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Natalizumab is associated with early improvement of working ability in relapsing-remitting multiple sclerosis patients: WANT observational study results

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Abstract

Background

The Work Ability in Natalizumab-Treated MS Patients (WANT) study assessed work ability, quality of life, and cognitive processing speed during natalizumab treatment.

Methods

WANT was a 1-year, prospective, multicenter observational study conducted in Italy. Inclusion criteria included relapsing-remitting multiple sclerosis (MS), natalizumab treatment, full-time worker status, and loss of working hours due to MS as measured by the Work Productivity and Activity Impairment Questionnaire for MS (WPAI:MS). The primary endpoint was change in WPAI:MS domain scores after 1 year on natalizumab. Secondary endpoints included change

in annualized relapse rate (ARR), Multiple Sclerosis Impact Scale (MSIS-29) score, and Symbol Digit Modalities Test (SDMT) score.

Results

At enrollment, the 91 patients had a mean age of 38.3 (standard deviation [SD], 9.0) years and a mean ARR of 1.5 (SD, 0.8). After 1 year, improvements were observed in all WPAI:MS domains, with significant reductions in Absenteeism (−4.2 [SD, 26.0], p = 0.0190) and Work Productivity Loss (−7.2 [SD, 28.6]; p = 0.0456). These changes were accompanied by a low ARR (0.1), and 87.9% of patients were relapse free. Significant improvement was observed in MSIS-29 physical and psychological domains (reductions of 2.8 [SD, 11.6; p = 0.0295] and 6.3 [SD, 15.6; p = 0.0007], respectively) and SDMT score (increase of 2.4 [SD, 7.9; p = 0.0006]). Adverse events were reported in 32 of 104 patients (30.8%).

Conclusions

The reductions in Absenteeism and Work Productivity Loss and the improved physical and psychological functioning reported after 1 year of natalizumab treatment in real-world settings extend our understanding of natalizumab's efects on patient-centric and health economics outcomes.

Introduction

Common symptoms of multiple sclerosis (MS), including fatigue, reduced motor and coordination skills, depression, and visual and cognitive impairment, may severely impair patients' ability to perform normal daily activities and their quality of life. The progressive and chronic nature of MS also has a major impact on patients' social life and ability to work [1, 2]. Up to one-third of the total costs associated with MS are due to loss of productivity, and patients with the disease lose more than 10 working days per year [3]. In addition, MS has a major impact on the quality of life of caregivers [4].

Natalizumab (Tysabri; Biogen, Cambridge, MA, USA), a monoclonal antibody approved for the treatment of relapsing-remitting MS (RRMS) [5], is highly efective on clinical and radiological measures of MS disease activity [6,7,8,9]. Natalizumab is also associated with an improvement in cognitive function [10,11,12], vision [13], and patient-reported outcomes such as fatigue [10, 14, 15].

Some studies have also suggested that natalizumab may increase work productivity in MS patients [16, 17]. Further investigation in diferent study populations could be useful to

confirm the efect of natalizumab on work productivity. The quality of life and work ability of the caregivers of patients treated with natalizumab should also be investigated.

The Work Ability in Natalizumab-Treated MS Patients (WANT) study aimed to evaluate whether natalizumab treatment was associated with an improvement in patients' ability to work during the first year of treatment. It also assessed the efects of natalizumab on patients' quality of life, fatigue, walking speed, cognitive function, and clinical and radiological measures of disease. In addition, for patients with caregivers, the study investigated the work ability and quality of life of these caregivers.

Patients and methods

Study setting and design

WANT was an observational, prospective multicenter study on Italian patients with RRMS eligible for natalizumab therapy. The study started in July 2013. Patients were enrolled during an 18-month period and subsequently followed up for 1 year after beginning natalizumab treatment. All patients signed an informed consent before enrollment, and the study protocol was approved by local ethics committees.

