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ORIGINAL RESEARCH ARTICLE

Real-World Outcomes in Fingolimod-Treated Patients with Multiple Sclerosis in the Czech Republic: Results from the 12-Month GOLEMS Study

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Abstract

Background and Objective Once-daily oral fingolimod is approved in the EU as escalation treatment for adult patients with highly active relapsing multiple sclerosis (MS). The efficacy and safety profiles of fingolimod have been well established in a large clinical development programme and several papers reflecting the experience with fingolimod in real-world settings have been published to date. The GOLEMS study was designed to evaluate the efficacy, safety and tolerability of fingolimod and the impact of fingolimod treatment on disability progression and work capability in patients with MS in routine clinical practice in the Czech Republic.

Methods GOLEMS was a national, multicentre, non-interventional, single-arm study conducted to analyse the outcomes of a minimum of 12 months of fingolimod therapy on primary and secondary endpoints. The primary endpoint was to assess the proportion of relapse-free patients and severity of MS relapses in patients treated with fingolimod for 12 months. Secondary endpoints included assessment of changes in disability progression evaluated by the Expanded Disability Status Scale (EDSS) score and work capability assessment measured through voluntary completion of the WPAI-GH questionnaire. The predictive factors for relapse-free status during fingolimod treatment were also analysed.

Results Of the 240 enrolled patients, 219 completed the 12-month treatment period at the time of final analysis. In the efficacy set ($N = 237$), the proportion of relapse-free patients increased from 47 patients (19.6 %; 95 % confidence interval [CI] 14.8–25.2) in the year before fingolimod initiation to 152 patients (64.1 %; 95 % CI 58.0–70.2) after 1 year of fingolimod treatment. Of the 85 patients who experienced at least one relapse after 1 year of fingolimod treatment, 53 (62.4 %; 95 % CI 51.7–71.9) reported only one relapse, while 25 (29.4 %; 95 % CI 20.8–39.8) and seven (8.2 %; 95 % CI 4.0–16.0) patients had $\geq$2 relapses, respectively. No significant changes were observed in EDSS scores over the 12-month treatment period compared with baseline. The absolute number of relapses during 2 years before initiation of fingolimod treatment and baseline EDSS scores were identified as significant independent predictors for 'being relapse-free' during the 12-month fingolimod treatment period. No trend was established in work capability or number of missed days at work due to the large proportion of missing data. Of 240 enrolled patients, 27 (11.3 %) patients discontinued the study at or before the 12-month visit, 16 (6.7 %) discontinued because of adverse events related to study drug. Only six (2.5 %) patients reported serious adverse events related to the study drug.

Conclusion The results confirm the favourable safety and efficacy profile of fingolimod under real-world conditions, consistent with phase III trials.

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Key Points

Fingolimod is an approved oral therapy for patients with multiple sclerosis (MS).

The GOLEMS study confirmed the efficacy of fingolimod in patients with MS under real-world settings.

These data support the safety and tolerability of fingolimod in clinical practice.

1 Introduction

In the EU, once-daily oral fingolimod 0.5 mg (FTY720; Gilenya®, Novartis Pharma AG) is approved for the management of adult patients with highly active forms of relapsing multiple sclerosis (MS), including those who fail to respond to first-line disease-modifying therapy (DMT) [1]. Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator that prevents the egress of auto-reactive lymphocytes from lymph nodes, thereby reducing their infiltration into the central nervous system (CNS) [2, 3]. Phase III trials have shown superior efficacy of fingolimod compared with intramuscular interferon (IFN)-β-1a (1-year TRANSFORMS study) and placebo (2-year FREEDOMS and FREEDOMS II studies) [4–6]. As of the second quarter of 2016, approximately 155,000 patients have been treated with fingolimod in both clinical trials and post-marketing settings, and the total patient exposure is approximately 343,000 patient-years [7].

Real-world studies complement the pivotal 'randomized-controlled' clinical trials conducted for approval process in providing evidence on the safety and efficacy of a drug under routine clinical practice [8]. The **G**ilenya (FingOLimod) in prescribing conditions defined by the CzEch regulator of drug reiMburSement (GOLEMS) study was planned to provide the requested healthcare outcomes data from MS patients receiving fingolimod under real-life conditions to the Health Authority and General Health Insurance Company of the Czech Republic.

In this report, we present the results from the GOLEMS study, which investigated the effects of 12-month fingolimod treatment on the incidence and severity of relapses, disability progression and work capability in patients with MS.

2 Patients and Methods

2.1 Study Design and Patients

GOLEMS was a multicentre, observational, non-interventional, single-arm study designed to assess treatment outcomes in patients with MS receiving a minimum of 12 months of fingolimod therapy in the Czech Republic. All existing MS centres in the Czech Republic were asked to participate in the study. Fingolimod prescription was at the discretion of the treating physician and patient and was independent of participation in the study. Patients were included in accordance with the locally approved prescribing limitation by the Czech regulator for the reimbursement of drugs. Patients with MS who initiated fingolimod treatment at study entry or within 6 months before study entry as part of routine medical care were included in the study. All patients were assessed and monitored as per the revised label issued on 20 March 2012 and provided written informed consent form. Study visits were performed at baseline (treatment initiation), month 1, month 3 and every 3 months up to month 12, followed by every 6 months until the end of the 36-month study period. Women of child-bearing potential were informed about the potential risk of fingolimod use to the fetus, about the need for effective contraception and about the recommended 2-month wash-out period before a planned pregnancy.

