Analysis of oral disease-modifying therapies using real-world data from the German NeuroTransData multiple sclerosis registry

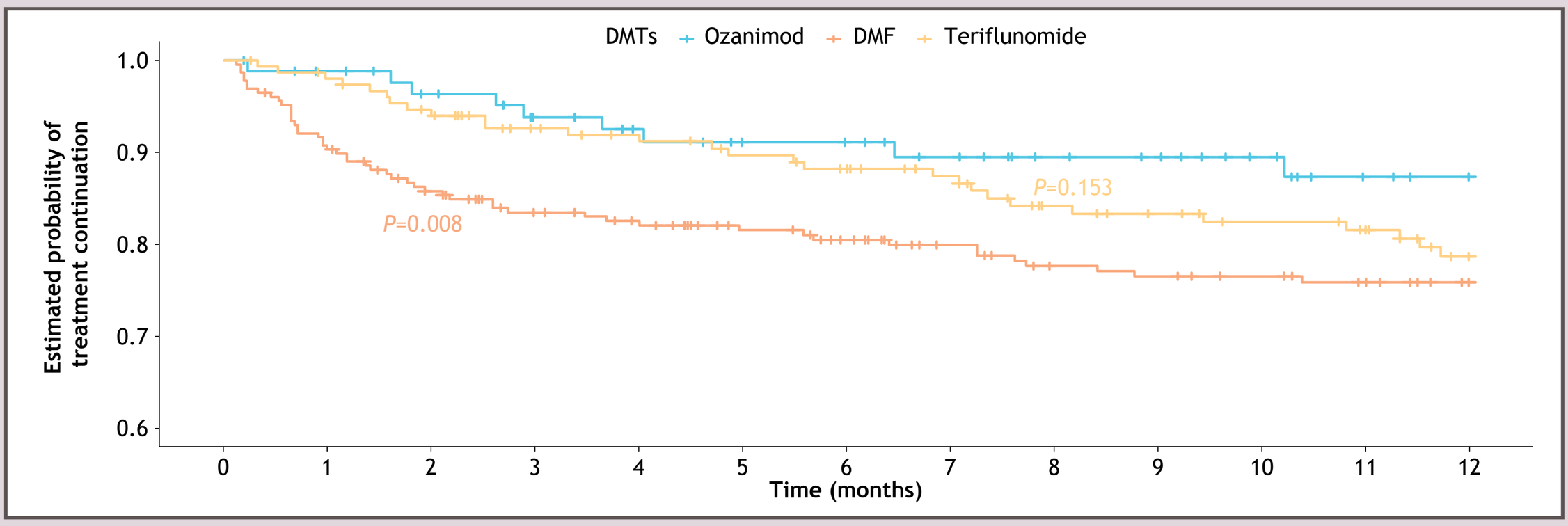
P1602

Stefan Braune,[1] Yanic Heer,[2] Jana B. Jarecki,[2] Mel Zürcher,[2] Erik DeBoer,[3] Christian Wisskirchen,[4] Mousumi Biswas[3]

[1]NeuroTransData GmbH, Neuburg an der Donau, Germany; [2]Rewoso AG, Zürich, Switzerland; [3]Bristol Myers Squibb, Princeton, NJ, USA; [4]Bristol Myers Squibb, Munich, Germany

- **Persistence was higher with ozanimod than with DMF and teriflunomide (Figure 2)**
  - **At 6 months, 91% of patients receiving ozanimod were persistent, compared with 81% receiving DMF and 88% receiving teriflunomide**
  - **At 12 months, 87% of patients receiving ozanimod were persistent, compared with 76% receiving DMF and 79% receiving teriflunomide**

Figure 2. Time to discontinuation of ozanimod, DMF, or teriflunomide in patients with full covariate information



DMF, dimethyl fumarate; DMT, disease-modifying therapy.

