Conceptualization, Methodology, Investigation, Writing - review & editing, Visualization, Supervision. **Michael Lang:** Investigation, Writing - review & editing, Visualization. **Björn Tackenberg:** Investigation, Writing - review & editing, Visualization. **Stephan Schmidt:** Investigation, Writing - review & editing, Visualization. **Holger Albrecht:** Investigation, Writing - review & editing, Visualization. **Luisa Klotz:** Investigation, Writing - review & editing, Visualization. **Judith Haas:** Investigation, Writing - review & editing, Visualization. **Christoph Lassek:** Investigation, Writing - review & editing, Visualization. **Christian Cornelissen:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing, Visualization. **Benjamin Ettle:** Methodology, Formal analysis, Investigation, Writing - review & editing, Visualization.

Declaration of Competing Interest

TZ has received speaker fees and travel expenses for scientific meetings, and has been a steering committee member of clinical trials or participated in advisory boards and clinical trials for Almirall, Bayer, BAT, Biogen, Celgene, Merck, Roche, Novartis, Sanofi, and Teva.

ML has received travel grants, speaker fees, financial research support, or consultancy fees from Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, and Teva.

BT has received speaker fees, travel expenses, and consultancy fees from Alexion, Bayer Vital, Biogen, Celgene, CSL Behring, Grifols, Merck Serono, Novartis, Octapharma, Roche, Sanofi Genzyme, Teva, and UCB.

SS has received speaker fees and travel expenses for scientific meetings, and has participated in advisory boards for clinical trials for Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, and Teva.

HA has received travel expenses for scientific meetings or compensation for participation in advisory boards and clinical studies for Almirall, Bayer Healthcare, Biogen Idec, Merck Serono, Genzyme, Novartis, Sanofi-Aventis, and Teva.

LK has received fees for lecturing and serving on advisory boards, as well as travel expenses for attending meetings and financial research support from Biogen, the German Research Foundation, Merck, Novartis, Roche, and Sanofi Genzyme.

JH has received fees for lecturing and serving on advisory boards from Bayer, Biogen, Novartis, Roche, Sanofi Genzyme, and Teva.

CL has received speaker fees, travel expenses, and consultancy fees from Novartis.

CC was a paid employee of Novartis Pharma GmbH, Nuremberg, Germany at the time of this study.

BE is a paid employee of Novartis Pharma GmbH, Nuremberg, Germany.

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References

Berger, J.R., 2017. Classifying PML risk with disease modifying therapies. Mult. Scler. Relat. Disord. 12, 59–63.

Butzkueven, H., Weller, B., Giacomini, P.S., Cohan, S., Ziemssen, T., Kropshofer, H., Bellman, S., Sienkiewicz, D., 2017. Effectiveness and safety of fingolimod in patients with multiple sclerosis switched from natalizumab: results from TRANSITION — a 2-year observational study [poster]. In: Presented at the 7th joint ECTRIMS-ACTRIMS