2.2 Sample Size

A total of 240 patients were enrolled over 2 years in this study. Assuming a 5 % drop-out rate, it was expected that data from 228 patients with a minimum observation period of 12 months would be available for statistical analysis at the end of the study. This sample size was estimated to provide sufficient precision for the frequency of patients without relapse (95 % confidence interval [CI] 74–85; CI width 11 %).

2.3 Study Endpoints

The primary endpoints were the proportion of relapse-free patients and severity of MS relapses in patients treated with fingolimod for 12 months. The key secondary endpoints were the incidence and severity of relapses after treatment initiation at each post-baseline visit. In addition, changes in the Expanded Disability Status Scale (EDSS) scores and work capability (Work Productivity and Activity Impairment-General Health [WPAI-GH] scores and number of missed days at work) from baseline to 12 months were assessed. Patients voluntarily completed the WPAI:GH

questionnaire and answered a question about number of missed days at work if they were employed. The safety profile of fingolimod, including adverse events (AEs) and serious AEs (SAEs), was also assessed. In addition to primary efficacy results, the proportion of relapse-free patients was assessed in the subgroup of patients treated with natalizumab before initiating fingolimod treatment.

Medical health records collected during clinical practice by the investigating physicians were used as the data source in this study. Data were collected using the web-based software OpenClinica®, an electronic data capture system compliant with the guidelines of Good Clinical Practice (21 CFR Part 11). All investigators and study personnel using OpenClinica® were trained, and physicians directly entered data into the system. Coherence checks and correction of data were performed for validation of data in the system.

2.4 Statistical Analysis

Three datasets were used for analysis: all-treated dataset, efficacy dataset and completed set. The all-treated dataset consisted of all enrolled patients with available data over 12 months after the start of Gilenya therapy and patients who discontinued the study. The efficacy set consisted of all treated patients with the exception of three patients for whom the last visit recorded was at month 3 or sooner and the reason for discontinuation was not due to treatment failure or adverse events. The completed set consisted of all patients who completed the 12-month observation period. With exception of the three patients (as described above), the efficacy set included discontinued patients which might cause overestimation of relapse-free patients due to the fact that after discontinuation relapses were not recorded. Analysis using the completed set might cause underestimation of relapse-free patients due to the fact that patients who might have discontinued due to lack of efficacy (and relapses) were not in the completed set. Results using the efficacy dataset were interpreted as primary results. The completed set was used for sensitivity analysis which showed very similar results to the efficacy set (as described in Sect. 3); therefore, occurrence of potential selective bias was excluded.

Data were analysed descriptively including 95 % CIs. Wald asymptotic CIs were calculated to determine the percentage of relapse-free patients, while the frequency and severity of relapses were evaluated using Wilson CIs, which are appropriate when percentages are close to 0 or 100.

The EDSS score was recorded at every visit: Baseline, month 1 (M1), month 3 (M3), month 6 (M6) and month 12 (M12), and an additional EDSS score was performed during relapses to evaluate the severity of relapse. As the study was non-interventional, visit scheduled was not strictly completed. MS relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event [9]. The relapse severity was graded as: mild (EDSS increase by 0.5 point, or 1-point change in one to three functional system (FS) scores), moderate (EDSS increase by 1 or 2 points, or 2-point FS change in one or two systems, or 1-point change in four or more systems), or severe (exceeding moderate criteria) [10].

Multivariate logistic regression was used to identify baseline characteristics, which are strongly predictive of being relapse-free during 12 months of fingolimod therapy. The following baseline characteristics were included into the multivariate logistic regression: age, duration of diagnosis, number of relapses during the previous year, severity of last relapse (mild/moderate/severe), previous MS therapy (any interferon or glatiramer acetate/natalizumab in the period at least 3 months before beginning therapy with fingolimod/other medication), EDSS score at baseline (≤ 3 vs. >3) and number of relapses during the last 2 years (0–2 vs. ≥ 3). The level of significance was set to 5 %; therefore, characteristics not associated with the probability of being relapse-free after 12 months of treatment were excluded, and only significant independent predictors were retained in the final model. In addition, the effect of EDSS scores on the proportion of relapse-free patients was presented using Kaplan–Meier (KM) curves. KM curves for EDSS score at baseline of ≤ 3 versus >3 were compared using log-rank test. Within-patient changes from baseline in EDSS score were calculated and analysed only descriptively because the results of descriptive analysis showed no change to be tested. Data were statistically analysed using SAS software version 9.4 (SAS, Cary, NC, USA).

