Final results of the PANGAEA 2.0 study: Treatment benefits of fingolimod for active RRMS patients switching from other DMTs

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Disclosures

Cordula Weiss is an employee of Novartis Pharma GmbH, Germany.

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Background and Objective

Background

- 85% of Multiple Sclerosis (MS) patients are initially diagnosed with relapsing-remitting MS (RRMS).[1]
- 60% will convert to secondary progressive MS (SPMS) within 20 years due to evolvement of the disease over time.[2,3]
- Inconsistent criteria to define the transition from RRMS to SPMS and previous lack of treatment options led to late and mostly retrospective diagnosis of SPMS.[4,5]
- In the treatment of RRMS, individualized sequential therapies can be used to optimize the outcome if there is an understanding of the efficacy and overall impact of sequential switching.
- The PANGAEA 2.0 study is a post-authorization, non-interventional study in MS patients. The study aims to better understand the disease progression of MS and especially the conversion from RRMS to SPMS with the goal to develop new diagnostic tools.

Objective

- The objective of the non-interventional PANGAEA 2.0 study is the assessment of the effectiveness of fingolimod in disease active patients with RRMS switching from other disease-modifying therapies (DMTs).

1. Rio J, et el.; Curr Opin Neurol. 2011; 24(3), 230-237; 2. Tremlett H, et al. Mult Scler. 2008;14:314–24; 3. Scalfari A, et al. J Neurol Neurosurg Psychiatry. 2014;85:67–75; 4. Lublin FD, et al. Neurology. 2014;83(3):278-286; 5. Shirani A, et al. Neurotherapeutics. 2016; 13(1): 58–69.

Methods

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Study design

- Non-interventional real-world evidence study (**Figure 1**).
- Observational phase: 3 years with documented visits every 3 months.
- 2,579 disease-active RRMS-patients at 240 neurological practices and clinics in Germany enrolled, 966 patients completed the study
- 2,372 patients included in the analysis.

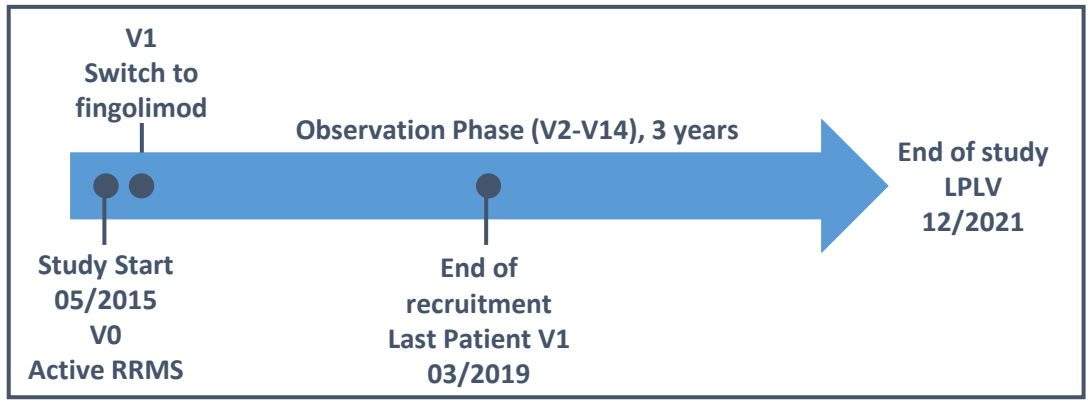

Figure 1: Study design PANGAEA 2.0.

