BMJ Neurology Open

Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS)

Lutz Achtnichts,[1] Chiara Zecca,[2,3] Oliver Findling,[1] Christian P Kamm,[4,5] Stefanie Mueller,[6] Jens Kuhle,[7] Andreas Lutterotti,[8] Claudio Gobbi,[2,3] Camille Viviani,[9] Emanuela Villiger-Borter,[9] Krassen Nedeltchev[1]

To cite: Achtnichts L, Zecca C, Findling O, *et al*. Correlation of disability with quality of life in patients with multiple sclerosis treated with natalizumab: primary results and post hoc analysis of the TYSabri ImPROvement study (PROTYS). *BMJ Neurology Open* 2023;**5**:e000304. doi:10.1136/bmjno-2022-000304

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjno-2022-000304).

Received 29 March 2022
Accepted 09 October 2022

For numbered affiliations see end of article.

Correspondence to
Dr Lutz Achtnichts;
lutz.achtnichts@ksa.ch

Dr Oliver Findling;
oliver.findling@ksa.ch

ABSTRACT

Background In patients with multiple sclerosis (MS), relapses and disability progression have been associated with decreased health-related quality of life (HRQoL).

Methods PROTYS, a prospective, multicentre, single-arm, observational study in seven Swiss MS centres, evaluated correlations between change in disability status (measured through the Expanded Disability Status Scale (EDSS)) and HRQoL changes (measured through the global Multiple Sclerosis International Quality of Life (MusiQoL) index questionnaire) in 35 patients with relapsing remitting MS on natalizumab for 1 year. In addition, several other scales were also used, such as: Multiple Sclerosis Intimacy and Sexuality Questionnaire-19, EuroQoL-5 Dimension, and Fatigue Scale of Motor and Cognitive Function. A post hoc analysis further assessed the association between HRQoL changes after 1 year and the MusiQoL subscores and other patient-reported outcome (PRO) measures.

Results At 1 year, patients were categorised into 'EDSS improved' (6/35), 'EDSS stable' (28/35) and 'EDSS worsened' (1/35). Mean disability scores decreased for 'EDSS improved' and 'EDSS stable' but increased for 'EDSS worsened'. Mean MusiQoL index score for 'EDSS improved' increased from 61.2 at baseline to 66.3 at 1 year, while the 'EDSS stable' group increased from 67.9 to 70.8. No meaningful statistical relationship was observed between EDSS group and changes in MusiQoL score. For the post hoc analysis, patients were categorised in 'MusiQoL improved' (n=21) and 'MusiQoL worsened' (n=14) groups. MusiQoL subscores for 'symptoms,' 'psychological well-being' and 'activities of daily living', as well as scores for several related PRO measures, correlated with improvement of the MusiQoL global index. There was no correlation between the changes in MusiQoL global index and EDSS score.

Conclusions Natalizumab treatment for 1 year resulted in either improved or stable EDSS status in most patients, and although no significant relationship was observed between global HRQoL change and EDSS change, several domains of HRQoL seemed to improve with natalizumab treatment.

Trial registration number NCT02386566.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Multiple sclerosis (MS) is associated with impaired health-related quality of life (HRQoL). Though existing studies note improvement in HRQoL with natalizumab treatment, the current evidence on how disease progression is correlated with HRQoL—in particular with specific HRQoL domains—is limited.

WHAT THIS STUDY ADDS

⇒ Our results suggest that natalizumab treatment of patients with MS appears to improve several domains of HRQoL: fatigue, symptoms, overall health state, sexual dysfunction and work productivity, regardless of whether disease progression (as measured by Expanded Disability Status Scale scores) was stable or improved.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results highlight important factors of the HRQoL of patients with MS, and specifically underline the need to further evaluate how the different domains of HRQoL are affected.