Patients

Patients aged 18–65 years with confirmed MS (according to the McDonald criteria [18]) were eligible for inclusion if they met the following requirements: (i) the patient was eligible to be treated with natalizumab in accordance with the criteria of the Italian Drugs Agency (Agenzia Italiana del Farmaco [AIFA]) criteria (see Online Resource 1); (ii) a clinical decision had been made to treat the patient with natalizumab; (iii) the patient had received one infusion of natalizumab at the time of enrollment (patients were recruited at the time of the first administration of natalizumab and were enrolled in the study before the second administration of the drug); (iv) the patient was currently working full time; (v) the patient had a score of at least 1 on the second question of the Work Productivity and Activity Impairment Questionnaire for MS (WPAI:MS) (i.e., a patient-reported loss of at least 1 working hour due to the illness during the previous week) [19]; and (vi) the patient had an Expanded Disability Status Scale (EDSS) score of 0.0–5.5. Exclusion criteria were as follows: (i) inability to independently complete the study's questionnaire; (ii) time of work already planned in the following year for any reason; (iii) alcohol and/or drug abuse; (iv) pregnancy and/or breastfeeding; and (v) simultaneous participation in other studies.

Each patient was free to withdraw from the study at any time without the obligation to provide a reason.

Treatment

All patients received natalizumab 300 mg intravenously once every 4 weeks. In case of treatment discontinuation for any reason, investigators could continue to follow patients and their caregivers in the study. There were no restrictions on prior or concomitant drugs or medical procedures.

Assessments

The primary endpoints of the study were the changes in each of the WPAI:MS domain scores (Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment) after 1 year of treatment compared with scores at enrollment. The secondary endpoints of the study were the change from enrollment at 1 year in the following: (i) mean EDSS score and annualized relapse rate (ARR); (ii) radiological parameters; (iii) Multiple Sclerosis Impact Scale (MSIS-29) domain scores; (iv) Fatigue Status Scale (FSS) score; (v) Timed 25-Foot Walk (T25FW) score; (vi) Symbol Digit Modalities Test (SDMT) score; (vii) Work Productivity and Activity Impairment, Mood and Mental State for Caregivers (WPAI:MM-CG) domain scores; and (viii) Short Form-12 Health Survey (SF-12) domain scores.

The following assessments were made by the investigators during on-study visits, in accordance with the normal clinical practice of each center: (i) tabulation of the number of on-study relapses and re-evaluation of EDSS score; (ii) measurement of magnetic resonance imaging (MRI) disease parameters (T2-weighted hyperintense, T1-hypointense, and gadolinium-enhancing [Gd+] MS lesions in the brain and spinal cord) at enrollment and at least annually or more frequently, in accordance with clinical practice; (iii) measurement of walking speed on the T25FW test; and (iv) assessment of cognitive function via the SDMT, which is used to measure attention in MS patients and it is considered the most sensitive test for cognitive deterioration in MS [20].

The WPAI:MS, MSIS-29, and FSS questionnaires were administered during study visits. The WPAI:MS questionnaire, consisting of six questions, evaluates ability to work and capacity to carry out daily activities over the preceding 7 days. The WPAI:MS, an adapted version of the general WPAI questionnaire, assesses results over four independent domains: the percentage of time lost due to the disease (Absenteeism), the percentage of impediment during work activity (Presenteeism), the percentage of lost working days (Work Productivity Loss), and the percentage of impediment to carrying out normal activities (Activity Impairment). In all domains, scores are recorded on a 0–100 scale, with higher scores representing greater impairment [19, 21]. The MSIS-29 questionnaire includes 20 questions investigating the impact of MS on patients' physical well-being and 9 questions on the psychological impact of the disease. The numerical score obtained ranges from 0 to 100, with lower scores representing better quality of life [22]. The FSS questionnaire is composed of nine statements on the state of fatigue during the previous week. Responses range from 1 to 7, with 1

representing the lowest level of agreement with the statement and 7 representing the highest. An overall score ≥ 36 indicates a state of fatigue [23].