Introduction

- The clinical efficacy and safety profile of ozanimod has been assessed for the treatment of patients with multiple sclerosis (MS) in the SUNBEAM and RADIANCE trials[1,2]
- Little is known about the use of ozanimod in real-world German settings compared with use of other oral disease-modifying therapies (DMTs) for relapsing-remitting MS (RRMS), such as teriflunomide, dimethyl fumarate (DMF), ponesimod, or diroximel fumarate (DRF) in treatment-naive patients or those without highly active disease

Objectives:
- To describe the baseline demographics and clinical characteristics of patients with RRMS initiating treatment with ozanimod, DMF, or teriflunomide[a] and the reasons for the discontinuation of these DMTs in the real world
- To assess and compare time to treatment discontinuation in patients receiving ozanimod, DMF, or teriflunomide

[a]DRF and ponesimod were excluded from this analysis because of insufficient sample sizes in the data source used for this study. Fingolimod was excluded from this analysis because in Germany it is used in different populations of patients with MS (ie, patients with highly active disease).[3]

Methods

Study design

- This retrospective, observational, longitudinal cohort study included outpatients with MS
- The data source was the German NeuroTransData (NTD; NeuroTransData GmbH, Neuburg an der Donau, Germany) disease-specific MS outpatient registry,[4] with a total of 119 neurologists in 59 offices
  - NTD is purely office-based, with no hospitals included in the network
- All data (ie, patient demographics; clinical, therapy, and diagnosis data; and reasons for discontinuation) contributing to the analysis were collected by physicians and study nurses during regular office visits through a web-based platform[5]
  - Routine visits typically occurred 3 or 4 times annually
- Study period: May 20, 2020 (EMA approval date for ozanimod), to March 1, 2023
- Inclusion criteria
  - Diagnosis of RRMS or "initial manifestation of MS" (ICD-10 G35.0 or G35.1)
  - Aged ≥18 years
  - Had ≥1 prescription of ozanimod, DMF, or teriflunomide
  - Therapy initiation in the study period
- Exclusion criteria
  - Diagnosis of secondary progressive MS or primary progressive MS
- Patients were grouped into 3 cohorts based on therapy: ozanimod, DMF, or teriflunomide
- Index date was defined as the start of ozanimod, DMF, or teriflunomide treatment
- Patients were followed until a therapy stop date or until the end of the study (in the absence of a therapy stop)

Primary outcomes

- Frequency of DMT discontinuation and time to DMT discontinuation (ie, day of last dose of DMT)
- Reasons for discontinuation

Secondary outcomes

- Baseline clinical characteristics in each DMT cohort

Statistical analysis

- Patient demographics and physician-reported clinical characteristics (ie, age, sex, time since MS manifestation, number of previous DMTs, exposure time, and Expanded Disability Status Scale [EDSS] scores) obtained at or within 3 months of initiation of the index DMT (baseline) were summarized (ie, means, SDs, and proportions)
- Statistical significance of baseline differences between the ozanimod and DMF and ozanimod and teriflunomide cohorts were assessed using unpaired Wilcoxon tests for continuous variables (ie, age, time since manifestation, and exposure time) and by Fisher exact test for discrete variables (ie, number of relapses in previous years, number of previous DMTs, sex, and existence of gadolinium-enhancing lesions)
- In addition, effect size of differences were assessed using standardized mean differences[6]
- Reasons for discontinuation, predefined and selected by the physician from a drop-down menu, were categorized and summarized (ie, means, SDs, and proportions)
  - Categories included lack of efficacy, side effects, patient choice, actual or planned pregnancy, and other
- Time to discontinuation was analyzed using Kaplan-Meier plots and multivariate Cox regression adjusting for EDSS score, number of previous DMTs, number of relapses in the year before the index date, age, and sex for all patients with complete covariate information, resulting in adjusted hazard ratios (aHRs), 95% confidence intervals (CIs), and *P* values
- The proportions of persistent patients at 6 and 12 months were determined using a Kaplan-Meier estimator