1. INTRODUCTION

In patients with multiple sclerosis (MS), frequent relapses and disability progression have been associated with decreased health-related quality of life (HRQoL).[1–5] Balance problems, spasticity and depression have been shown to have the most detrimental effect on HRQoL in relapsing–remitting MS

(RRMS),[6] while fatigue and impaired gait are reported by many patients as the most disabling symptoms.[7 8]

The potential impact of disease-modifying therapies (DMTs) on HRQoL is actively being investigated.[9] Evidence on the potential impact of treatment with the DMT natalizumab on HRQoL is limited, though the existing studies note improvement in HRQoL with natalizumab.[3 9–17] Natalizumab treatment has been shown to stabilise or improve disability over time, when measured with the Expanded Disability Status Scale (EDSS),[18–22] and improve fatigue,[23 24] visual function.[25] In addition, natalizumab treatment has shown improvements in physical and psychological measures of HRQoL.[3 10]

Associations between EDSS changes and HRQoL changes in patients treated with natalizumab have, until now, not been investigated. Thus, the aim of the PROTYS study was to evaluate the relationships between EDSS change and changes in HRQoL, as measured by the global Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) index in patients with RRMS treated with natalizumab for 1 year. A post hoc analysis assessed the association between improvement or worsening in HRQoL after 1 year of natalizumab treatment and the scores of patient-reported outcome (PRO) measures assessing a variety of domains.

This work presents the primary result of the PROTYS study combined with the post hoc analyses.

2. METHODS

2.1 Study Design

The PROTYS study (NCT02386566) was a phase IV, prospective, multicentre, observational study to assess the correlation of EDSS with quality of life in patients with MS newly treated with natalizumab. Patients were enrolled over a 2-year period from October 2014 to October 2016 at seven sites in Switzerland.

The primary objective of the PROTYS study was to investigate the associations between categories of change in disability (EDSS) with HRQoL (MusiQoL) at 3 month intervals up to 1 year in a real-life setting of patients with RRMS who started treatment with natalizumab.

Due to low patient numbers, the recruitment goal of the PROTYS study was not met. In December 2016, due to futility in the interim analysis, the decision was taken to stop recruitment and to analyse the population of patients already enrolled. Because of this we were unable to evaluate association between categories of EDSS change and HRQoL, which was the primary outcome of the study. Nevertheless, a subsequent post hoc analysis on the complete PROTYS per-protocol population aimed to identify which factors influence HRQoL based on the MusiQoL index in patients after 1 year of treatment with natalizumab. The secondary objectives of the PROTYS study are reported in online supplemental information.

The primary objectives of the post hoc analysis were the correlation between the change from baseline to end of study (EOS) in the scores described in detail in Section 2.4, in the annual relapse rate (ARR), the ARR of relapses requiring steroid treatment, and the change after 1 year of natalizumab treatment in the global MusiQoL questionnaire index (categorised as improved or worsened after 1 year).

2.2 Population

Inclusion and exclusion criteria are presented in online supplemental table 1. This observational study included patients who were starting treatment in compliance with the official guidelines of Swissmedic (the Swiss authority for authorisation and supervision of therapeutic products). The decision to prescribe natalizumab was made prior to and independently of the study.

The per-protocol population was defined as patients who completed a full year of natalizumab treatment, received at least eight natalizumab infusions within the year, and had both EDSS and MusiQoL scores available at baseline and at 1 year. The post hoc analysis was also performed on the per-protocol population.

2.3 Treatment

Patients meeting the inclusion criteria were treated with natalizumab 300 mg (Tysabri, Biogen, Cambridge, Massachusetts, USA) intravenous infusion, administered every 4 weeks as specified in the Swiss product label.

2.4 Measures and assessments

Neurological disability was assessed through EDSS assessment at 3 month intervals.[26] All EDSS raters were trained and certified. Based on EDSS scores at baseline and at 1 year, the patients were divided into three groups: 'EDSS improved' (≥1.0-point decrease sustained for at least 12 weeks), 'EDSS stable' (changes sustained for <12 weeks or with changes <1.0) and 'EDSS worsened' (≥1.0-point increase sustained for at least 12 weeks).