For patients with caregivers, the WPAI:MM-CG and SF-12 questionnaires were administered to caregivers during study visits. The WPAI:MM-CG questionnaire quantifies the loss of caregiver's productivity as a combination of time lost at work and the reduced work productivity over the preceding 7 days [24]. The SF-12 questionnaire, a shortened version of the SF-36 questionnaire, evaluates caregivers' quality of life. The questionnaire includes eight domains of the SF-36: physical function, physical role limitations, social function, emotions, mental state, vitality, pain, and general state of health. The calculated score is obtained by combining the physical and mental components, and the result ranges from 0 to 100, with higher scores representing better quality of life [25].

Adverse events occurring during the study or already present during the observational period were recorded throughout the study. Serious adverse events were defined as those resulting in or potentially resulting in death, requiring or extending hospitalization, causing persistent or significant disability, or classified as birth defects. Investigators reported their assessment of the severity of adverse events and the potential relationship of these event to natalizumab treatment as well as the actions taken in response and patient outcomes.

Data analysis

It was calculated that a sample size of 90 patients would provide an ~ 80% power level to detect an efect size of 0.30 (viz., the diferences in each of the four domain scores of the WPAI scale) with a significance threshold equal to $\alpha = 0.05$. Based on a predicted dropout rate of 15% during the first year of the study, 105 patients were enrolled.

The safety population included all patients with available safety data, while the population for longitudinal analyses included patients who met enrollment criteria and had data available at enrollment and 1 year. Data were analyzed using descriptive statistics. Comparisons of assessed variables between time points were performed using the paired Student t test, with p values < 0.05 considered statistically significant. In addition to mean change in WPAI:MS domain scores over 1 year, the percentages of patients with WPAI:MS domain scores that decreased (i.e., improved), increased (i.e., worsened), or remained unchanged from enrollment to 1 year were also evaluated.

Exploratory analyses evaluated the association between change in the four WPAI:MS domain scores and change in ARR, EDSS score, and SDMT score after 1 year using the Spearman correlation coeficient. Relationships between distributions of changes in the four WPAI:MS

domain scores and change in EDSS, ARR, and SDMT were evaluated using the Mann-Whitney U test.

All analyses were performed using SAS 9.4 and Enterprise Guide 7.1.

Results

Population

A total of 106 patients were enrolled. Two patients immediately discontinued the study due to withdrawal of consent and simultaneous participation in another study. Safety data were available for 104 patients. The analysis population included 91 patients; 13 patients withdrew during the conduct of the study (see Online Resource 2).

At enrollment, patients had a mean age of 38.3 years, a mean ARR of 1.5, and a mean EDSS score of 2.8 (Table 1).

WPAI:MS domain scores

We observed an improvement in all the four domains of the WPAI:MS score from enrollment to 1 year, though only the reductions in the Absenteeism score, with a mean change of −4.2 ($p = 0.0190$), and the Work Productivity Loss score, with a mean change of −7.2 ($p = 0.0456$), reached statistical significance (Fig. 1a). After 1 year of observation, the majority of patients reported an improvement or a stabilization in all WPAI:MS domains (Fig. 1b). Consistent with the significant reductions seen in Absenteeism and Work Productivity Loss, these domains had the greatest proportions of patients (67.1% and 61.5%, respectively) with improved scores.

Secondary endpoints

The mean ARR was low (0.1), and 80 of 91 patients (87.9%) were relapse free during the 1 year of observation. EDSS score remained unchanged from enrollment in 54 patients (60.0%) and decreased in 27 patients (30.0%) during the study; a small but statistically significant mean change of −0.2 ($p = 0.0068$) was observed (Table 2). At 1 year, no statistically significant change in T25FW times was observed, though 39 of 83 patients (47.0%) exhibited numerically reduced T25FW times, and 64 of 83 patients (77.1%) did not show a clinically significant decline (a > 20% increase in time) [26] in walking ability.

