

Delayed-release Dimethyl Fumarate Significantly Reduced Relapse-Based Outcomes vs. Interferon, Glatiramer Acetate or Teriflunomide: Pairwise Propensity-Matched Comparative Effectiveness Analyses of the German NeuroTransData Registry

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Conclusions

- In pairwise propensity score-matched populations from the NTD MS registry, DMF treatment was associated with significantly higher proportions of relapse-free patients and lower ARR vs. treatment with IFN, GA or TERI.
- There was no evidence of a difference in time to discontinuation between DMF and its comparators.
- Consistent results were obtained based on a sensitivity analysis applying pairwise censoring.
- Results of a separate analysis of the NTD MS registry comparing DMF with fingolimod are reported elsewhere (poster P651).

Introduction

- Delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) has demonstrated favourable efficacy in Phase 3 clinical trials (DEFINE, NCT00420212; CONFIRM, NCT00451451), and compared with glatiramer acetate (GA) as a reference group, in patients with relapsing-remitting multiple sclerosis (RRMS).^{1,2}
- However, no randomised controlled trials have directly compared efficacy outcomes between DMF and either interferon (IFN) or teriflunomide (TERI).
 - In a post hoc analysis of the CONFIRM study, as well as a matching-adjusted indirect comparison, DMF was associated with significantly reduced risk of inflammatory disease activity (as a composite of relapse and magnetic resonance imaging activity) and greater clinical efficacy compared with GA, respectively.^{1,3,4}
 - Indirect comparisons of clinical trial data also have demonstrated favourable effectiveness outcomes with DMF relative to IFN and TERI.
- Across real-world comparative effectiveness studies, DMF was associated with significantly greater effectiveness than IFN, GA and TERI, as measured by relapse outcomes.⁵⁻⁷
- 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 effectiveness of MS treatments.

Objectives

- To assess the comparative effectiveness of DMF with IFN, GA or TERI using data from the NTD MS registry.

Methods

Patients

- Inclusion criteria:**
 - Age ≥18 years at therapy initiation;
 - Treatment-naïve or pre-treated patients with first-line therapy (GA/TERI for IFN; IFN/TERI for GA; IFN/GA for TERI);
 - 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 pre-treatment with any disease-modifying therapy other than those mentioned above.

Study Design

- Analysis data were sourced on 1 October 2016 from the NTD MS registry.
 - The DMF cohort underwent 1:1 pairwise propensity score matching (PSM) to comparator cohorts (GA, IFN, TERI).
 - 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 endpoint was time to first relapse (TFR).
- Secondary endpoints included:
 - Annualised 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

- TFR, TTD and time to 3- and 6-month EDSS confirmed disability progression were analysed using a Kaplan-Meier approach and Cox marginal regression model.
- ARR was analysed using a generalised estimating equation Poisson regression model, taking into account the clustered nature of the matched design.
- Non-pairwise (non-simultaneous) censoring was applied as the primary analysis method with a pre-defined sensitivity analysis using pairwise (simultaneous) censoring accounting for differential follow-up time.

Results

Patients and Matching

- DMF cohorts matched to the IFN (n=439), GA (n=535) and TERI (n=388) cohorts had similar post-matched baseline characteristics and treatment history (Table 1).
- C-statistics were in the range of 0.524–0.539.
- Median (25th quantile, 75th quantile) exposure times are presented in Table 2.

Time to First Relapse and ARR

- Significant reductions on TFR were observed for the DMF cohorts relative to their respective comparator cohorts, as indicated by the corresponding hazard ratios (HR; Figure 1).
- The proportions of relapse-free patients by Kaplan-Meier estimates were higher for the DMF vs. comparator cohorts (Figure 2).
- ARR was significantly reduced for the DMF cohorts vs. their respective comparator cohorts (Figure 3).