Meeting. Paris, France.
Calabresi, P.A., Radue, E.W., Goodin, D., Jeffery, D., Rammohan, K.W., Reder, A.T., Vollmer, T., Agius, M.A., Kappos, L., Stites, T., Li, B., Cappiello, L., von Rosenstiel, P., Lublin, F.D., 2014. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 13 (6), 545–556.
Capobianco, M., di Sapio, A., Malentacchi, M., Malucchi, S., Matta, M., Sperli, F., Bertolotto, A., 2015. No impact of current therapeutic strategies on disease re-activation after natalizumab discontinuation: a comparative analysis of different approaches during the first year of natalizumab discontinuation. Eur. J. Neurol. 22 (3), 585–587.
Clerico, M., Schiavetti, I., De Mercanti, S.F., Piazza, F., Gned, D., Brescia Morra, V., Lanzillo, R., Ghezzi, A., Bianchi, A., Salemi, G., Realmuto, S., Sola, P., Vitetta, F., Cavalla, P., Paolicelli, D., Trojano, M., Sormani, M.P., Durelli, L., 2014. Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurol. 71 (8), 954–960.
Cohen, J.A., Barkhof, F., Comi, G., Hartung, H.P., Khatri, B.O., Montalban, X., Pelletier, J., Capra, R., Gallo, P., Izquierdo, G., Tiel-Wilck, K., de Vera, A., Jin, J., Stites, T., Wu, S., Aradhye, S., Kappos, L., 2010. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 402–415.
Cohen, M., Maillart, E., Tourbah, A., De Seze, J., Vukusic, S., Brassat, D., Anne, O., Wiertlewski, S., Camu, W., Courtois, S., Ruet, A., Debouverie, M., Le Page, E., Casez, O., Heinzlef, O., Stankoff, B., Bourre, B., Castelnovo, G., Rico, A., Berger, E., Camdessanche, J.P., Defer, G., Clavelou, P., Al Khedr, A., Zephir, H., Fromont, A., Papeix, C., Brochet, B., Pelletier, J., Lebrun, C., Club Francophone de la Sclerose en,Plaques, I., Club Francophone de la Sclerose en, 2014. Switching from natalizumab to fingolimod in multiple sclerosis: a French prospective study. JAMA Neurol. 71 (4), 436–441.
Comi, G., Gold, R., Dahlke, F., Sinha, A., von Rosenstiel, P., Tomic, D., Kappos, L., 2015. Relapses in patients treated with fingolimod after previous exposure to natalizumab. Mult. Scler. 21 (6), 786–790.
Diem, L., Nedeltchev, K., Kahles, T., Achtnichts, L., Findling, O., 2018. Long-term evaluation of NEDA-3 status in relapsing-remitting multiple sclerosis patients after switching from natalizumab to fingolimod. Ther. Adv. Neurol. Disord. 11, 1756286418791103.
European Medicines Agency, 2018. EMA confirms recommendations to minimise risk of brain infection PML with Tysabri. Available from: https://www.ema.europa.eu/news/ema-confirms-recommendations-minimise-risk-brain-infection-pml-tysabri (Accessed 22 November 2018).
Gilenya E.P.A.R., 2018. Gilenya summary of product charactierstics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002202/WC500104528.pdf (Accessed 25 April 2018).
Giovannoni, G., Naismith, R.T., 2014. Natalizumab to fingolimod washout in patients at risk of PML: when good intentions yield bad outcomes. Neurology 82 (14), 1196–1197.
Guarnera, C., Bramanti, P., Mazzon, E., 2017. Comparison of efficacy and safety of oral agents for the treatment of relapsing-remitting multiple sclerosis. Drug Des. Devel. Ther. 11, 2193–2207.
Guger, M., Enzinger, C., Leutmezer, F., Kraus, J., Kalcher, S., Kvas, E., Berger, T., Austrian, M.S.T.R., 2019. Switching from natalizumab to fingolimod treatment in multiple sclerosis: real life data from the Austrian MS Treatment Registry. J. Neurol. 266 (11), 2672–2677.
Havla, J., Kleiter, I., Kumpfel, T., 2013a. Bridging, switching or drug holidays - how to treat a patient who stops natalizumab? Ther. Clin. Risk Manag. 9, 361–369.
Havla, J., Tackenberg, B., Hellwig, K., Meinl, I., Krumbholz, M., Seitz, F., Eienbroker, C., Gold, R., Hohlfeld, R., Kleiter, I., Kumpfel, T., 2013b. Fingolimod reduces recurrence of disease activity after natalizumab withdrawal in multiple sclerosis. J. Neurol. 260 (5), 1382–1387.
Hoepner, R., Havla, J., Eienbroker, C., Tackenberg, B., Hellwig, K., Meinl, I., Hohlfeld, R., Gold, R., Kumpfel, T., Kleiter, I., 2014. Predictors for multiple sclerosis relapses after switching from natalizumab to fingolimod. Mult. Scler. 20 (13), 1714–1720.
Izquierdo, G., Damas, F., Paramo, M.D., Ruiz-Pena, J.L., Navarro, G., 2017. The real-world effectiveness and safety of fingolimod in relapsing-remitting multiple sclerosis patients: an observational study. PLoS ONE 12 (4), e0176174.
Jokubaitis, V.G., Li, V., Kalincik, T., Izquierdo, G., Hodgkinson, S., Alroughani, R., Lechner-Scott, J., Lugaresi, A., Duquette, P., Girard, M., Barnett, M., Grand'Maison, F., Trojano, M., Slee, M., Giuliani, G., Shaw, C., Boz, C., Spitaleri, D.L., Verheul, F., Haartsen, J., Liew, D., Butzkueven, H., Group, M.S.S., 2014. Fingolimod after natalizumab and the risk of short-term relapse. Neurology 82 (14), 1204–1211.
Kappos, L., Radue, E.W., Comi, G., Montalban, X., Butzkueven, H., Wiendl, H., Giovannoni, G., Hartung, H.P., Derfuss, T., Naegelin, Y., Sprenger, T., Mueller-Lenke, N., Griffiths, S., von Rosenstiel, P., Gottschalk, R., Zhang, Y., Dahlke, F., Tomic, D., group, T., 2015. Switching from natalizumab to fingolimod: a randomized, placebo-controlled study in RRMS. Neurology 85 (1), 29–39.