SDMT scores were also improved over 1 year, with a mean score increase of 2.4 (p = 0.0006; Table 2). In total, 48 (60.0%) of 80 patients exhibited an increase in SDMT score, while 6 (7.5%) maintained a stable score over 1 year. Based on the MSIS-29 questionnaire, the percentages of patients with improved or unchanged quality of life after 1 year on natalizumab were 45 (57.0%) and 8 (10.1%) for physical activities, respectively, and 50 (58.1%) and 7 (8.1%) for psychological aspects, respectively. Significant mean decreases of 2.8 points (p = 0.0295) in the physical domain and of 6.3 points (p = 0.0007) in the psychological domain were observed (Table 2).

Brain Gd+ lesions were significantly reduced, from a mean (standard deviation [SD]) of 1.1 (1.9) at enrollment to 0.5 (1.8) after 1 year (p = 0.0078), with a stable lesion load in the brain and spinal cord, assessed as the number of lesions on T2- and T1-weighted scans (Table 2).

Exploratory analysis

At 1 year, there was a statistically significant association between improvement in Absenteeism score and reduction in EDSS score (p = 0.0161) and ARR (p = 0.0268) (Table 3), though the Spearman correlation coeficients were low (−0.1658 and −0.0992, respectively). For all other exploratory analyses, no statistically significant correlations were identified.

Caregivers

Of the 91 patients in the analysis population, 14 (15.4%) had caregivers. The majority (11 of 14 [78.6%]) of the caregivers were female and their mean (SD) age was 46.3 (14.4) years (range, 26–69 years). Nearly all (13 of 14 [92.9%]) were immediate family members, including six spouses or partners, five parents, one son or daughter, and one cousin. They had been a caregiver to the patient for a median (range) of 4.5 (0.2–12.0) years. Caregivers reported a mean (SD) of 7.4 (7.3) hours of patient care daily. Median baseline EDSS score was 4.3 among patients with a caregiver compared with 2.0 in patients without a caregiver. Caregivers of six patients with an EDSS score of at least 4.0 reported assisting the patient for ≥ 6 h per day.

Work productivity loss was observed in two caregivers, and eight reported activity impairment. Overall, significant changes in caregivers' quality of life were not observed, and the limited available data did not allow us to more fully address this endpoint.

Safety

The 104 patients in the safety population were exposed to natalizumab for a mean (SD) of 351.6 (70.3) days. Over the 1-year study, 32 patients (30.8%) had at least one adverse event and two patients (1.9%) reported at least one serious adverse event (two events of lower back

pain and one event each of cruralgia and leg pain in one patient and urinary tract infection in the other patient), all of which were unrelated to natalizumab treatment (Table 4). Seven patients each experienced ≥ 1 treatment-related adverse event (including mild tachycardia, mild fatigue, insomnia, urticaria, allergic skin reaction, increase of γ-glutamyltransferase, headache, and balance dificulty).

Compliance with ethical standards

Conflicts of interest RC has received lecture fees and/or travel grants

from Biogen, Celgene, Genzyme, Novartis, and Sanofi. VBM has received funding for travel, speaker honoraria, and research support from

Bayer Schering, Biogen, Merck Serono, and Sanofi Genzyme. MM has

received consulting fees, speaker honoraria, and travel grants from

Almirall, Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, and Teva.

CG has received funding for invited speaker or travel expenses for attending meetings from Biogen, Genzyme, Merck Serono, Novartis,

Sanofi, and Teva. CS has received speaker honoraria from Biogen and

Teva, honoraria for serving on advisory boards from Merck and Sanofi,

and travel grants from Biogen, Merck, Novartis, Roche, and Teva. RT has

received funding for travel or speaker honoraria from Alfa Wasserman,

Bayer, Biogen, CLS Bering, Merck Serono, Novartis, Roche, Sanofi, and

Teva. NDR has received speaker honoraria from Biogen, Genzyme,

Novartis, and Sanofi, funding for participation in advisory boards from

Novartis and Sanofi Genzyme, and support for travel to scientific meetings from Almirall, Biogen, Novartis, Roche, Sanofi Genzyme, and Teva.

SM and VZ are employees of and may hold stock and/or stock options in

Biogen. FP has received personal compensation for speaking and serving

on advisory boards from Almirall, Bayer, Biogen, Celgene, Merck,

Novartis, Roche, Sanofi, and Teva.