Assessment

- Clinic: Laboratory, ophthalmic, and physical evaluation
- MS-activity: Magnetic Resonance Imaging (MRI), MS Activity Scale Score (MS-AS), Expanded Disability Status Scale (EDSS)
- Functional domains: Symbol Digit Modalities Test (SDMT), EDSS
- Patient's perspective: United Kingdom Neurological Disability Scale (UKNDS), Fatigue Scale For Motor And Cognitive Functions (FSMC), Multiple Sclerosis Impact Scale-29 items (MSIS-29), EuroQol-5D (EQ-5D), Work Productivity and Activities Impairment (WPAI-MS)
- Physician's perspective: Clinical Global Impression (CGI), progression questionnaire
- Socioeconomic factors: Multiple Sclerosis Health Resource Survey (MS-HRS)

PANGAEA 2.0 Patient Characteristics

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Variable	PANGAEA 2.0
Number of patients (n)	2,372
Age (years) (± SD)	39.2±10.9
Female (%)	71.2%
Time since first MS diagnosis, n=2,300 (years) (± SD)	7.1±6.6
EDSS, n=2,118 (mean score) (± SD)	2.4±1.5
FSMC, n=1,953 (mean score) (± SD)	53.4±21.2
SDMT, n=1,717 (mean score) (± SD)	50.3±16.2
Patients with ≥1 relapse (24 months before study start) (%)	71.2%

Table 1: Patient characteristics at baseline (screening).

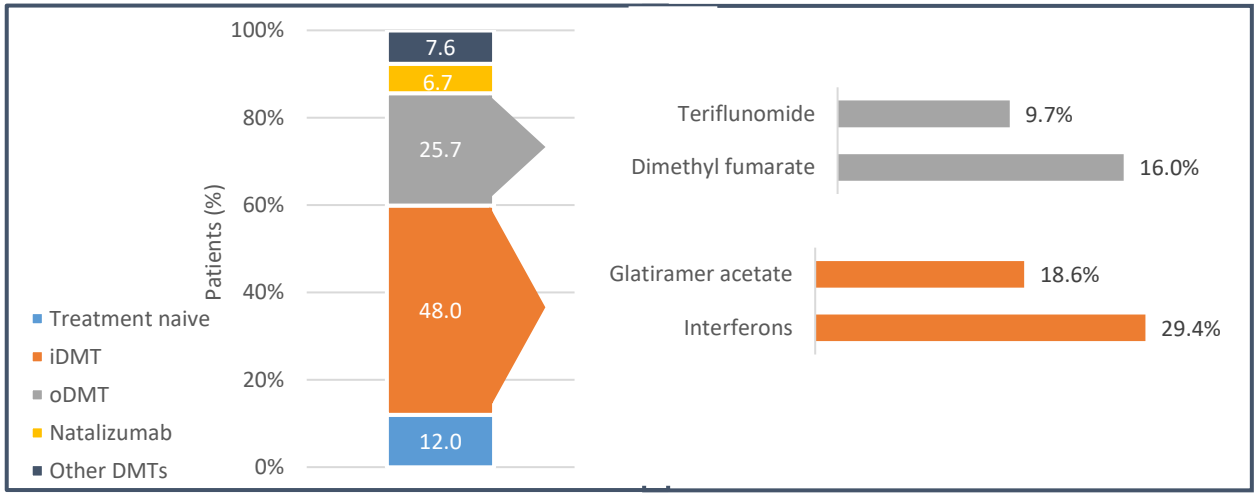

Figure 2: Last pretreatment before switch to fingolimod, n=2,372.
iDMT: injectable disease modifying therapy (glatiramer acetate, interferons); oDMT: oral disease modifying therapy (teriflonumide, dimethyl fumarate)

- Baseline data of the PANGAEA 2.0 study population show patient characteristics of the analysis set (**Table 1**) .
- The predominantly female RRMS patients are on average 39.2±10.9 years old and received their MS diagnosis 7.1±10.9 years before inclusion into the study.
- While 12.0% of patients were treatment naive, nearly half the study population was treated with an iDMT (injectable disease modifying therapy) before switching to fingolimod.
- About one quarter of patients received an oDMT (oral disease modifying therapy) as last pretreatment.