Kappos, L., Radue, E.W., O'Connor, P., Polman, C., Hohlfeld, R., Calabresi, P., Selmaj, K., Agoropoulou, C., Leyk, M., Zhang-Auberson, L., Burtin, P., 2010. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N. Engl. J. Med. 362 (5), 387–401.
Kornek, B., 2015. An update on the use of natalizumab in the treatment of multiple sclerosis: appropriate patient selection and special considerations. Patient Prefer Adherence 9, 675–684.
Kramer, J., Tenberge, J.G., Kleiter, I., Gaissmaier, W., Ruck, T., Heesen, C., Meuth, S.G., 2017. Is the risk of progressive multifocal leukoencephalopathy the real reason for natalizumab discontinuation in patients with multiple sclerosis? PLoS ONE 12 (4), e0174858.
Laroni, A., Brogi, D., Brescia Morra, V., Guidi, L., Pozzilli, C., Comi, G., Lugaresi, A., Turrini, R., Raimondi, D., Uccelli, A., Mancardi, G.L., 2017. Safety and tolerability of fingolimod in patients with relapsing-remitting multiple sclerosis: results of an open-label clinical trial in Italy. Neurol. Sci. 38 (1), 53–59.
Leurs, C.E., van Kempen, Z.L., Dekker, I., Balk, L.J., Wattjes, M.P., Rispens, T., Uitdehaag, B.M., Killestein, J., 2017. Switching natalizumab to fingolimod within 6 weeks reduces recurrence of disease activity in MS patients. Mult. Scler 1352458517726381.
Lo Re, M., Capobianco, M., Ragonese, P., Realmuto, S., Malucchi, S., Berchialla, P., Salemi, G., Bertolotto, A., 2015. Natalizumab discontinuation and treatment strategies in patients with multiple sclerosis (MS): a retrospective study from two Italian MS centers. Neurol. Ther. 4 (2), 147–157.
Mehling, M., Johnson, T.A., Antel, J., Kappos, L., Bar-Or, A., 2011. Clinical immunology of the sphingosine 1-phosphate receptor modulator fingolimod (FTY720) in multiple sclerosis. Neurology 76 (8 Suppl 3), S20–S27.
Prosperini, L., Annovazzi, P., Capobianco, M., Capra, R., Buttari, F., Gasperini, C., Galgani, S., Solaro, C., Centonze, D., Bertolotto, A., Pozzilli, C., Ghezzi, A., 2015. Natalizumab discontinuation in patients with multiple sclerosis: profiling risk and benefits at therapeutic crossroads. Mult. Scler. 21 (13), 1713–1722.
Salhofer-Polanyi, S., Baumgartner, A., Kraus, J., Maida, E., Schmied, M., Leutmezer, F., 2014. What to expect after natalizumab cessation in a real-life setting. Acta Neurol. Scand. 130 (2), 97–102.
Sehr, T., Proschmann, U., Thomas, K., Marggraf, M., Straube, E., Reichmann, H., Chan, A., Ziemssen, T., 2016. New insights into the pharmacokinetics and pharmacodynamics of natalizumab treatment for patients with multiple sclerosis, obtained from clinical and in vitro studies. J. Neuroinflammation 13 (1), 164.
Trojano, M., Tintore, M., Montalban, X., Hillert, J., Kalincik, T., Iaffaldano, P., Spelman, T., Sormani, M.P., Butzkueven, H., 2017. Treatment decisions in multiple sclerosis - insights from real-world observational studies. Nat. Rev. Neurol. 13 (2), 105–118.
Kompetenznetz Multiple Sklerose, 2018. Qualitaetshandbuch MS / NMOSD: empfehlungen zur therapie der Multiple Sklerose/Neuromyelitis-optica-Spektrum-Erkrankungen fuer Aerzte. Available from: https://www.kompetenznetz-multiplesklerose.de/fachinformationen/qualitaetshandbuch/ (Accessed 3 December 2018). German.
Tysabri E.P.A.R., 2018. Tysabri summary of product charactierstics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf (Accessed 25 April 2018).
Ziemssen, T., De Stefano, N., Pia Sormani, M., Van Wijmeersch, B., Wiendl, H., Kieseier, B.C., 2015a. Optimizing therapy early in multiple sclerosis: an evidence-based view. Mult. Scler. Relat. Disord. 4 (5), 460–469.
Ziemssen, T., Derfuss, T., de Stefano, N., Giovannoni, G., Palavra, F., Tomic, D., Vollmer, T., Schippling, S., 2016. Optimizing treatment success in multiple sclerosis. J. Neurol. 263 (6), 1053–1065.
Ziemssen, T., Kern, R., Cornelissen, C., 2015b. The PANGAEA study design - a prospective, multicenter, non-interventional, long-term study on fingolimod for the treatment of multiple sclerosis in daily practice. BMC Neurol. 15, 93.
Ziemssen, T., Lang, M., Tackenberg, B., Schmidt, S., Albrecht, H., Klotz, L., Haas, J., Lassek, C., Couto, C.A., Findlay, J.A., Cornelissen, C., group, P., 2019. Real-world persistence and benefit-risk profile of fingolimod over 36 months in Germany. Neurol. Neuroimmunol. Neuroinflamm. 6 (3), e548.
Ziemssen, T., Lang, M., Tackenberg, B., Schmidt, S., Albrecht, H., Klotz, L., Haas, J., Lassek, C., Medin, J., Cornelissen, C., group, P., 2018. Clinical and demographic profile of patients receiving fingolimod in clinical practice in Germany and the benefit-risk profile of fingolimod after 1 year of treatment: initial results from the observational, noninterventional study PANGAEA. Neurotherapeutics 15 (1), 190–199.
Zivadinov, R., Uher, T., Hagemeier, J., Vaneckova, M., Ramasamy, D.P., Tyblova, M., Bergsland, N., Seidl, Z., Dwyer, M.G., Krasensky, J., Havrdova, E., Horakova, D., 2016. A serial 10-year follow-up study of brain atrophy and disability progression in RRMS patients. Mult. Scler. 22 (13), 1709–1718.