Ethics approval and informed consent All patients signed an informed

consent before enrollment, and the study protocol was approved by local

ethics committees.

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Characteristic	Evaluable patients ($N = 91$)
Female, *n* (%)	57 (62.6)
Race, white, *n* (%)	90 (98.9)
Age, years	
Mean (SD)	38.3 (9.3)
Median (range)	38 (20–62)
Weight, mean (SD), kg	65.4 (12.3)
Height, mean (SD), cm	167.1 (8.7)
Patients with non–MS-related concomitant conditions, *n* (%)[a]	18 (19.8)
Allergies	4 (4.4)
Hypertension	4 (4.4)
Autoimmune diseases	3 (3.3)
Diabetes	2 (2.2)
Nervous system diseases (other than MS)	2 (2.2)
Hematologic disorders	1 (1.1)
Liver diseases	1 (1.1)
Other[b]	14 (15.4)
EDSS score	
Mean (SD)	2.8 (1.5)
Median (range)	2.5 (0.0–5.5)
Number of relapses in the last year	
Mean (SD)	1.5 (0.8)[c]
Median (range)	1 (1–5)[c]
Disease duration	
Mean (SD)	7.9 (7.1)
Median (range)	5.3 (0.1–30.8)

EDSS Expanded Disability Status Scale, *MS* multiple sclerosis, *SD* standard deviation

[a] Patients could have more than one concomitant disease

[b] Other non–MS-related concomitant diseases were reported as calculus of bile duct, cardiac arrhythmia, depression, dyslipidemia, dysthyroidism, frontal headache, gastritis, gastroesophageal reflux, gout, hypercholesterolemia, insomnia, mild mitral insufficiency, ovarian cyst, and ulcerative proctitis