Time to Treatment Discontinuation

- No evidence of difference in TTD was observed for the DMF cohorts vs. their respective comparator cohorts:
 - HR (95% CI; P value): DMF vs. IFN, 0.88 (0.70–1.11; .293); DMF vs. GA, 0.93 (0.75–1.15; .488); DMF vs. TERI, 1.12 (0.83–1.52; .444);
 - Proportion of patients free of TTD events: DMF 81.3% vs. IFN 79.1%, DMF 81.4% vs. GA 77.3%, DMF 82.1% vs. TERI 83.6% (12 months); DMF 67.2% vs. IFN 62.5%, DMF 65.9% vs. GA 63.6%, DMF 69.6% vs. TERI 71.8% (24 months).

Time to Confirmed Disability Progression

- Kaplan-Meier estimates for time to 6-month confirmed EDSS progression are presented in Figure 4. 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.

Sensitivity Analyses

- Sensitivity analyses using pairwise censoring showed consistent results between the DMF and comparator cohorts for each comparison.

Table 1. Baseline factors in the DMF and respective IFN, GA and TERI post-matched cohorts

Characteristic	DMF vs. IFN				DMF vs. GA				DMF vs. TERI			
	DMF n=439	IFN n=439	Standardised difference	P value ^a	DMF n=535	GA n=535	Standardised difference	P value ^a	DMF n=388	TERI n=388	Standardised difference	P value ^a
Female, %	71.1	74.5	0.077	.301	71.8	71.2	0.012	.885	67.8	66.8	0.022	.813
Mean (SD) age, y	39.1 (10.39)	39.9 (10.87)	0.079	.358	39.0 (10.74)	38.9 (10.34)	-0.011	.932	44.2 (10.29)	44.1 (9.67)	-0.017	.621
Median (Q25, Q75) EDSS score	1.5 (1, 2.5)	1.5 (0, 2.25)	-0.022	.830	1.5 (1, 2.5)	1.5 (1, 2.5)	0.003	.639	2 (1, 3)	2 (1, 3)	-0.044	.572
Mean (SD) disease duration, mo	81.0 (83.8)	86.8 (99.3)	0.063	.858	78.0 (80.4)	78.2 (80.6)	0.003	.963	122.5 (104.1)	119.6 (102.1)	-0.028	.730
Prior DMT, %			0.058	.025			0.027	.392			0.055	.737
0	74.7	77.0			60.9	62.2			36.1	38.4		
1	24.6	22.6			38.9	37.6			54.9	53.6		
2	0.7	0.5			0.2	0.2			9.0	8.0		
Relapses in last 12 months, %			0.079	.682			0.047	.882			0.090	.410
0	64.2	66.1			63.2	64.9			69.6	67.0		
1	30.3	28.5			29.3	28.2			26.3	28.6		
≥2	5.5	5.5			7.4	6.9			4.1	4.1		
Relapses in last 24 months, %			0.082	.644			0.035	.958			0.116	.620
0	58.3	60.8			57.2	58.3			57.7	55.2		
1	30.8	27.8			28.8	27.7			33.2	34.0		
≥2	11.0	11.4			14.0	14.0			9.0	10.8		
C-statistic ^b	0.539				0.524				0.533			