3 Results

A total of 240 patients were enrolled, and all were included in the all-treated set for final analysis. At the end of 12 months or earlier 27 (11.3 %) patients discontinued the study. The efficacy dataset had a total of 237 patients. Three patients' with data available only up to the 3-month visit and reason for discontinuation not related to safety or efficacy issues were excluded from the efficacy analysis, since absence of relapse might have been due to the short observation period. A total of 219 patients completed the 12-month treatment period and were included in the completed data set. The distribution of patients in the all-treated, efficacy and completed sets at the time of final analysis is presented in Fig. 1.

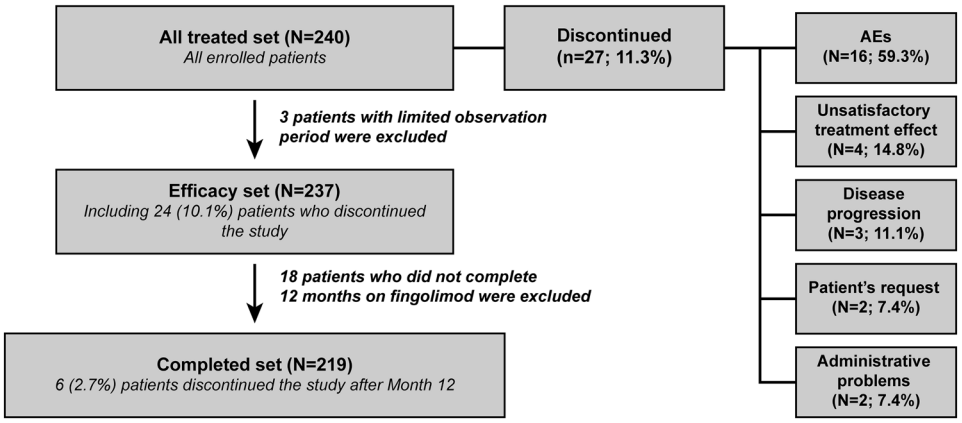

Fig. 1 Allocation of subjects in different data sets analysed in the GOLEMS study. *AEs* adverse events

3.1 Demographics and Baseline Characteristics

Table 1 presents the demographics and baseline characteristics of all enrolled patients ($N = 240$). Patients were predominantly females (70.4 %), with an average age of 37.4 years. At baseline, the mean time since the first MS symptom before study entry was 10.4 years, and the mean EDSS score was 3.4. Based on available data from 23 patients at baseline, the mean number of missed days at work within 3 months before study entry was 8.3. Of 240 enrolled patients, 47 (19.6 %) did not experience any relapse, 54 (22.5 %) reported one relapse, 102 (42.5 %) reported two relapses and 37 (15.4 %) experienced >2 relapses within 1 year prior to fingolimod initiation. All analysed patients had received previous treatment with any DMT before receiving fingolimod. Fifty-nine patients out of 240 included were treated with natalizumab before initiating fingolimod (Table 2). All patients switched directly from natalizumab to fingolimod. There were 29 (49 %) patients who were relapse-free in the year prior to initiation of fingolimod treatment. The mean duration of the wash-out period after natalizumab termination was 105.8 days, median 87 days.

3.2 Effect of Fingolimod Treatment on MS Relapse Status

3.2.1 Efficacy Set

Among 237 patients, 152 (64.1 %; 95 % CI 58.0–70.2; Fig. 2a) did not report any relapse as compared to the previous year with only 47 patients (19.6 %; 95 % CI 14.8–25.2) reporting to be relapse-free. Of the 24 discontinued patients, ten were relapse-free and had received treatment for an average of 145.9 (range 14–305) days.

3.2.2 Completed Set

Out of 219 patients, 142 (64.8 %; 95 % CI 58.5–71.2) did not have any relapse over 12 months of fingolimod treatment.

All the results presented below are based on the efficacy set.

3.3 Effects of Fingolimod Treatment on Frequency and Severity of Relapse

Fingolimod reduced the average number of relapses per patient (0.61, 95 % CI 0.48–0.73) after 12 months of therapy compared with the mean number of relapses per patient (1.56; 95 % CI 1.43–1.69) 12 months prior to the study entry, which represents a reduction of 0.96 (95 % CI 0.80–1.11) relapses, and relative reduction of 65.4 % (95 % CI 57.7–73.0). Of the 85 patients with relapses, 25 (29.4 %) and seven (8.2 %) reported ≥2 relapses, respectively, during the 12-month treatment, compared with 102 (42.5 %) and 37 (15.4 %) patients in the year before fingolimod treatment (Fig. 2a). Out of the total 125 relapses reported within 12 months of fingolimod treatment, the proportions of mild, moderate and severe relapses were 46.4 % (95 % CI 37.9–55.1), 44.8 % (95 % CI 36.4–53.5) and 8.8 % (95 % CI 5.0–15.1), respectively (Fig. 2b). The mean EDSS score performed during relapse was 4.36 (95 % CI 4.11–4.61).