[c] Data on number of relapses in the prior year were missing for one patient

Table 1 Characteristics of patients at enrollment

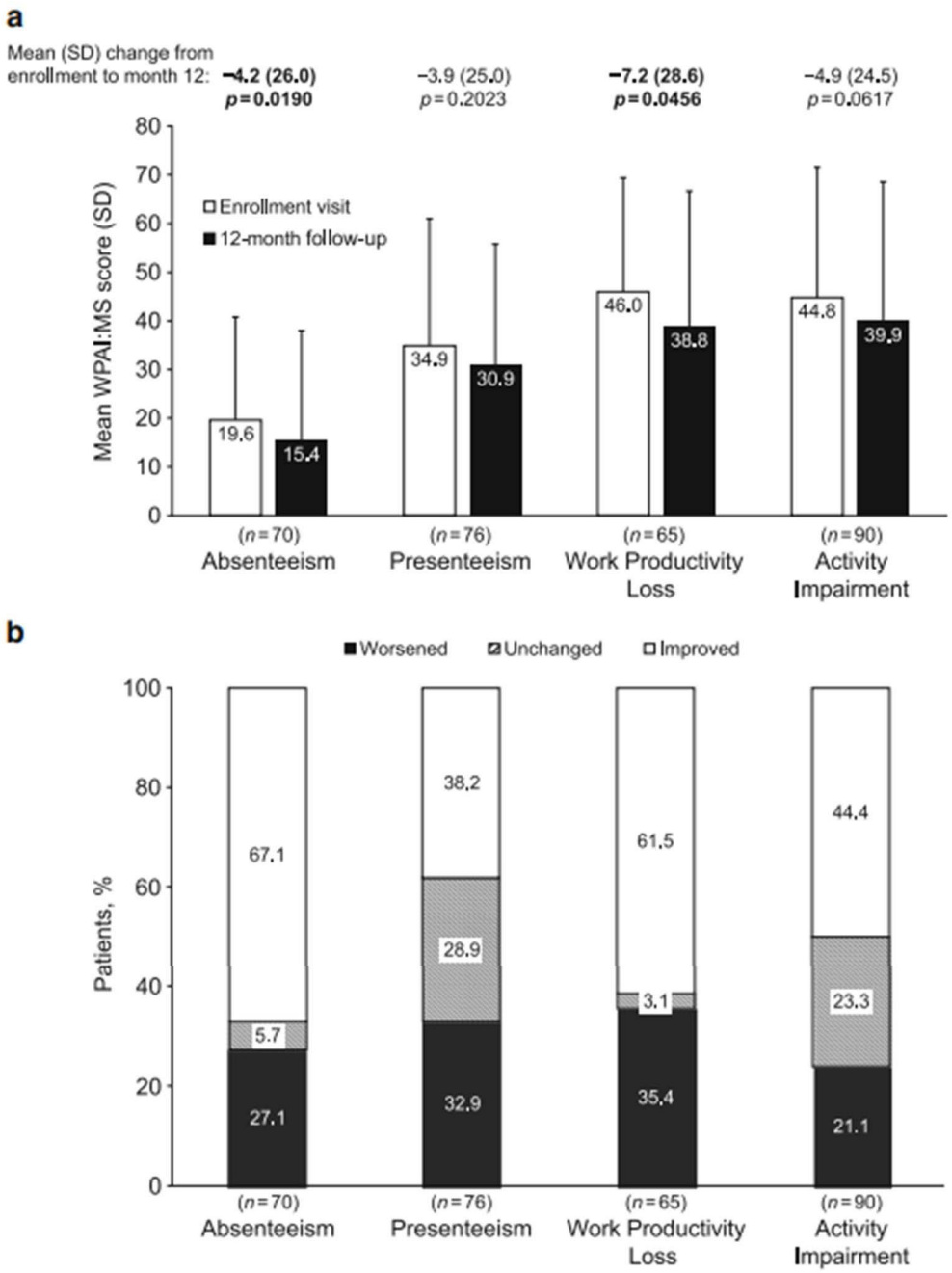

Fig. 1 (a) Changes in the WPAI:MS domains and (b) percentage of patients with improved, unchanged, or worsened ability to work from enrollment to 1 year. Each parameter is given as a percentage of the total number of available workdays. MS, multiple sclerosis; SD, standard error; WPAI:MS, Work Productivity and Activity Impairment Questionnaire for MS

Other evaluations	*n*	Enrollment visit, mean (SD)	1-year follow-up, mean (SD)	Mean change (SD)	*p* value
Clinical outcomes					
EDSS score	90	2.8 (1.5)	2.6 (1.6)	−0.2 (0.6)	0.0068
T25FW	83	10.6 (10.3)	9.7 (8.8)	−0.9 (6.9)	0.1355
ARR	87	1.4 (0.7)	0.1 (0.4)	−1.3 (0.8)	< 0.0001
SDMT	80	45.3 (14.6)	47.7 (14.5)	2.4 (7.9)	0.0006
MSIS-29 physical	79	47.5 (16.7)	44.7 (16.5)	−2.8 (11.6)	0.0295
MSIS-29 psychological	86	54.6 (17.9)	48.2 (16.7)	−6.3 (15.6)	0.0007
FSS total score	85	36.9 (17.1)	35.2 (16.8)	−1.7 (12.8)	0.4317
MRI outcomes					
No. of hypointense lesions in T1-weighted sequences in brain	30	10.1 (13.2)	9.5 (11.7)	−0.6 (9.5)	0.9766
No. of hypointense lesions in T1-weighted sequences in spinal cord	14	2.2 (3.6)	1.4 (2.6)	−0.8 (2.9)	1.0000
No. of hyperintense lesions in T2-weighted sequences in brain	28	25.6 (32.1)	23.9 (30.7)	−1.8 (19.8)	0.5000
No. of Gd+ lesions in brain	31	1.1 (1.9)	0.5 (1.8)	−0.6 (1.1)	0.0078
No. of Gd+ lesions in spinal cord	16	0.7 (2.0)	0.0 (0.0)	−0.7 (2.0)	0.2500

ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *FSS* Fatigue Status Scale, *Gd+* gadolinium-enhancing, *MRI* magnetic resonance imaging, *MSIS-29* Multiple Sclerosis Impact Scale, *SDMT* Symbol Digit Modalities Test, *T25FW* Timed 25-Foot Walk