Results

- The study included 117 patients receiving ozanimod, 309 receiving DMF, and 214 receiving teriflunomide
- Patients had similar mean exposure times in the ozanimod (8.3 months), DMF (8.0 months), and teriflunomide (9.0 months) cohorts (**Table 1**)
- At baseline, all cohorts were broadly similar (**Table 1**)
  - Mean EDSS scores ranged from 1.6 to 2.0
  - Mean age and time since MS manifestation were statistically significantly different for ozanimod vs teriflunomide or DMF; however, standardized mean differences were below 0.5, corresponding to small differences[6]
  - The ozanimod cohort had a larger proportion of pretreated patients; 42% receiving ozanimod had ≥2 prior DMTs, compared with 27% in the DMF cohort (*P*=0.01) and 30% in the teriflunomide cohort (*P*=0.07)

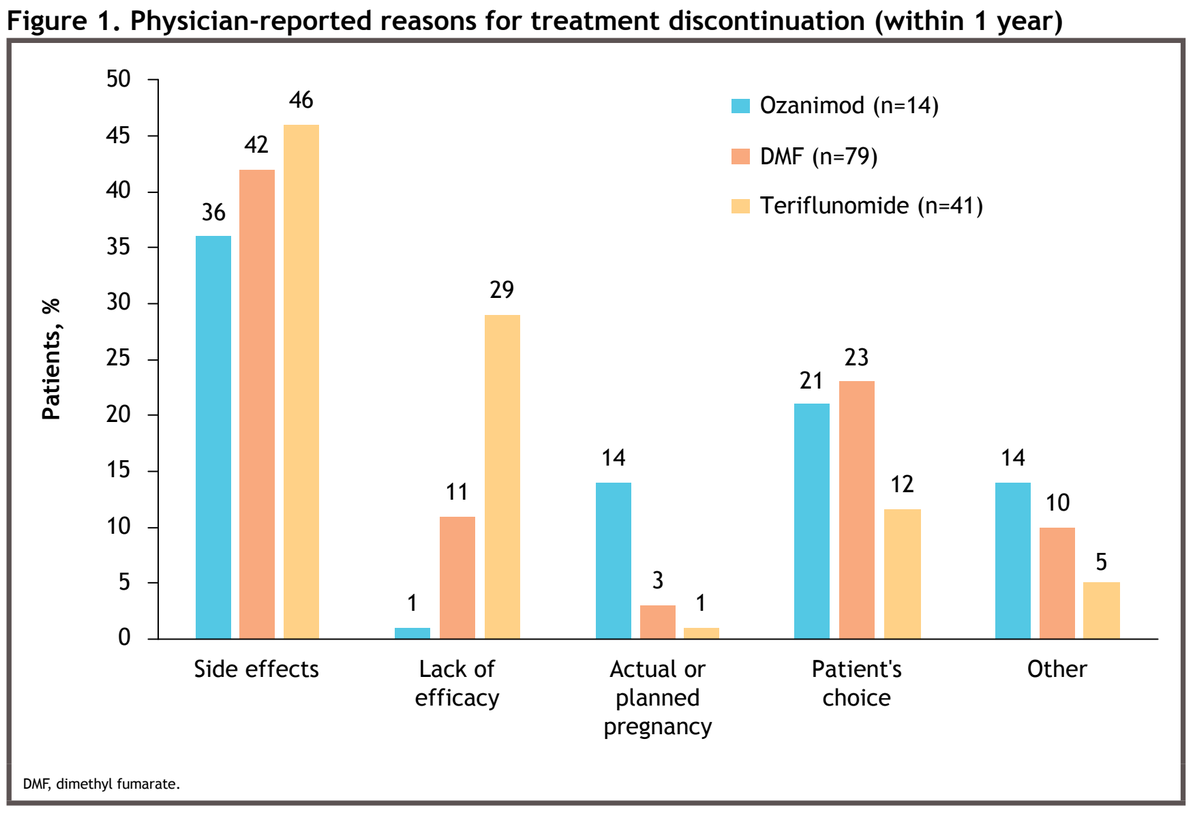
Table 1. Baseline demographic and clinical characteristics