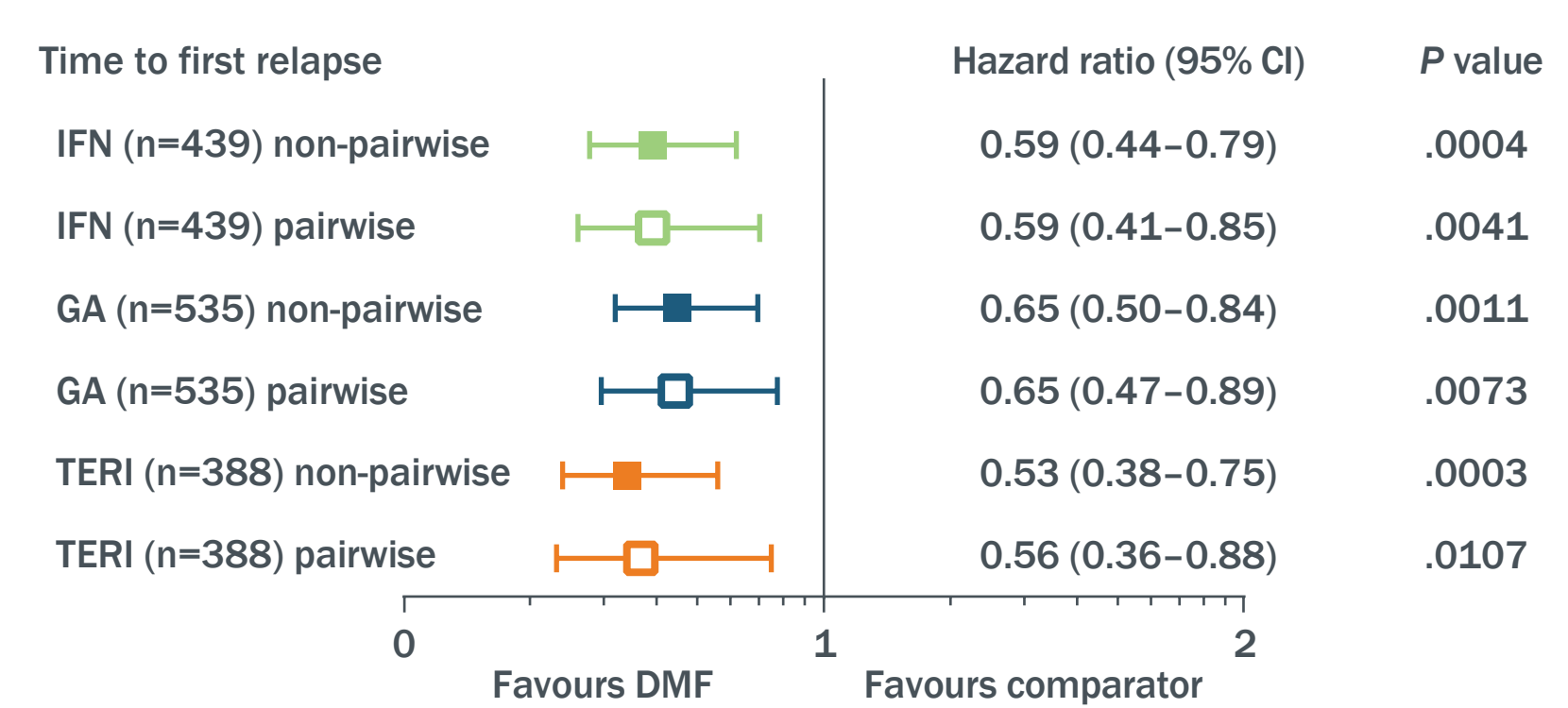
DMF = delayed-release dimethyl fumarate; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; Q = quantile; TERI = teriflunomide
Standardised difference = Cohen's d (effect size)
^aWilcoxon signed-rank test was used for continuous characteristics and McNemar test for binary discrete characteristics. Stuart-Maxwell test was used for discrete characteristics with >2 categories
^bC-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

Table 2. Exposure times for the DMF and IFN, GA and TERI cohorts

Therapy	n	Median	Q25	Q75
DMF vs. IFN				
IFN	439	18.924	7.852	33.593
DMF	439	15.967	7.573	23.524
DMF vs. GA				
GA	535	15.474	6.817	35.811
DMF	535	16.361	7.573	23.655
DMF vs. TERI				
TERI	388	13.405	5.881	22.825
DMF	388	17.528	7.680	24.000