PANGAEA 2.0 Results

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- At screening, most patients had EDSS scores ≤2.5 with the treatment naive group presenting with the lowest overall EDSS scores followed by the subgroup who was on iDMTs before switching to fingolimod (**Figure 3**).
- Patients who had received natalizumab as their last pretreatment presented with EDSS scores in higher categories compared to other subgroups.
- Over 3 years, the mean EDSS total score remained on a relatively stable level in the subgroups who were treatment naive or had received iDMTs and oDMTs as their last pretreatment (**Figure 4**).
- The EDSS of the subgroup previously treated with natalizumab appeared to be less stable compared to other subgroups and showed the highest increase after 3 years.

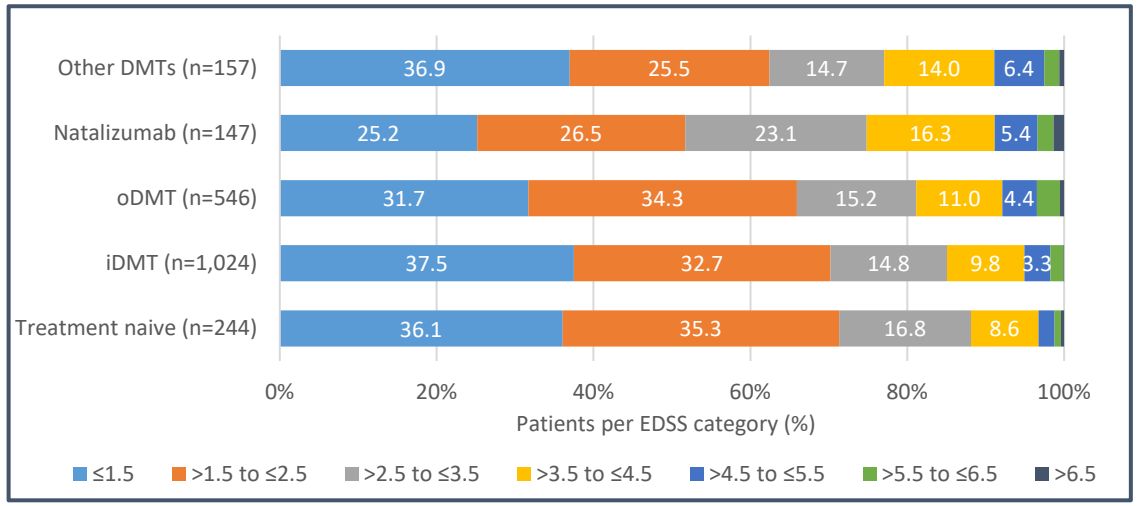

Figure 3: EDSS (categorial), subgroups by pretreatment at screening, n=2,133. Values <3% omitted for clarity.