Characteristic		Ozanimod (n=117)	DMF (n=309)	*P* value (DMF vs ozanimod)	Standardized mean difference (DMF vs ozanimod)	Teriflunomide (n=214)	*P* value (teriflunomide vs ozanimod)	Standardized mean difference (DMF vs ozanimod)
Age, y, mean (SD)		41.6 (11.04)	39.0 (10.74)	**0.03**	0.24	44.2 (10.55)	**0.04**	0.24
Exposure time, y, mean (SD)		0.7 (0.33)	0.7 (0.37)	0.99	0.06	0.8 (0.33)	0.06	0.17
Time since MS manifestation, y, mean (SD)		9.9 (9.31)	7.5 (7.79)	**0.03**	0.27	10.3 (8.82)	0.48	0.05
Sex	Male, n (%)	26 (22.2)	67 (21.7)			56 (26.2)		
	Female, n (%)	85 (72.6)	242 (78.3)	0.69	0.04	158 (73.8)	0.69	0.06
	Missing, n (%)	6 (5.1)	0 (0.0)			0 (0.0)		
EDSS score at index date	Mean (SD)	1.99 (1.46)	1.63 (1.46)	0.26	0.25	1.89 (1.49)	0.77	0.07
	Missing, n (%)	26 (22.2)	78 (25.2)			56 (26.2)		
Number of previous DMTs	0, n (%)	35 (29.9)	124 (40.1)			70 (32.7)		
	1, n (%)	33 (28.2)	103 (33.3)	**0.01**	0.33	80 (37.4)	0.07	0.26
	>1, n (%)	49 (41.9)	82 (26.5)			64 (29.9)		
Number of relapses in past year, mean (SD)		0.5 (0.66)	0.51 (0.69)	0.90	0.05	0.36 (0.57)	0.20	0.20
GD-enhancing lesions	Detected, n (%)	10 (8.5)	36 (11.7)			24 (11.2)		
	Not detected, n (%)	24 (20.5)	93 (30.1)	0.83	0.03	60 (28.0)	0.99	0.02
	Missing, n (%)	83 (70.9)	180 (58.3)			130 (6.7)		

DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GD, gadolinium; MS, multiple sclerosis; SD, standard deviation.

- Treatment discontinuations within 1 year were lowest in the ozanimod cohort (n=14 [12%]), followed by teriflunomide (n=41 [19%]) and DMF (n=79 [26%])
  - Matching-adjusted indirect comparisons of clinical trial data found significantly lower risk of overall adverse events and discontinuations due to adverse events with ozanimod vs DMF[7] and teriflunomide[8]
- Reasons for discontinuation were largely similar for all treatment cohorts, with side effects (36%-46%) and patient's choice (12%-23%) being the most common (**Figure 1**)

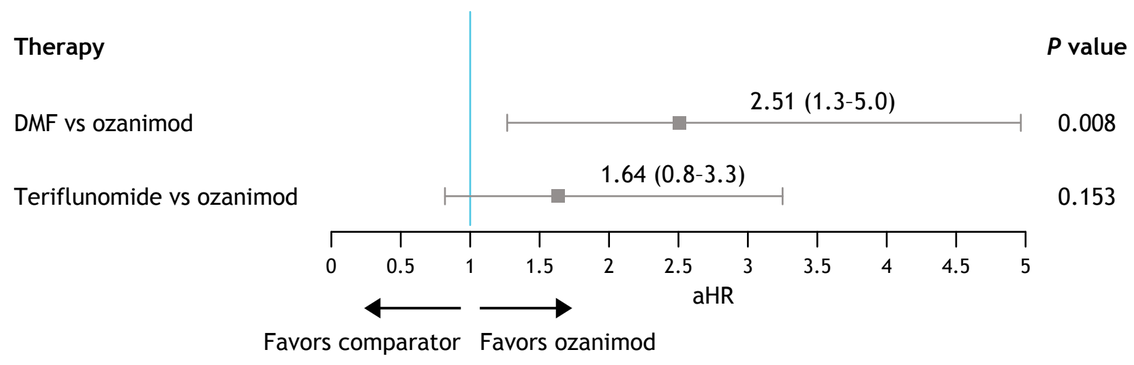
Figure 1. Physician-reported reasons for treatment discontinuation (within 1 year)



DMF, dimethyl fumarate.