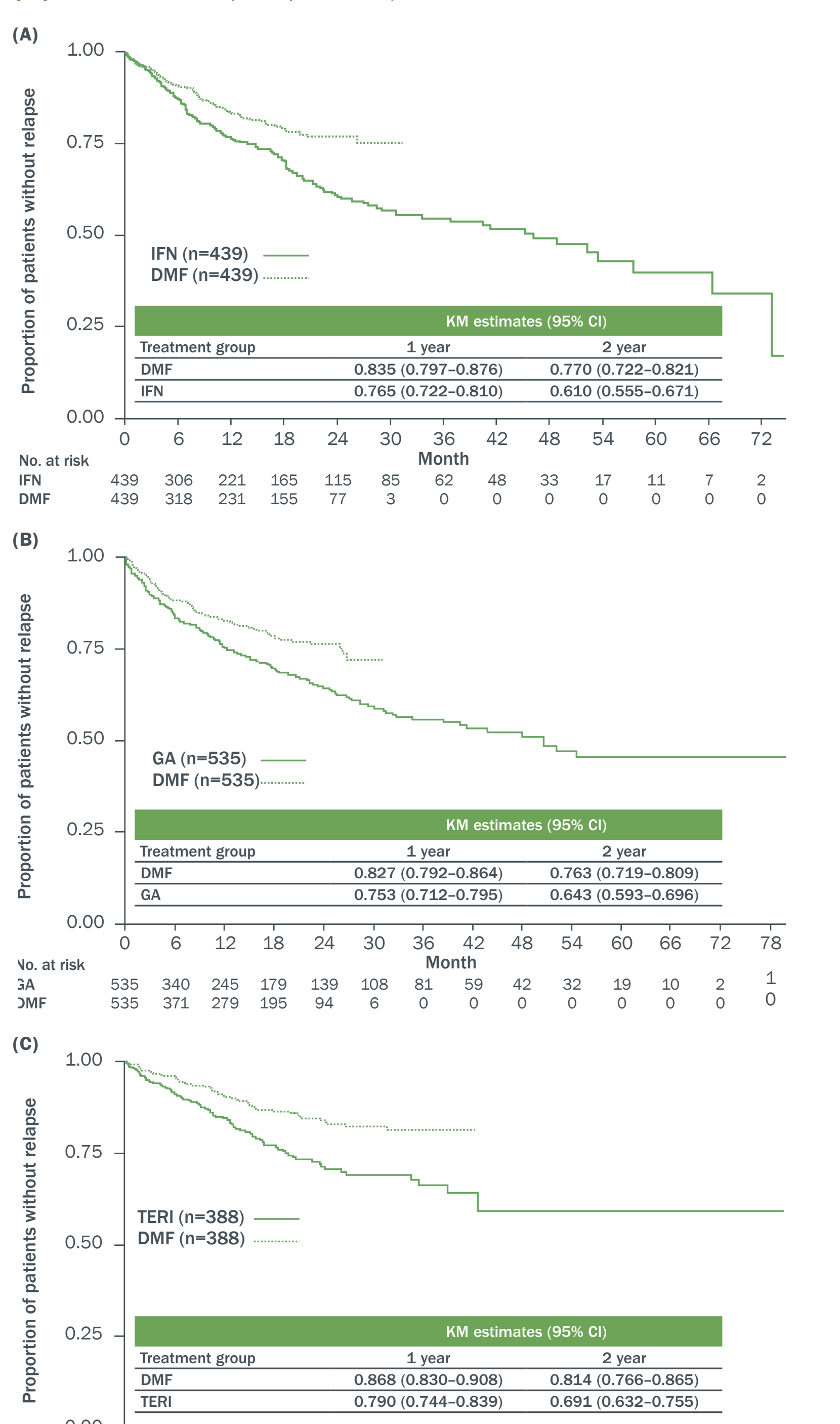
DMF = delayed-release dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; Q = quantile; TERI = teriflunomide

Figure 1. Hazard ratios for time to first relapse events for the DMF vs. IFN, GA and TERI cohorts