The overall QoL was measured through self-administered MusiQoL questionnaire at baseline and at year 1.[27]

At each study visit, the self-administered tests and questionnaires were used except for the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19), which was administered only at study visits 3 and 5. Further information on the self-administered tests and questionnaires can be found in online supplemental information. The study assessments are described in online supplemental table 2.

Participants entered responses to all questionnaires either on paper or directly into an electronic case report form (eCRF) using tablet computers, with the exception of the symbol DMT scores (paper version), which were calculated and entered into the eCRF by study staff.

Relapses were recorded and ARRs calculated. Relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical

demyelinating event, present for at least 24 hours and not accompanied by fever or infection.

2.5 Safety

All patients received standard care throughout the observation period. All serious adverse events (SAEs) were recorded. Tests for anti-John Cunningham virus (JCV) antibodies and brain MRI scans were performed according to the standard of care and collected if performed.

2.6 Statistical analyses

2.6.1 PROTYS study

A power calculation was performed prior to the PROTYS study, specifically a one-way analysis of variance with α=0.05, 80% power, two sided and common SD=22. This resulted in the estimated recruitment total of 88 patients being sufficient to answer the research question. An attrition rate of 20% would result in 72 patients in the per-protocol population (24 for each EDSS category, equally distributed). All analyses were performed on the per-protocol population. For the primary outcome, an increase of 10 points in MusiQoL score for the EDSS improved group and a decrease of 10 points in MusiQoL score for the EDSS worsened group were estimated to be required for statistical power. Descriptive statistics (n, mean, median, minimum, maximum and SD) were performed for continuous variables, and frequency distributions (n, %) were used to describe discrete variables. Missing data were substituted by carrying forward the last valid post-baseline observation (last observation carried forward). To test for significant differences between the means at different time points, the Wilcoxon signed-rank test or the Student's t-test were used as specified. P values less than 0.05 were deemed significant.

2.6.2 Post hoc analysis

Changes in PROs over the course of treatment were investigated for the total population using the Wilcoxon Mann-Whitney test. Statistical endpoints of the assessment of the correlation between the various PRO endpoints are described in online supplemental table 3. Spearman's correlation coefficients were used to investigate relationships between the change over 1 year in the MusiQoL global index, MusiQoL sub scores and other PROs. Analyses were run separately in the overall study population (N=35) and in the subgroup of patients with improvement in MusiQoL global index (n=21) and with worsened MusiQoL global index (n=14). For the post hoc analysis, the MusiQoL categories of 'improved' and 'worsened' at 1 year versus baseline were defined as: 'improved' equals change in the global MusiQoL index >0, and 'worsened' equals change in the global MusiQoL index<0. The post hoc analysis statistical endpoints are described in online supplemental information. All statistical analyses of the study data were performed according to the predefined statistical analysis plan by ACG+using SAS V.9.4 or a newer version.

2. RESULTS

3.1 Patient characteristics

In the PROTYS study, 48 patients with RRMS were screened for inclusion into the study (online supplemental figure 1). The baseline characteristics of the per-protocol population are shown in table 1. In the post hoc analysis, the per-protocol population of 35 patients was included. The per-protocol population was subdivided into two subgroups, one with MusiQoL global index improved (n=21) and one with MusiQoL global index worsened (n=14).

3.2 Disability status

In the PROTYS study, after 1 year of natalizumab treatment, 6/35 patients (17.1%) were assessed as 'EDSS improved', 28/35 patients (80.0%) as 'EDSS stable' and 1/35 (2.9%) as 'EDSS worsened'. In the 'EDSS improved' group: median disability score was 4.00 (Q1, Q3: 2.00, 5.00; range: 2.00–3.50) at baseline and 2.00 (Q1, Q3: 1.00, 3.00; range: 1.00–3.50) at EOS (median change=−1.50; Q1, Q3: −2.50 to −1.00; range: −2.50 to −1.00) (figure 1). In the 'EDSS stable' group: median disability score was 3.00 (Q1, Q3: 2.00, 3.5; range: 1.00–5.50) at baseline and 2.50 (Q1, Q3: 2.00, 3.50; range: 1.50–5.50) at EOS (median change=0; Q1, Q3: −0.50, 0.00; range: −1.00 to 0.50) (figure 1). The patient assessed as 'EDSS worsened' had an EDSS score of 2.0 at baseline and 3.0 at EOS, sustained for at least 12 weeks. As only one patient showed worsening the subsequent analyses of the primary results were performed comparing the 'EDSS improved' and 'EDSS stable' groups. Results on the mean change from baseline in number of relapses are available in online supplemental information.