Table 2 Changes in clinical and MRI outcomes from enrollment to 1 year

WPAI:MS domain	EDSS score change at 1 year, *n* (%)			SDMT score change at 1 year, *n* (%)			ARR at 1 year, *n* (%)	
	Unchanged	Improved	Worsened	Unchanged	Improved	Worsened	ARR = 0	ARR > 0
Change in WPAI:MS—Absenteeism								
Unchanged	3 (4.3)	0 (0.0)	1 (1.4)	0 (0.0)	4 (6.6)	0 (0.0)	2 (2.9)	2 (2.9)
Improved	36 (52.2)	8 (11.6)	3 (4.3)	3 (4.9)	24 (39.3)	12 (19.7)	44 (64.7)	2 (2.9)
Worsened	7 (10.1)	9 (13.0)	2 (2.9)	1 (1.6)	11 (18.0)	6 (9.8)	17 (25.0)	1 (1.5)
p value	0.0161			0.7759			0.0268	
Change in WPAI:MS—Presenteeism								
Unchanged	17 (22.7)	4 (5.3)	1 (1.3)	2 (3.0)	11 (16.7)	6 (9.1)	20 (26.7)	2 (2.7)
Improved	15 (20.0)	10 (13.3)	4 (5.3)	1 (1.5)	17 (25.8)	7 (10.6)	27 (36.0)	2 (2.7)
Worsened	15 (20.0)	8 (10.7)	1 (1.3)	2 (3.0)	14 (21.2)	6 (9.1)	23 (30.7)	1 (1.3)
p value	0.3885			0.9266			0.8572	
Change in WPAI:MS—Work Productivity Loss								
Unchanged	2 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (3.1)	0 (0.0)
Improved	28 (43.8)	8 (12.5)	4 (6.3)	2 (3.5)	23 (40.4)	10 (17.5)	38 (59.4)	2 (3.1)
Worsened	13 (20.3)	8 (12.5)	1 (1.6)	2 (3.5)	13 (22.8)	5 (8.8)	20 (31.3)	2 (3.1)
p value	0.5216			0.9199			0.6579	
Change in WPAI:MS—Activity Impairment								
Unchanged	17 (19.1)	3 (3.4)	1 (1.1)	3 (3.8)	10 (12.7)	5 (6.3)	21 (24.1)	0 (0.0)
Improved	22 (24.7)	14 (15.7)	4 (4.5)	1 (1.3)	25 (31.6)	10 (12.7)	33 (37.9)	6 (6.9)
Worsened	15 (16.9)	9 (10.1)	4 (4.5)	2 (2.5)	13 (16.5)	10 (12.7)	25 (28.7)	2 (2.3)
p value	0.2958			0.3118			0.1494	

ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *SDMT* Symbol Digit Modalities Test, *WPAI:MS* Work Productivity and Activity Impairment Questionnaire for MS

Table 3 Distribution of changes in the four WPAI:MS domain scores with respect to change in EDSS and SDMT score and ARR after 1 year of treatment

Adverse events, *n* (%)	Safety population (*N* = 104)
Patients with ≥ 1 adverse event	32 (30.8)
Relapse	9 (8.7)
Fatigue	3 (2.9)
Headache	3 (2.9)
Bronchitis	2 (1.9)
Fever	2 (1.9)
Melanocytic nevi	2 (1.9)
Nausea	2 (1.9)
Patients with ≥ 1 treatment-related adverse event	7 (6.7)
Mild tachycardia	1 (1.0)
Mild fatigue, heavy feeling in legs, tingling of extremities, and headache	1 (1.0)
Insomnia	1 (1.0)
Urticaria	1 (1.0)
Allergic skin reaction	1 (1.0)
Increase of γ-glutamyltransferase	1 (1.0)
Patients with ≥ 1 adverse event that led to treatment discontinuation	4 (3.8)
Patients with ≥ 1 serious adverse event	2 (1.9)

Table 4 Incidence of adverse events occurring over 1 year