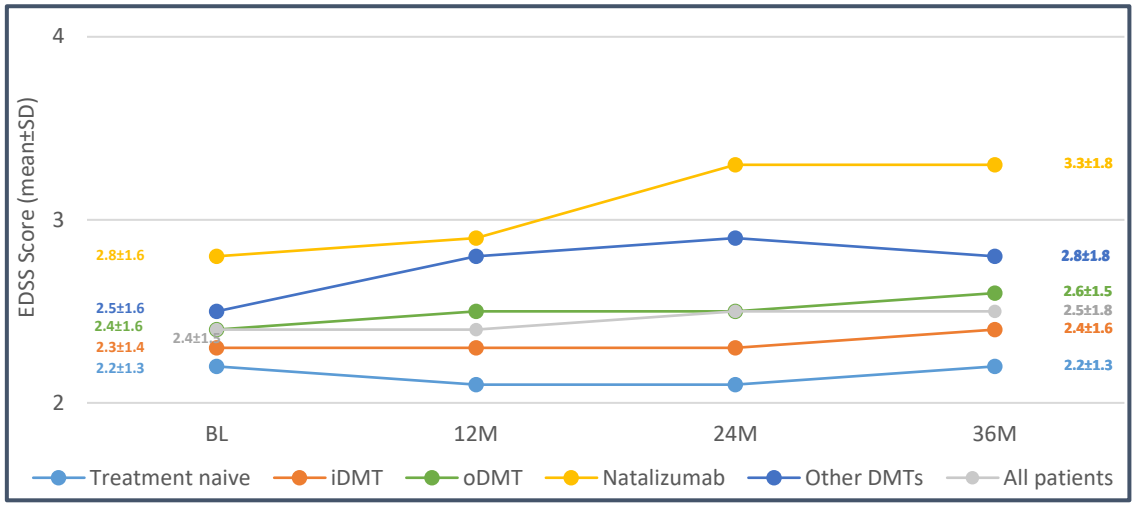

Figure 3: EDSS at baseline (BL) and over the observation period of 36 months (36M). Subgroups by pretreatment at screening. Standard deviation (SD; min. 1.2, max. 1.8) omitted for clarity.

Treatment naive: n=244, 143, 109, 85; iDMT: n=102, 582, 476, 399; oDMT: n=546, 293, 227, 172; natalizumab: n=147, 88, 57, 43; other DMTs: n=157, 90, 73, 54; Total: n=2,118, 1,196, 942, 753.

PANGAEA 2.0 Results

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Subgroup	Time period	n	ARR estimate	[95%CI]
Overall	ARR before fingolimod	2,228	1.1059	[1.0438; 1.1718]
	ARR after fingolimod start	2,372	0.2384	[0.2215; 0.2567]
Treatment naive	ARR before fingolimod	258	1.3566	[1.2163; 1.5131]
	ARR after fingolimod start	284	0.1708	[0.1405; 0.2077]
iDMT	ARR before fingolimod	1,089	1.2360	[1.1691; 1.3068]
	ARR after fingolimod start	1,138	0.2195	[0.2018; 0.2388]
oDMT	ARR before fingolimod	576	1.2813	[1.1884; 1.3813]
	ARR after fingolimod start	610	0.2641	[0.2370; 0.2943]
Natalizumab	ARR before fingolimod	149	0.7852	[0.6501; 0.9484]
	ARR after fingolimod start	159	0.3091	[0.2553; 0.3743]
other DMTs	ARR before fingolimod	156	0.9808	[0.8315; 1.1569]
	ARR after fingolimod start	181	0.2517	[0.2048; 0.3094]

Table 2: Annualized relapse rate (AAR). Poisson regression model adjusted for overdispersion including Dependent variable=number of relapses, offset-variable=observational time in [years]. CI = Confidence limit