3.3 PROTYS study MusiQoL index score (global HRQoL)

In the 'EDSS improved' group, the MusiQoL index score, representing global HRQoL, increased from a mean of 61.2 at baseline to 66.3 at 1 year (mean change=5.1 ± 6.4). In the 'EDSS stable' group, the MusiQoL index score increased from 67.9 at baseline to 70.8 at 1 year (mean change=2.9 ± 12.1) (table 1). There were no statistically significant differences between the groups.

Analyses of MusiQoL subscores showed that there were no significant differences between the EDSS groups in changes from baseline to 1 year. For the MusiQoL subparameter 'symptoms', the score increased in the 'EDSS improved group' from a mean of 56.3 at baseline to 71.9 at 1 year (mean change=15.6 ± 11.7), and in the 'EDSS stable' group from 64.3 at baseline to 69.4 at 1 year (mean change=5.1 ± 15.9; p=0.118) (table 2). There was no statistically significant difference between the EDSS groups in mean change from baseline to 1 year.

3.4 Post hoc analysis

The post hoc analysis was performed on the 'MusiQoL improved' (n=21) and 'MusiQoL worsened' (n=14) groups. Baseline characteristics and baseline values for scores are in table 2. No correlation was detected in the

Table 1 Patient characteristics (N=35; per-protocol population)

Age, years	
Mean±SD	36.8±10.96
Median (min., max.)	37.0 (22, 63)
Sex, n (%) female	21 (60.0)
Race, n (%) Caucasian	35 (100)
Education	
Primary education (basic, semiskilled), n (%)	9 (25.7)
Secondary education (eg, apprenticeship, technical college), n (%)	20 (57.1)
Tertiary education (university degree), n (%)	6 (17.1)
Occupation	
Employed, n (%)	23 (65.7)
Unemployed, n (%)	7 (20.0)
Housewife, n (%)	3 (8.6)
Undergoing further education, n (%)	2 (5.7)
Disease duration	
<1 year, n (%)	8 (22.9)
1–6 years, n (%)	12 (34.3)
6–12 years, n (%)	10 (28.6)
>13 years, n (%)	5 (14.3)
Patients with at least one prior DMT, n (%)	28 (80.0)
Previous interferon-β 1A SC treatment, n (%)	16 (45.7)
Previous interferon-β 1A IM treatment, n (%)	7 (20.0)
Previous interferon-β 1B treatment, n (%)	2 (5.7)
Previous fingolimod treatment, n (%)	11 (31.4)
Previous glatiramer acetate treatment, n (%)	7 (20.0)
Previous dimethyl fumarate treatment, n (%)	5 (14.3)
Previous teriflunomide treatment, n (%)	4 (11.4)
Previous natalizumab treatment, n (%)	1 (2.9)
Other treatment, n (%)	1 (2.9)
Relapses in history cv	
Yes	34 (97.1)
No	1 (2.9)
No of MS relapses in 12 months prior to natalizumab treatment	
Mean±SD	1.2±0.94
Median (min., max.)	0 (0, 4)
Baseline no of relapses requiring corticosteroid treatment per year in:	
EDSS improved group, mean±SD	0.9±0.9
EDSS stable group, mean±SD	0.6±0.6
Baseline EDSS score	
Mean±SD	3.04±1.19
Median (min., max.)	3.00 (1.00, 5.50)
Baseline MusiQoL score	
Mean±SD	66.7±13.8
Median (min., max.)	65.6 (40.2, 94.4)

DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IM, intramuscular; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life questionnaire; MusiQoL, Multiple Sclerosis International Quality of Life; SC, subcutaneous.