3.4 Independent Predictors for Being Relapse-Free

Logistic regression analysis showed that baseline EDSS scores and number of relapses within 2 years before fingolimod initiation were significant and independent predictors for being relapse-free during the 12-month fingolimod treatment period. Analysis using the completed set showed that patients with baseline EDSS score ≤3 had higher odds (odds ratio [OR] = 2.28, 95 % CI 1.23–4.07, $p = 0.005$) of not relapsing during 12 months of fingolimod therapy compared with patients for whom the baseline EDSS score was >3. Patients with ≤2 relapses during previous 2 years had higher odds of not relapsing on fingolimod therapy (OR = 3.27, 95 % CI 1.85–5.878, $p < 0.0001$) compared with patients who had >2 relapses.

Table 1 Demographics and baseline characteristics of the GOLEMS study patients

Characteristics		Value
Gender		
Male		71 (29.6)
Female		169 (70.4)
Age (years)		37.4 ± 9.3
Time since the first MS symptom before study entry (years)		10.35 ± 6.7
Relapse-free patients within 1 year before fingolimod initiation		47 (19.6)
Relapse-free patients on natalizumab before fingolimod within 1 year before fingolimod initiation		29 (49.2)
Frequency of relapses within 1 year before fingolimod initiation		
Patients with 1 relapse		54 (22.5)
Patients with ≥2 relapses		139 (57.9)
Relapse-free patients within 2 years before fingolimod treatment		35 (14.6)
Frequency of relapses within 2 years before fingolimod initiation		
Patients with 1 relapse		27 (11.3)
Patients with ≥2 relapses		178 (73.2)
EDSS score for last 3 months before study entry or at the initiation of fingolimod treatment		3.4 ± 1.3
Number of missed days at work during 3 months before study entry[a]		8.3 ± 20.0
Previous DMT treatment		
Copaxone	*n*, (%)	67 (27.9)
	Duration of treatment (mo)	46.5 ± 38.9
Tysabri (Natalizumab)	*n*, (%)	59 (24.6)
	Duration of treatment (mo)	26.7 ± 14.9
Rebif 44 μg (Interferon beta-1a)	*n*, (%)	46 (19.2)
	Duration of treatment (mo)	34.3 ± 38.2
Rebif 22 μg (Interferon beta-1a)	*n*, (%)	29 (12.1)
	Duration of treatment (mo)	36.1 ± 39.4
Avonex (Interferon beta-1a)	*n*, (%)	27 (11.3)
	Duration of treatment (mo)	42.3 ± 41.4
Betaferon (Recombinant interferon beta-1b)	*n*, (%)	22 (9.2)
	Duration of treatment (mo)	57.7 ± 35.2
Other[b]	*n*, (%)	12 (5.0)
	Duration of treatment (mo)	82.8 ± 56.9
Azathioprine	*n*, (%)	6 (2.5)
	Duration of treatment (mo)	101.8 ± 57.2
Extavia	*n*, (%)	7 (2.9)
	Duration of treatment (mo)	19.7 ± 14.6
IVIG	*n*, (%)	4 (1.7)
	Duration of treatment (mo)	43.8 ± 41.5

Values are expressed as mean ± SD or *n* (%)

CI confidence interval, *DMT* disease modifying therapy, *EDSS* Expanded Disability Status Scale, *GOLEMS* Gilenya (FingOLimod) in prescribing conditions defined by the **CzEC**h regulator of drug reimbursement, *MS* multiple sclerosis, *SD* standard deviation

[a] $n = 23$

[b] Other medication: Teriflunomide, Prednisone, Cladribine, Dimethyl fumarate, Ocrelizumab, Methylprednisolone

3.5 Kaplan–Meier (KM) Analysis of Relapse-Free Patients and Time to First Relapse

EDSS score at baseline was significantly associated with the proportion of relapse-free patients. Further exploration using KM estimates showed that the proportion of relapse-free patients was higher (68.1 %) in the subgroup of patients with a baseline EDSS score ≤3 compared with those with an EDSS score >3 at baseline (50.9 %; log-rank test $p = 0.0060$; Fig. 3).

Table 2 Demographics and baseline characteristics of patients treated with natalizumab before study start ($n = 59$)

Characteristics	Value
Gender	
Male	16 (27.1)
Female	43 (72.9)
Age (years)	37.7 ± 9.7
Time since the first MS symptom before study entry (years)	12.3 ± 6.4
Relapse-free patients within 1 year before fingolimod initiation	29 (49.2)
Frequency of relapses within 1 year before fingolimod initiation	
Patients with 1 relapse	16 (27.1)
Patients with ≥2 relapses	14 (23.7)
Relapse-free patients within 2 years before fingolimod treatment	22 (37.3)
Frequency of relapses within 2 years before fingolimod initiation	
Patients with 1 relapse	13 (22.0)
Patients with ≥2 relapses	24 (40.7)
EDSS score for last 3 months before study entry or at the initiation of fingolimod treatment	3.5 ± 1.3
Number of missed days at work during 3 months before study entry[a]	23.3 ± 36.2

Values are expressed as mean ± SD or *n* (%)

CI confidence interval, *EDSS* Expanded Disability Status Scale, *GOLEMS* Gilenya (FingOLimod) in prescribing conditions defined by the CzEch regulator of drug reimbursement, *MS* multiple sclerosis, *SD* standard deviation

