Delayed-release Dimethyl Fumarate Demonstrated No Evidence of Difference in Clinical Outcomes Versus Fingolimod in Patients With RRMS: Pairwise Propensity-Matched Comparative Effectiveness Analyses of the German NeuroTransData Registry

P1.373

Braune S,[1] Grimm S,[2] van Hövell P,[2] Freudensprung U,[3] Hyde R,[3] Bergmann A,[1] for the NTD Study Group[1]

[1]NeuroTransData, Neuburg, Germany; [2]PwC Digital Services, Zurich, Switzerland; [3]Biogen International GmbH, Zug, Switzerland

Conclusions

- In pairwise propensity score–matched populations from the NTD MS registry, no evidence of difference between DMF and FTY was observed across all clinical effectiveness outcomes assessed (TTFR, ARR, time to confirmed disability progression).
- Consistent results were obtained based on a sensitivity analysis applying pairwise censoring.
- TTD was significantly longer among FTY- vs. DMF-treated patients.
- Results of a separate analysis of the NTD MS registry comparing DMF with GA, IFN, and TERI are reported elsewhere (poster P351).

Introduction

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) has demonstrated favorable efficacy in Phase 3 clinical trials (DEFINE, NCT00420212; CONFIRM, NCT00451451) in patients with relapsing-remitting multiple sclerosis (RRMS).[1,2]
  - However, no head-to-head randomized controlled trials comparing the effectiveness of DMF with fingolimod (FTY) in patients with RRMS have yet been conducted.
- In real-world comparative effectiveness studies of patients with RRMS, treatment with DMF was associated with no evidence of difference vs. FTY across several effectiveness measures.[3-6]
- The NeuroTransData (NTD) MS registry is a German practice network comprising data from ~25,000 outpatients with RRMS with regular 3-month follow-ups, which can support real-world comparisons of the effectiveness of MS treatments.

Objective

- To assess the comparative effectiveness of DMF with FTY using data from the NTD MS registry.

Methods

Patients

- Inclusion criteria:
  - Age ≥18 years at therapy initiation;
  - Two RRMS patient populations: 1. FTY-ALL, including patients who were treatment naive or pretreated with glatiramer acetate (GA), interferons (IFNs), and/or teriflunomide (TERI) as first-line therapy; 2. FTY-EMA, including patients meeting the European Medicines Agency label for FTY;
  - For FTY-EMA, on-therapy relapse ≤12 months (to mirror EMA label);
  - One or more relapse(s) and/or Expanded Disability Status Scale (EDSS) assessment(s) after index therapy initiation;
  - EDSS baseline value exists.
- Patients were excluded if they received pretreatment with any disease-modifying therapy other than GA, IFNs, or TERI.

Study Design

- Analysis data were sourced on October 1, 2016 from the NTD MS registry.
  - DMF cohorts underwent a 1:1 pairwise propensity score match (PSM) to FTY cohorts.
  - PSM factors used for matching were: age, sex, disease duration, treatment history, baseline EDSS score, and total relapses in the past 12/24 months.
- The primary outcome was time to first relapse (TTFR).
- Secondary outcomes included:
  - Annualized relapse rate (ARR);
  - Time to treatment discontinuation (TTD).
- Time to 3- and 6-month EDSS confirmed disability progression was included as an exploratory outcome.

Statistical Analysis

- No formal sample size was precalculated as available data already captured within the NTD registry were used.
- TTFR, TTD, and time to 3- and 6-month EDSS confirmed disability progression were analyzed using a Kaplan-Meier approach and Cox marginal regression model.
- ARR was analyzed using a generalized estimating equation Poisson regression model, taking into account the clustered nature of the matched design.
- Nonpairwise censoring was applied as the primary analysis method with a predefined sensitivity analysis using pairwise censoring accounting for differential follow-up time.

Results

Patients and Matching

- The DMF cohort matched to the FTY-ALL cohort had similar postmatched baseline characteristics and treatment history (Table).
  - Similar matching was seen for the DMF and FTY-EMA cohorts (Table).
  - Better propensity score matching was observed in the FTY-ALL population, as indicated by the C-statistic of 0.519 vs. 0.586 (FTY-EMA).
- Median (25th quantile, 75th quantile) exposure times were 16.3 (7.6, 23.7) months for the DMF cohort and 24.1 (8.6, 41.1) months for the FTY-ALL cohort.
  - DMF cohort, 15.3 (7.0, 22.6) months vs. FTY-EMA, 22.5 (7.6, 34.4) months.