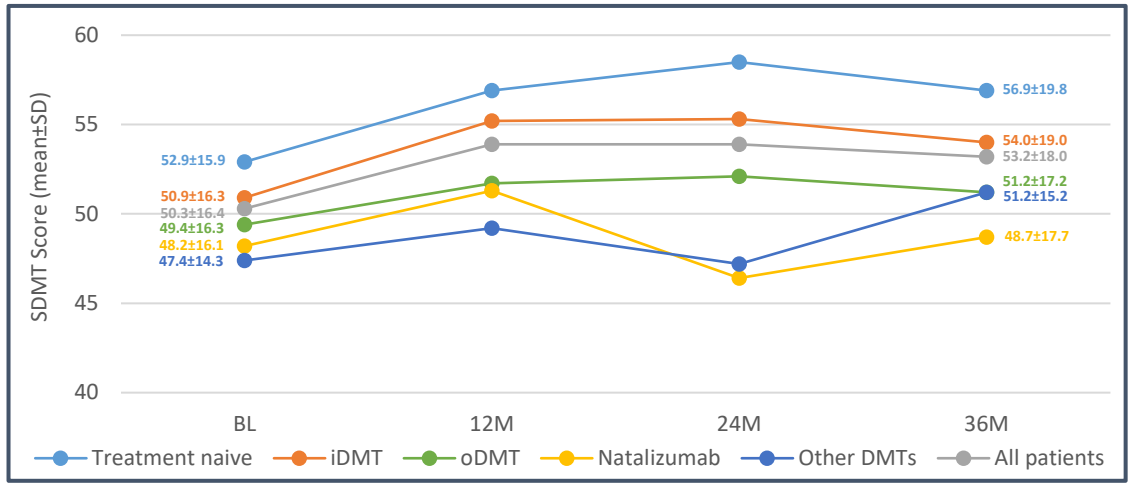

Figure 5: SDMT score at baseline (BL) and over the observation period of 36 months (36M). Subgroups by pretreatment at screening. Standard deviation (SD; min. 14.3, max. 19.8) omitted for clarity.

Treatment naive: n=197, 112, 81, 57; iDMT: n=832, 458, 369, 296; oDMT: n=461, 231, 169, 131; natalizumab: n=115, 61, 36, 23; other DMTs: n=112, 57, 43, 39; Total: n=1,717, 919, 698, 558, 546.

- Overall, the ARR decreased over time after switching to fingolimod (**Table 2**). Pairwise comparison of ARRs after start of fingolimod between subgroups revealed statistically meaningful p-values (<0.05) on a descriptive level for post-fingolimod ARRs in the subgroups:
- Significant differences after starting fingolimod were observed in the treatment naive group vs. iDMT pretreated (p=0.0210), oDMT pretreated (p=0.0001), natalizumab pretreated (p<0.0001) and pretreated with other DMTs (p=0.0075) as well as the iDMt pretreated group vs. oDMT pretreated (p=0.0082) and natalizumab pretreated (p=0.0013).
- The mean SDMT improved slightly during the observation period in all subgroups (**Figure 5**).

PANGAEA 2.0 Results

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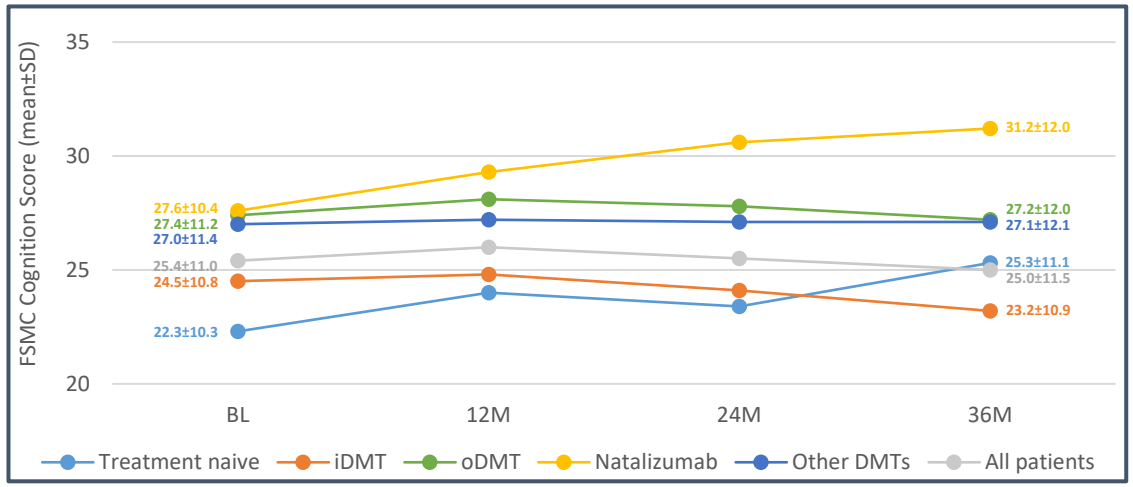

Figure 6: FSMC cognition score at baseline (BL) and over the observation period of 36 months (36M). Subgroups by pretreatment at screening. Standard deviation (SD; min. 10.3, max. 12.3) omitted for clarity.

Treatment naive: n=220, 126, 83, 70; iDMT: n=951, 521, 395, 301; oDMT: n=518, 271, 185, 129; natalizumab: n=136, 67, 42, 24; other DMTs: n=141, 65, 43, 38; Total: n=1,966, 1,050, 748, 562.