[a] $n = 6$

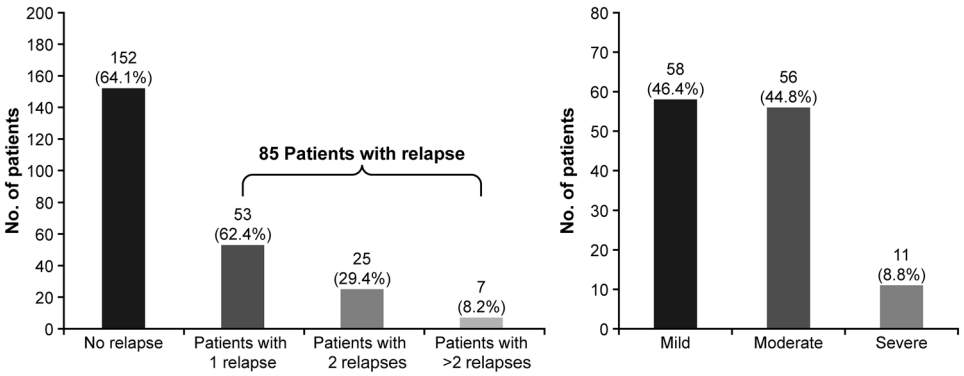

Fig. 2 **a** Effect of 12 month fingolimod treatment on frequency of relapses ($N = 237$). **b** Severity of relapses ($n = 125$[a]). [a]Total number of relapses reported in 85 patients of efficacy set ($N = 237$)

3.6 Changes in Disability Progression and Work Capability Assessment

Disability progression, as assessed by EDSS scores, remained constant over the observation period. EDSS score was 3.4 ± 1.3 at baseline and 3.4 ± 1.4 at 12 months (Tables 1, 3). Within-patient differences between the baseline value and EDSS score at 12 months was 0.05 ± 0.56 (95 % CI −0.02 to 0.13), the median value of the change was 0. For analysis of change in work capability assessment, data were available at baseline from 23 patients, and even fewer responses were available for the treatment period. Descriptive analysis of data did not indicate any trends in change from baseline. Mean values of within-patient changes in EDSS score from baseline ranged from −0.01 to 0.05 at individual post-baseline visits (95 % CI of means included 0 at all post-baseline visits), median values of the change were 0 at all post-baseline visits. Since the response rate was approximately 10 % and a large set of data was missing, no detailed analysis in terms of trends of changes in these parameters was performed.

3.7 Relapse Status in Patients Receiving Natalizumab before Fingolimod Initiation

Of the 59 patients who had received natalizumab before fingolimod, 31 (52.5 %) were without relapse within the first 12 months on fingolimod compared with 29 (49.2 %) relapse-free patients in the last year prior to fingolimod initiation. Out of 28 patients with relapses after 1 year of treatment with fingolimod, 12 (42.9 %) had mild relapses, while ten (35.7 %) and six (21.4 %) had moderate and severe relapses, respectively (Fig. 4).

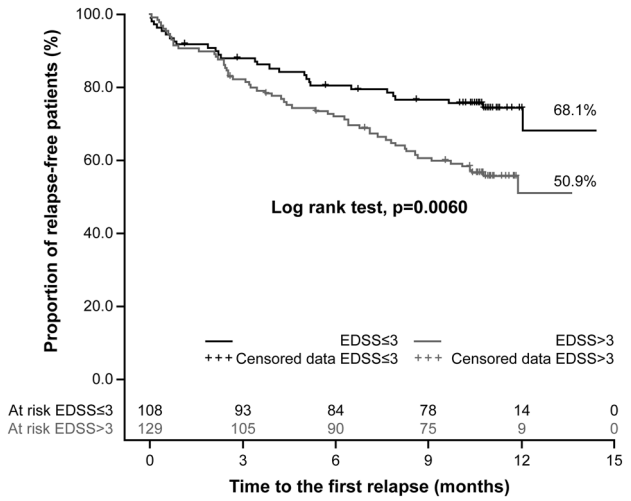

Fig. 3 Proportion of relapse free patients in the efficacy set ($N = 237$) by baseline EDSS score (Kaplan–Meier analysis). Kaplan–Meier plot depicts the proportion of relapse-free patients in the subgroups of patients with a baseline EDSS score ≤3 compared with an EDSS score >3 at baseline. *EDSS* Expanded Disability Status Scale

3.8 Adverse Events and Serious Adverse Events

Of the 240 patients included in the analysis, 84 (35.0 %) reported 109 AEs, ten (4.2 %) reported 11 SAEs and six (2.5 %) reported SAEs related to the study drug. In 53 (22.1 %) patients, AEs were judged as related to the study drug. No deaths were reported during the study (Tables 4, 5). Liver function test results were abnormal in 4.6 % of patients at baseline. During the patient visit from M1 to M12, abnormal liver function test results were reported in 15.3–29.4 % of patients (Table 6). Liver function abnormality was asymptomatic and led to discontinuation of fingolimod only in four patients. The mean lymphocyte counts were 0.571–0.654 $\times$ 10^9/L over the course of the 12-month fingolimod treatment period. Sixteen patients (6.7 %) discontinued the treatment due to the following AEs: macular oedema ($n = 3$), lymphopenia ($n = 3$), liver transaminase elevation ($n = 2$), hepatopathy ($n = 2$), pain ($n = 2$) and gynaecological infection ($n = 4$). First-dose cardiac