Time to First Relapse and ARR

- There was no evidence of difference in TTFR as indicated by the hazard ratio (HR) and 95% CI between DMF vs. FTY-ALL (Figure 1A).
  - The proportions of relapse-free patients at Years 1 and 2 by Kaplan-Meier estimates are presented in Figure 2A.
- There was no evidence of difference in ARR between the DMF and FTY cohorts (Figure 1B).

Time to Treatment Discontinuation

- Compared with matched DMF cohorts, FTY patients had a significantly longer TTD.
  - TTD HR (95% CI; *P* value) for the DMF vs. FTY-ALL cohorts was 1.76 (1.34–2.31; *P*<.0001).
  - TTD HR (95% CI; *P* value) for the DMF vs. FTY-EMA cohorts was 3.31 (1.75–6.24; *P*<.0002).

Time to Confirmed Disability Progression

- Kaplan-Meier estimates for time to 6-month confirmed EDSS progression are presented in Figure 2B. Similar results also were observed for time to 3-month confirmed EDSS progression (data not shown).
  - Longer exposure/follow-up time is needed to draw meaningful conclusions for this endpoint.

Subgroup and Sensitivity Analyses

- Subgroup analysis using the FTY-EMA patient population led to consistent results for each comparison.
- Sensitivity analyses using pairwise censoring showed consistent results between the DMF and FTY cohorts for each comparison.

Table. Baseline factors in the DMF and respective FTY-ALL and FTY-EMA cohorts

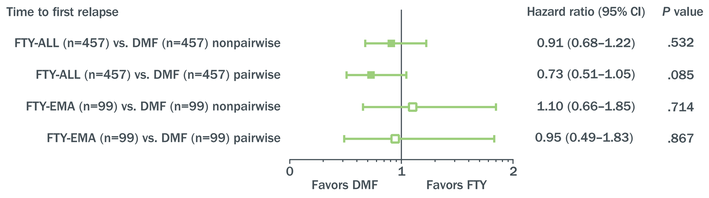
	DMF vs. FTY-ALL				DMF vs. FTY-EMA			
Type	DMF n=457	FTY n=457	Standardized difference	*P* value[a]	DMF n=99	FTY n=99	Standardized difference	*P* value[a]
Female, %	72.6	73.5	0.020	.824	75.8	81.8	0.149	.345
Mean (SD) age, y	39.9 (11.0)	40.2 (9.7)	0.029	.713	37.8 (9.6)	37.1 (9.6)	–0.065	.624
Median (Q25, Q75) EDSS score	2 (1, 3.5)	2 (1, 3)	0.030	.689	2 (1, 3.25)	2 (1.5, 3)	–0.015	.87
Mean (SD) disease duration, mo	104.8 (93.4)	108.1 (92.4)	0.036	.578	95.2 (81.9)	93.9 (72.8)	–0.016	.955
Prior DMT, %			0.023	.909			0.151	.361
0	23.0	22.1			–	–		
1	63.7	64.1			82.8	76.8		
≥2	13.3	13.8			17.2	23.2		
Relapses in last 12 months, %			0.059	.715			0.141	.450
0	59.1	59.3			1.0	1.0		
1	31.1	30.6			72.7	66.7		
≥2	9.8	10.0			26.2	32.3		
Relapses in last 24 months, %			0.045	.967			0.106	.219
0	50.5	49.5			–	–		
1	29.3	30.6			48.5	44.4		
≥2	20.1	19.9			51.5	55.6		
C-statistic[b]	0.519				0.586			

DMF = delayed-release dimethyl fumarate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; FTY = fingolimod; FTY-ALL = all fingolimod-treated patients with relapsing-remitting multiple sclerosis; FTY-EMA = patients with relapsing-remitting multiple sclerosis meeting the European Medicines Agency label for fingolimod; Q = quantile

[a]Wilcoxon signed-rank test was used for continuous characteristics and McNemar test for binary discrete characteristics. Stuart-Maxwell test was used for discrete characteristics with >2 categories

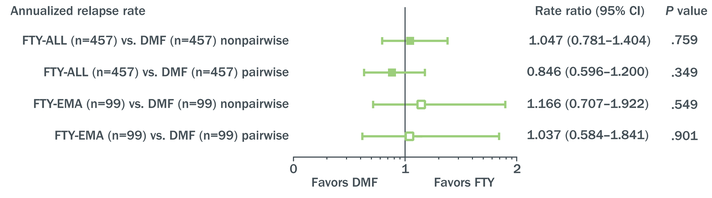
[b]C-statistic is a measure of balance in matched data and ranges from 0.5–1.0 with the minimum value indicating that the propensity score model is perfectly balanced and has no ability to discriminate between the cohorts after matching