- Compared with ozanimod, the risk of discontinuation was significantly higher with DMF (aHR: 2.5 [95% CI: 1.3-5.0]; *P*=0.008) but was not significantly different with teriflunomide (aHR: 1.6 [95% CI: 0.8-3.3]; *P*=0.153) (**Figure 3**)

Figure 3. aHRs for treatment discontinuation



aHR, adjusted hazard ratio; DMF, dimethyl fumarate.

Limitations

- The sample sizes were relatively small, particularly for the ozanimod and teriflunomide cohorts (117 and 214 patients, respectively), and the number of discontinuation events was low
- The limited exposure time of 8 to 9 months overall is not sufficient to support analysis of long-term persistence
- Owing to different treatment guidelines in Germany, these data may not reflect real-world use of oral DMTs in other EU countries

Conclusions

- At baseline, patients with RRMS receiving ozanimod were comparable to patients receiving DMF and teriflunomide, particularly with respect to EDSS score
  - The higher use of prior DMTs in the ozanimod population can be explained by German treatment guidelines, which recommend use of ozanimod only if class 1 DMTs (ie, DMF, teriflunomide, or interferon) do not achieve disease control
- In the first year of treatment, ozanimod had a significantly lower risk of discontinuation (2.5 times lower) than DMF, suggesting higher persistence with ozanimod
- Future research is needed to evaluate the impact of ozanimod persistence on other outcomes

References

1. Cohen JA et al. *Lancet Neurol* 2019;18(11):1021-1033. https://doi.org/10.1016/S1474-4422(19)30238-8.
2. Comi G et al. *Lancet Neurol* 2019;18(11):1009-1020. https://doi.org/10.1016/S1474-4422(19)30239-X.
3. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Fingolimod (neues Anwendungsgebiet). https://www.g-ba.de/downloads/40-268-3789/2016-05-19_AM-RL-XII_Fingolimod_nAWG_D-198_TrG.pdf. May 19, 2016. Accessed September 11, 2023.
4. NeuroTransData GmbH. NTD database. https://www.neurotransdata.com/en. Accessed August 15, 2023.
5. Bergmann A et al. *Front Dig Health* 2021;3:633427. https://doi.org/10.3389/fdgth.2021.633427.
6. Sullivan GM, Feinn R. *J Grad Med Educ*. 2012;4:279-282. https://doi.org/10.4300/JGME-D-12-00156.1.
7. Cohan S et al. *CNS Drugs* 2021;35:795-804. https://doi.org/10.1007/s40263-021-00805-0.
8. Cohan S et al. *Mult Scler Relat Disord* 2021;52:102972. https://doi.org/10.1016/j.msard.2021.102972.

Acknowledgments

- The authors thank Arnfin Bergmann of the NeuroTransData Study Group for his support during the collection of data used in this analysis and Komal Singh of Bristol Myers Squibb for her contributions to the study design and critical review of the results
- This study was supported by Bristol Myers Squibb (Princeton, NJ, USA)
- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Eleanor Bush, MA, of Peloton Advantage, LLC, an OPEN Health company, and funded by Bristol Myers Squibb

Disclosures

- **SB:** Received honoraria from Kassenärztliche Vereinigung Bayerns and health maintenance organizations for patient care and from Biogen, CSL Behring, NeuroTransData, Novartis, Octapharma, Roche, and Sanofi for consulting, project management, clinical studies, and lectures; and received honoraria and expense compensation as a board member of NeuroTransData
- **YH, JBJ, and MZ:** Employees of Rewoso AG, which received funding from Bristol Myers Squibb for the conduct of this study
- **ED, CW, and MB:** Employees and/or shareholders of Bristol Myers Squibb

Presented at the 9th Joint ECTRIMS-ACTRIMS Meeting; 11-13 October 2023; Milan, Italy

Email: sbraune@neurotransdata.com