Table 3 Baseline and clinical findings of fingolimod real-world studies conducted in different countries

Characteristics	GOLEMS ($N = 240$)	Kuwait registry ($N = 175$) [19]	Academic center in Middle East ($N = 122$) [23]	Portuguese real-world population ($N = 104$) [24]	PANGAEA study [25]
Gender					
Female	169 (70.4)	132 (75.4)	77 (63.1)	64 (61.54)	2.884 (71.9)
Male	71 (29.6)	43 (24.6)	45 (36.9)	36 (38.4)	1.126 (28.1)
Mean age (years)	37.4 ± 9.3	33.3 ± 9.2	35.3 ± 9.9	39.0 ± 9.35	39.1 ± 10.0
Mean disease duration (years)	10.35 ± 6.7	7.2 ± 5.2	7.4 ± 6.6	10.29 ± 7.27	8.2 ± 6.3
Mean duration on fingolimod (mo)	10.77 ± 2.2	21.7±9.1	19.18±11.0	21.37 ± 10.57	879.2 ± 516.4 days
Pre-treatment patient characteristics					
Relapse-free patients	47 (19.6%)	57 (32.6 %)	21 %	–	
ARR	–	–	1.16	1.04	1.5
EDSS score	3.4±1.3	2.60 ± 1.44	2.3 ± 1.5	2.5	3.0±1.7
MRI activity	–	136 (77.7%)		–	
Post-treatment patient characteristics					
Relapse-free patients	152 (64.1 %)	151 (86.3 %)[a]	77.3 %[c]	–	68.5–75.5 %
ARR	–	–	0.29[c]	0.5[a]	0.43[a]
EDSS score	3.4±1.4	2.26 ± 1.49[b]	1.9 ± 1.7[d]	2.0[e]	2.89–2.91
MRI activity	–	32 (18.3 %)[a]	–	–	
Safety					
Adverse events	84 (35.0 %)	43 (24.6 %)	76 (62.3 %)	59 (56.7 %)	
Discontinuation/withdrawal	16 (6.7 %)	20 (11.4 %)	2 (1.6 %)	10.6 %	

ARR Annualized Relapse Rate, *EDSS* Expanded Disability Status Scale, *MRI* magnetic resonance imaging, *PANGAEA* Post-Authorization Non-interventional German sAfety study of GilEnyA in RRMS patients

[a] $p < 0.001$

[b] $p = 0.031$

[c] $p < 0.0001$

[d] $p = 0.001$

[e] $p = 0.145$

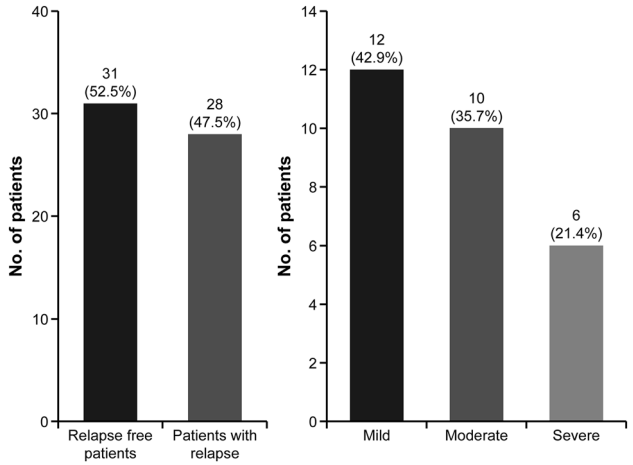

Fig. 4 **a** Effect of 12-month fingolimod treatment among patients treated with natalizumab before study start ($N = 59$). **b** Severity of relapses ($n = 28$[a]). [a]Total number of relapses reported in patients treated with natalizumab before fingolimod. Natalizumab was administered within 1 year before fingolimod treatment start

monitoring was prolonged in four patients due to transitional non-clinically significant electrocardiogram (ECG) atypia ($n = 1$), atrioventricular (AV) block first degree ($n = 1$) and just for prevention of any cardiovascular effect ($n = 2$). One patient reported pregnancy after 483 days of initiating fingolimod and subsequently terminated the treatment.