'improved' and 'worsened' MusiQoL groups between the changes from baseline in the MusiQoL global index at 1 year and sex or educational level. No significant differences in sex or educational level between the 'improved' and 'worsened' groups were found (Fisher's exact test). The baseline characteristics of patients with an improved MusiQoL index and worsened MusiQoL index appear to be different between the groups (table 3). Baseline, EOS and change from baseline to EOS for MusiQoL index shown in table 4.

There was no correlation between baseline MusiQoL and change in MusiQoL global index from baseline to 1 year (figure 2). A summary of the negative or no

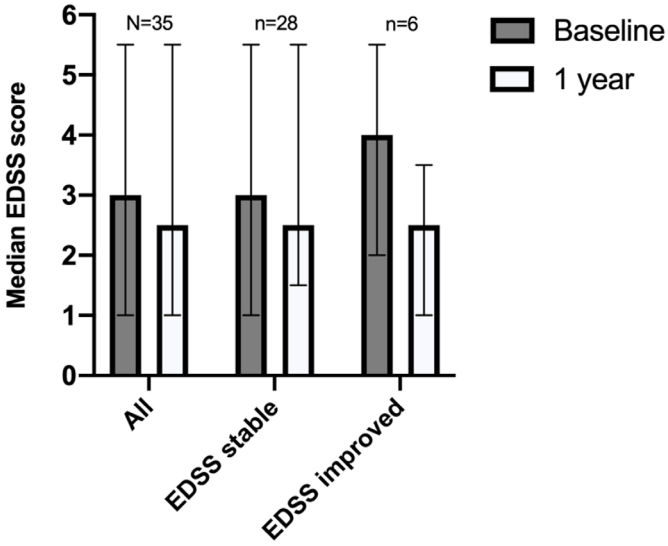


Figure 1 Median EDSS scores at baseline and at 1 year (EOS). N=6 patients (17.1%) were assessed as 'EDSS improved' (≥1.0 increase sustained for at least 12 weeks), and n=28 patients were assessed as 'EDSS stable' (changes sustained for <12 weeks or changes of <1.0). The single patient with progressed EDSS from 2.0 at baseline and 3.0 at EOS is not separately shown in the graph. EDSS, Expanded Disability Status Scale; EOS, end of study.

Table 2 Global HRQoL in patients with RRMS at baseline and 1 year after starting treatment with natalizumab as measured through the MusiQoL questionnaire