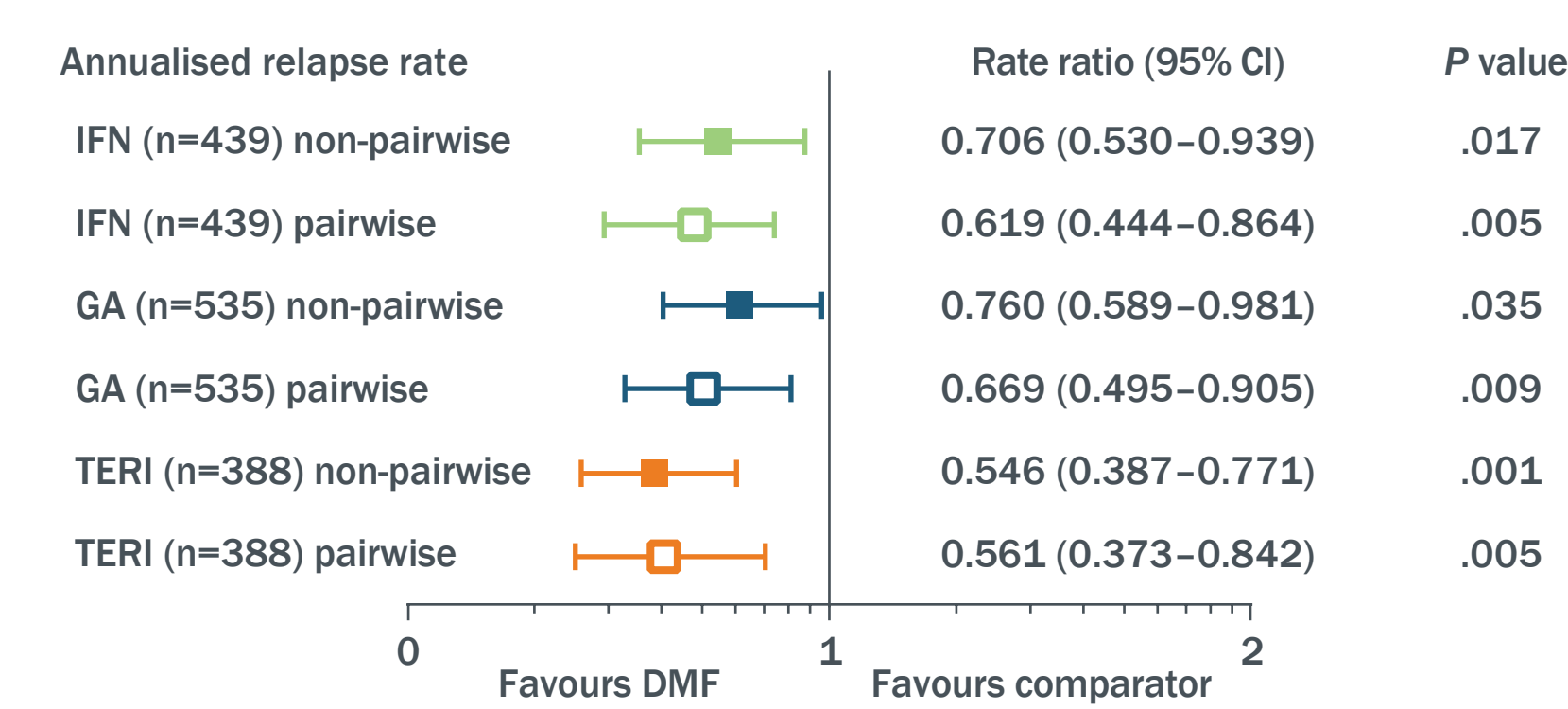
DMF = delayed-release dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; TERI = teriflunomide

Figure 2. Time to first relapse for the DMF vs. (A) IFN, (B) GA and (C) TERI cohorts (non-pairwise)