4 Discussion

The primary objective of the present study was to evaluate the incidence and severity of MS relapses in patients treated with fingolimod. In this study a majority of patients treated with fingolimod remained relapse-free (64.1 %); the proportion of relapse-free patients was lower than that observed in the phase III FREEDOMS study (70.4 %) and TRANSFORMS study (82.6 %) and phase II (75–77 %) trials [4, 5, 11]. In both the phase II and phase III studies the populations of patients had shorter disease duration and lower baseline EDSS than patients in the GOLEMS study. Moreover, in both the FREEDOMS and TRANSFORMS studies only the confirmed relapses were taken into account. The proportion of relapse-free patients after 12 months of fingolimod treatment in our study is similar to the proportion of relapse-free patients in the large post-marketing PANGAEA study (63.2 %) [12]. However, the proportion of relapse-free patients was high enough to demonstrate a clinical benefit for patients with MS. The efficacy set included discontinued patients, which might cause overestimation of relapse-free patients due to the fact that after discontinuation relapses were not recorded. On the other hand, analysis using the completed set might cause underestimation of relapse-free patients due to the fact that patients who might have discontinued due to lack of efficacy (and relapses) were not included in the

Table 4 Incidence of adverse events

Variable	AE count	*N* (%) of patients ($N = 240$)
Any AEs	109	84 (35.0)
SAEs	11	10 (4.2)
AEs related to study drug	62	53 (22.1)
Action taken		
No action required	38	34 (14.2)
Other concomitant medication prescribed	37	29 (12.1)
Study treatment permanently discontinued	13	13 (5.4)
Study treatment adjusted/temporarily interrupted	10	9 (3.8)
Study treatment permanently discontinued and other concomitant medication prescribed	4	4 (1.7)
Non-medicamentous therapy given	4	3 (1.3)
Study treatment adjusted/temporarily interrupted and other concomitant medication prescribed	2	2 (0.8)
Study treatment adjusted/temporarily interrupted, non-medicamentous therapy given and other concomitant medication prescribed	1	1 (0.4)
Outcome		
Resolved	72	57 (23.8)
No change in condition	22	22 (9.2)
Improvement of condition	13	12 (5.0)
Resolved with sequelae	1	1 (0.4)
Worsening of condition	1	1 (0.4)

AE adverse events, *SAEs* serious adverse events

Table 5 Listing of serious adverse events by patients

S. no	Gender	Time from treatment start [months] (derived)[a]	Diagnosis, description of AE	Causality[b]	Severity	Action taken	Outcome
1	Male	1.0	Severe MS relapse with hospitalisation need	No	Hospitalisation or prolongation of hospitalisation	No action taken	Resolved
2	Female	2.8	Suspected PML. PML was not confirmed based on repeated CSF examination. Determined as MS rebound	No	Other medically important event	Study treatment permanently discontinued due to this AE	Resolved with sequelae
3	Female	9.6	Recurrent epileptic seizures	No	Hospitalisation or prolongation of hospitalisation	Other concomitant medication prescribed	Resolved
		13.0	Epileptic seizure following confusion, postictal aphasia and right-side hemiparesis	No	Hospitalisation or prolongation of hospitalisation	No action taken	Resolved
4	Female	14.8	Herpes zoster on Th4-5 dermatomes	Yes	Hospitalisation or prolongation of hospitalisation	Other concomitant medication prescribed	Resolved
5	Female	0.5	Spastic bronchitis	Yes	Other medically important event	Study treatment permanently discontinued due to this AE, Other concomitant medication prescribed	Resolved
6	Male	2.1	Humerus fracture due to a car accident.	No	Hospitalisation or prolongation of hospitalisation	No action taken	Resolved
7	Female	5.6	Persistent gynaecological infections	Yes	Other medically important event	Study treatment permanently discontinued due to this AE	No change in condition
8	Male	6.9	Hepatopathy, liver transaminase elevation fivefold the upper limit of normal values	Yes	Other medically important event	Study treatment permanently discontinued due to this AE	Resolved
9	Male	0.9	Hepatopathy	Yes	Other medically important event	Study treatment permanently discontinued due to AE. Other concomitant medication prescribed	Improvement of condition
10	Female	0.6	Myalgia and arthralgia	Yes	Other medically important event	Study treatment permanently discontinued due to this AE	Improvement of condition

AE adverse event, *CSF* cerebrospinal fluid, *MS* multiple sclerosis, *PML* progressive multifocal leukoencephalopathy, *Th* thoracic

[a] Derived parameter: time from treatment start to the onset of adverse event in months

[b] *Causality* causality with administration of fingolimod

Table 6 Liver function test results by visit

Variable	Baseline	M1	M3	M6	M9	M12
No. of pts. tested	239	215	229	220	153	195
Abnormal results, *N* (%)	11 (4.6 %)	33 (15.3 %)	54 (23.6 %)	59 (26.8 %)	45 (29.4 %)	51 (26.2 %)
Values above 3× ULN, *N* (%)	0	6 (2.8 %)	15 (6.6 %)	17 (7.7 %)	11 (7.2 %)	16 (8.2 %)

M month, *ULN* upper limit of normal

completed set. The completed set was used for sensitivity analysis, which showed very similar results to the efficacy set (as described in the Results section); therefore, occurrence of potential selective bias was excluded. In the efficacy set ($N = 237$), treatment with fingolimod led to a reduction in the mean number of relapses per patient per year from 1.6 at baseline to 0.61 at 12 months (reduction of 65.4 %), indicating favourable disease control.