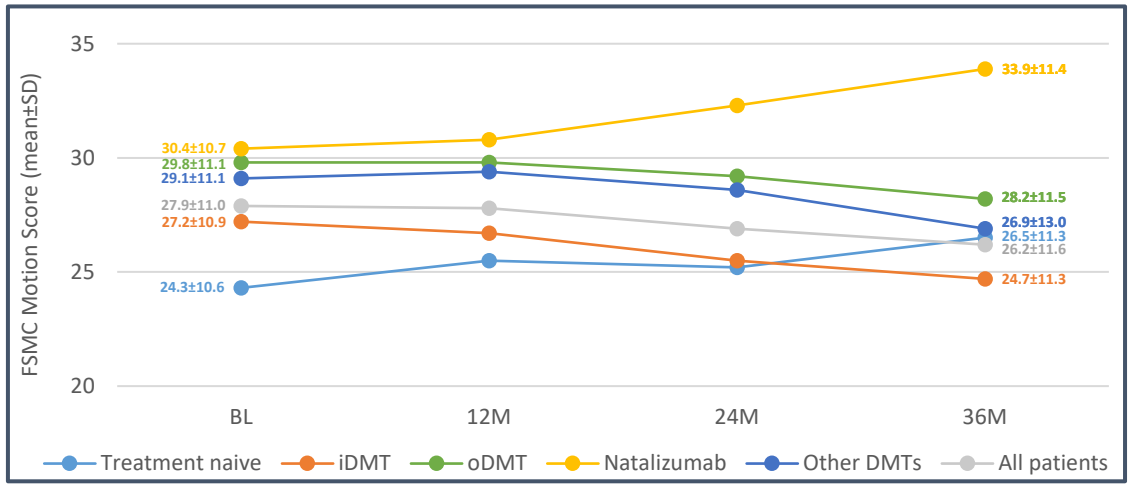

Figure 7: FSMC motion score at baseline (BL) and over the observation period of 36 months (36M). Subgroups by pretreatment at screening. Standard deviation (SD; min. 10.6, max. 13.0) omitted for clarity.

Treatment naive: n=219, 126, 83, 69; iDMT: n=950, 520, 395, 299; oDMT: n=518, 271, 185, 129; natalizumab: n=136, 67, 42, 23; other DMTs: n=141, 65, 43, 38; Total: n=1,964, 1,049, 748, 558.

- The FSMC cognition score remained stable for the group who had switched from iDMTs, oDMTs or other DMTs (**Figure 6**).
- Over 36 months on fingolimod, the FSMC motion scores of the same subgroups appeared to improve slightly (**Figure 7**).
- The treatment naive subgroup presented the lowest mean FSMC cognition and motor scores at screening; both scores increased over 36 months on fingolimod (**Figures 6, 7**) .
- Patients who had received natalizumab as the last pretreatment before switching to fingolimod presented with the highest FSMC cognition and motor scores at screening which further increased over the course of the observation period (**Figures 6, 7**).

Conclusions

- The predominantly female RRMS patients are about 39 years old and received their MS diagnosis about 7.1 years before inclusion into the study.
- Almost half the study population was treated with an iDMT before switching to fingolimod, about one quarter of patients had received an oDMT as last pretreatment and 12.0% of patients were treatment naive.
- Across all subgroups, AAR decreased over 3 years of fingolimod treatment and a delay in disease progression was observed.
- Treatment naive patients pretreated with iDMT and oDTM seemed to benefit slightly more compared to other subgroups while natalizumab pretreated patients showed less stable EDSS, SDMT and FSMC scores.

→ **PANGAEA 2.0 provides real-world insight into the effectiveness of fingolimod in disease-active RRMS-patients in Germany.**

→ **Overall, the disease burden remained relatively stable over 3 years on fingolimod, regardless of the previous therapy.**