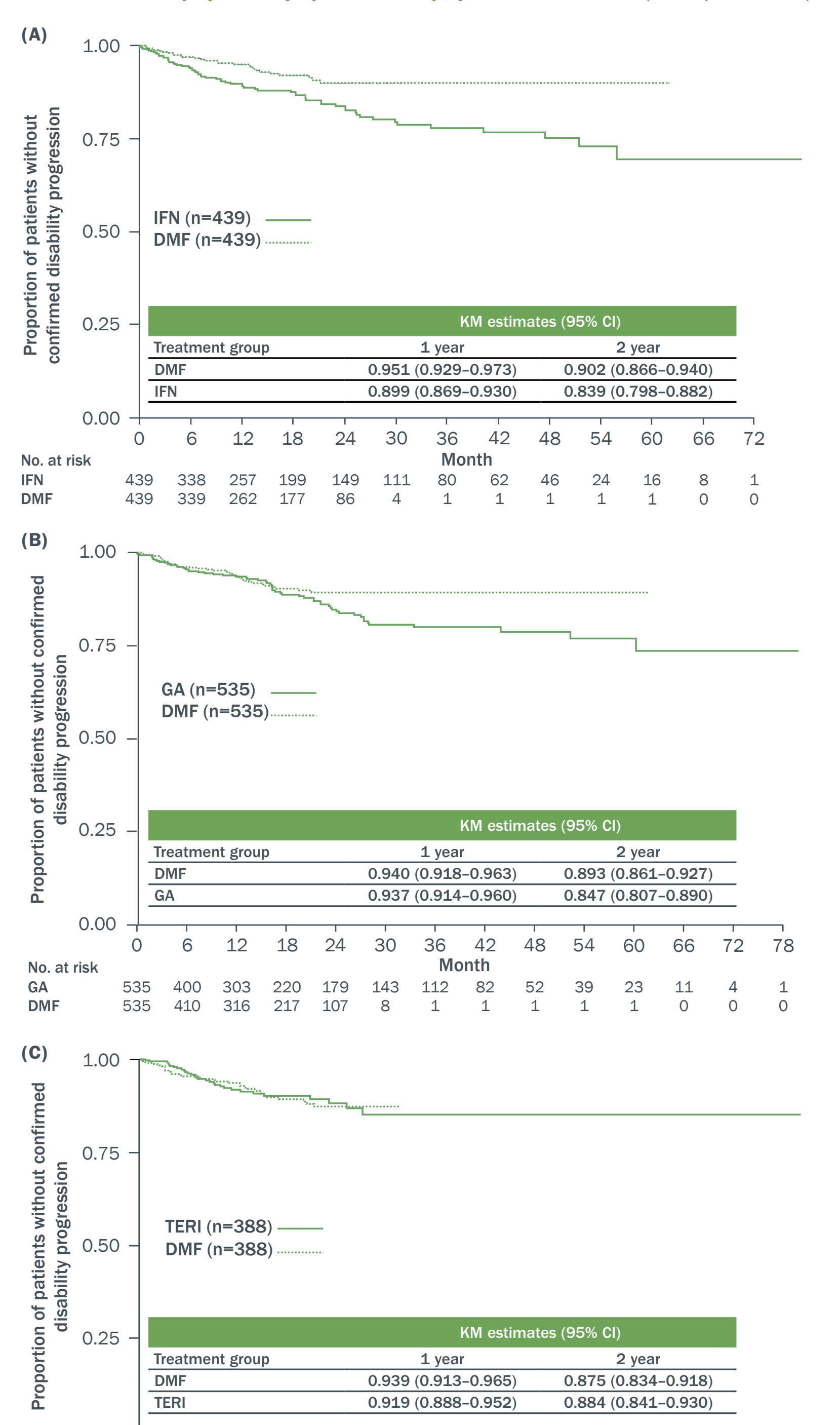
DMF = delayed-release dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; KM = Kaplan-Meier; TERI = teriflunomide

Figure 3. Annualised relapse rate ratios for the DMF vs. IFN, GA and TERI cohorts



DMF = delayed-release dimethyl fumarate; GA = glatiramer acetate; IFN = interferon; TERI = teriflunomide

Figure 4. Time to 6-month EDSS confirmed disability progression for the DMF vs. (A) IFN, (B) GA and (C) TERI cohorts (non-pairwise)



DMF = delayed-release dimethyl fumarate; EDSS = Expanded Disability Status Scale; GA = glatiramer acetate; IFN = interferon; KM = Kaplan-Meier; TERI = teriflunomide

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. Chan A, et al. *J Comp Eff Res.* 2017;6(4):313–323. 4. Kremenchutzky M, et al. *Mult Scler.* 2015;21(11)(suppl):P1063. 5. Boster A, et al. *Neuro Ther.* 2017;6(1):91–102. 6. Nicholas J, et al. *Neurology.* 2017;88(16)(suppl):P6.375. 7. Spielman T, et al. *Neurology.* 2017;88(16)(suppl):P6.372. **Disclosures** SG and PHH: 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 (Southport, CT, USA); funding was provided by Biogen.