In the present study, the proportion of relapse-free patients constantly decreased over time (approximately 91 % [M1] to 64 % [M12]). No trend could be established based on severity of relapses. Thus, it is challenging to draw a conclusion regarding the association between treatment and severity of relapses. Treatment with fingolimod was associated with stable EDSS scores over the 12-month observation period.

Results also suggest that patient with lower baseline EDSS scores are more likely to be relapse-free during fingolimod therapy, implying that early initiation of fingolimod treatment is for better relapse control. Furthermore, the number of relapses within 2 years prior to fingolimod initiation was also an independent predictor for being relapse-free. These results are consistent with the previous findings, which demonstrated that a better clinical outcome was most influenced by immunomodulatory treatment and lower EDSS score change during the relapse [13, 14]. Of note, Hoepner et al. identified an EDSS score >3 as a predictive factor for relapse; however, these observations were based on a different patient population comprising patients switching from natalizumab to fingolimod [15]. A subgroup investigation of the FREEDOMS trial also showed a consistent, significant effect of fingolimod versus placebo on ARR in patients who had relapse activity despite receiving interferon beta during the year before study enrolment and patients with an EDSS over 3.5 [16].

In the subgroup of patients treated with natalizumab ($N = 59$) before fingolimod the number of patients without relapses in the year prior to fingolimod initiation was not surprisingly higher (49.2 %) compared with the overall cohort (19.6 %). After 1 year of fingolimod treatment the number of patients keeping this beneficial treatment effect (i.e. remained stable without relapse) was even slightly increased (52.5 %). In the subgroup of patients switching from natalizumab to fingolimod a numerically higher percentage of patients (21.4 %) with severe relapses was noted compared with the overall analysis (12.9 %), probably owing to an overall lower patient number in this subgroup. Our results conflict with a recent report in which fingolimod showed lesser efficacy in patients switching from natalizumab and a higher proportion of patients showed clinical (41 %) or MRI activity (54 %) [17].

Treatment with fingolimod was well tolerated and no new safety issues emerged. The discontinuation rate at 12 months was lower (11.3 %) than that observed in phase III clinical trials (FREEDOMS discontinuation rate: 18.8 %; TRANSFORMS discontinuation rate: 12.4 %) and was mainly because of AEs (59.3 %) [4, 5].

The results of our study are similar to the 24-month interim results of the PANGAEA (Post-Authorization Non-interventional German sAfety study of GilEnyA in RRMS patients) study ($n = 2239$) conducted in Germany. The PANGAEA study investigated the safety, efficacy and pharmacoeconomic data from fingolimod-treated patients over 5 years [12, 18]. In PANGAEA, >63 % of patients were free from relapses during years 1 and 2, comparable to 64.1 % of relapse-free patients at 12 months in the GOLEMS study. After 12 months of fingolimod treatment, both studies showed a similar average number of relapses per patient-year (GOLEMS: 0.61, $N = 237$; PANGAEA: 0.42, $N = 2229$) and similar relapse reduction (GOLEMS: 67 %; PANGAEA: 72 %). Moreover, the safety profile of fingolimod was similar in both studies: 4.7 and 6.0 % of patients discontinued due to AEs in the PANGAEA and GOLEMS studies, respectively. No new safety signals were detected. An indirect comparison of studies conducted under real-world and clinical trial settings demonstrated similar results (Table 3) [4, 12, 18–22]. Treatment non-response is frequent and first-line therapies may not adequately control MS. Early switch to therapies with higher efficacy, such as fingolimod, may improve long-term outcomes and reduce irreversible damage, which correlates with the number of relapses and disability progression.

This non-interventional design of the study provides relevant information on the safety, efficacy and tolerability of drugs that may help in the treatment of patients with MS under real-world settings. One of the limitations was the

large amount of missing data for the assessment of changes in work capability due to the low response rate (~10 %) in completing the WPAI-GH questionnaires, which prevented any meaningful statistical interpretation. In this study, patients were observed only for 12 months; hence, results should be interpreted with caution in the absence of long-term follow-up.

5 Conclusion

In conclusion, the results of this 12-month GOLEMS study confirmed the favourable efficacy and safety profile of fingolimod, as evidenced by reductions in the frequency and severity of relapses and the low incidence of AEs under real-world conditions in the Czech Republic.

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Compliance with Ethical Standards

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Conflict of interest Veronika Tichá has received financial support for conference travel, consultant fees and speaker honoraria from Biogen Idec, Novartis, Merck Serono, Teva, Actelion and Receptos. Veronika Tichá is an employee of MS Center, Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital in Prague. Roman Kodým and Zuzana Počíková are employees of Novartis Pharma Czech Republic. Pavla Kadlecová is an employee of Aprova s.r.o. (contract research organisation).

Ethical statement The GOLEMS study was approved by the Ethics Committee of the General University Hospital, Prague, CR. Data in this project were collected via a system of electronic data capture OpenClinica®, a web-based software which supports Good Clinical Practice (GCP), regulatory guidelines such as 21 CFR Part 11, and is built on a modern architecture using leading open standards. Informed consent was obtained from all individual participants included in the study.

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