Figure 1A. Time to first relapse hazard ratios for the DMF vs. FTY-ALL and FTY-EMA cohorts



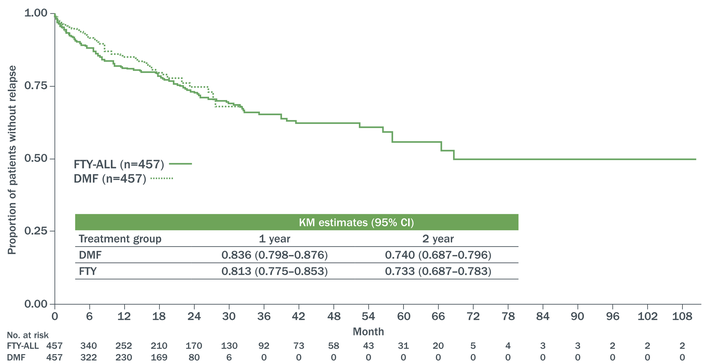
DMF = delayed-release dimethyl fumarate; FTY = fingolimod; FTY-ALL = all fingolimod-treated patients with relapsing-remitting multiple sclerosis; FTY-EMA = patients with relapsing-remitting multiple sclerosis meeting the European Medicines Agency label for fingolimod

Figure 1B. Annualized relapse rate ratios for the DMF vs. FTY-ALL and FTY-EMA cohorts



DMF = delayed-release dimethyl fumarate; FTY = fingolimod; FTY-ALL = all fingolimod-treated patients with relapsing-remitting multiple sclerosis; FTY-EMA = patients with relapsing-remitting multiple sclerosis meeting the European Medicines Agency label for fingolimod

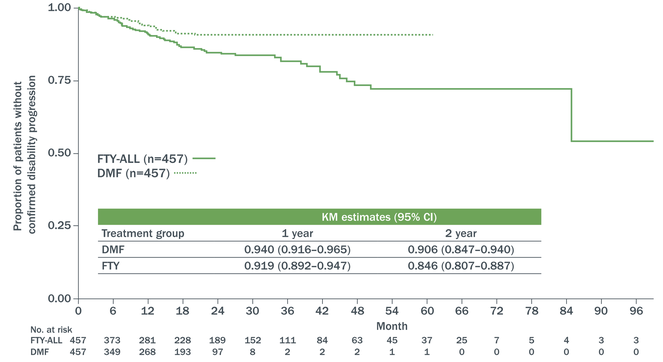
Figure 2A. Time to first relapse for the DMF vs. FTY-ALL cohorts (nonpairwise)



KM estimates (95% CI)		
Treatment group	1 year	2 year
DMF	0.836 (0.798–0.876)	0.740 (0.687–0.796)
FTY	0.813 (0.775–0.853)	0.733 (0.687–0.783)

DMF = delayed-release dimethyl fumarate; FTY = fingolimod; FTY-ALL = all fingolimod-treated patients with relapsing-remitting multiple sclerosis; KM = Kaplan-Meier

Figure 2B. Time to 6-month EDSS confirmed disability progression for the DMF vs. FTY-ALL cohorts (nonpairwise)



KM estimates (95% CI)		
Treatment group	1 year	2 year
DMF	0.940 (0.916–0.965)	0.906 (0.847–0.940)
FTY	0.919 (0.892–0.947)	0.846 (0.807–0.887)

DMF = delayed-release dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; FTY-ALL = all fingolimod-treated patients with relapsing-remitting multiple sclerosis; KM = Kaplan-Meier

References 1. Fox RJ, *et al.*; CONFIRM Study Investigators. *N Engl J Med*. 2012;367(12):1087-1097. 2. Gold R, *et al.*; DEFINE Study Investigators. *N Engl J Med*. 2012;367(12):1098-1107. 3. Boster A, *et al. Neurol Ther*. 2017;6(1):91-102. 4. Hersh C, *et al. Neurology*. 2017;88(16)(suppl):S31.003. 5. Nicholas J, *et al. Neurology*. 2017;88(16)(suppl):P6.375. 6. Spelman T, *et al. Neurology*. 2017;88(16)(suppl):P6.372.

Disclosures SG and PvH: employees of PwC, which was contracted to perform the statistical analysis for the NTD consortium; UF and RH: employees of and hold stock/stock options in Biogen; SB and AB: NTD members and have received honoraria from pharmaceutical companies for studies, consulting, and lectures. For this project, there were no conflicts of interest. Biogen did not have access to patient-level data associated with this registry analysis. **Acknowledgments** This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this poster was provided by Excel Scientific Solutions (Horsham, UK); funding was provided by Biogen.