	EDSS improved n=6			EDSS stable n=28			P value
Measure	**Baseline**	**1 year**	**Change**	**Baseline**	**1 year**	**Change**	**Wilcoxon***
MusiQoL index							
Mean±SD, Median (min., max.)	61.2±13.1 62.6 (41.4, 81.0)	66.3±10.3 70.7 (50.0, 75.3)	5.1±6.4 6.0 (–5.7, 12.7)	67.9±14.2 69.0 (40.2, 94.4)	70.8±17.7 71.8 (35.2, 97.9)	2.9±12.1 2.0 (–28.1, 31.4)	0.461
Subdomains							
Activity of daily living							
Mean±SD Median (min., max.)	56.8±21.8 60.9 (21.9, 81.3)	69.8±21.8 65.6 (46.9, 100.0)	13.0±19.4 12.5 (–9.4, 37.5)	60.3±28.1 59.8 (3.1, 100.0)	71.0±26.4 75.0 (12.5, 100.0)	10.7±19.3 7.8 (–32.1, 68.8)	0.805
Psychological well-being							
Mean±SD Median (min., max.)	53.1±32.5 56.3 (0.0, 93.8)	65.6±26.1 62.5 (31.3, 100.0)	12.5±35.6 12.5 (–43.8, 50.0)	66.7±25.9 71.9 (0.0, 100.0)	75.5±24.2 82.3 (25.0, 100.0)	8.9±27.8 6.3 (–50.0, 100.0)	0.637
Symptoms							
Mean±SD Median (min., max.)	56.3±15.8 56.3 (37.5, 81.3)	71.9±18.9 68.8 (50.0, 100.0)	15.6±11.7 12.5 (6.3, 37.5)	64.3±27.4 68.8 (12.5, 100.0)	69.4±27.4 71.9 (25.0, 100.0)	5.1±15.9 0.0 (–25.0, 56.3)	0.118
Relationships with friends							
Mean±SD Median (min., max.)	54.2±27.3 54.2 (25.0, 83.3)	54.2±24.6 50.0 (16.7, 91.7)	0.0±23.6 0.0 (–33.3, 25.0)	50.3±28.1 50.0 (0.0, 100.0)	53.0±28.4 54.2 (0.0, 100.0)	2.7±29.7 0.0 (–58.3, 75.0)	0.874
Relationships with family							
Mean±SD Median (min., max.)	58.3±23.6 58.3 (25.0, 83.3)	56.9±27.6 54.2 (25.0, 100.0)	–1.4±30.5 –12.5 (–25.0, 58.3)	78.3±23.3 83.3 (25.0, 100.0)	72.9±24.3 75.0 (0.0, 100.0)	–5.4±26.7 0.0 (–100.0, 50.0)	0.856
Sentimental and sexual life							
Mean±SD Median (min., max.)	64.6±9.4 62.5 (50.0, 75.0)	66.7±15.1 68.8 (50.0, 87.5)	2.1±20.0 –6.3 (-12.5, 37.5)	58.5±32.1 68.8 (0.0, 100.0)	56.7±34.8 56.3 (0.0, 100.0)	–1.8±22.0 0.0 (–50.0, 62.5)	0.782
Coping							
Mean±SD Median (min., max.)	60.4±35.7 75.0 (0.0, 87.5)	66.7±38.5 75.0 (0.0, 100.0)	6.3±28.2 6.3 (–37.5, 50.0)	67.0±30.8 75.0 (0.0, 100.0)	72.8±26.8 81.3 (12.5, 100.0)	5.8±27.1 6.3 (–87.5, 62.5)	0.963
Rejection							

Continued

Table 2 Continued

Measure		EDSS improved n=6			EDSS stable n=28			P value
		Baseline	1 year	Change	Baseline	1 year	Change	Wilcoxon*
	Mean±SD	79.2±18.8	87.5±19.4	8.3±21.9	83.0±22.9	83.5±23.8	0.4±20.5	0.683
	Median (min., max.)	87.5 (50.0, 100.0)	93.8 (50.0, 100.0)	0.0 (−12.5, 50.0)	93.8 (25.0, 100.0)	100.0 (25.0, 100.0)	0.0 (−75.0, 50.0)	
Relationships with healthcare systems								
	Mean±SD	68.1±17.0	61.1±17.2		82.7±14.7	82.7±17.1	0.0±23.6	0.498
	Median (min., max.)	70.8 (41.7, 91.7)	66.7 (33.3, 75.0)	−6.9±14.4 −4.2 (−33.3, 8.3)	75.0 (41.7, 100.0)	83.3 (33.3, 100.0)	0.0 (−66.7, 58.3)	

The nine subscores of the MusiQoL evaluate specific components of HRQoL. Patients with RRMS were grouped according to disability status on the EDSS. 'EDSS improvement' was defined as ≥1.0-point decrease in EDSS score sustained for at least 12 weeks, and 'EDSS stable group' was defined as changes in EDSS scores sustained for <12 weeks or with changes <1.0. 'EDSS progression' was defined as ≥1.0-point increase sustained for at least 12 weeks. The EDSS worsened patient (n=1) was not included in this analysis as per post hoc analysis plan.
*Assessment of differences between the 'EDSS improved' or 'EDSS stable' groups in change from baseline to 1 year.
EDSS, Expanded Disability Status Scale; HRQoL, health-related quality of life; MusiQoL, Multiple Sclerosis International Quality of Life; RRMS, relapsing-remitting multiple sclerosis.

correlations of the post hoc analysis results are detailed in online supplemental information.

In the 'improved' patients, three specific dimensions of MusiQoL, the 'symptoms' score (r=0.5294, p=0.0136), the 'psychological well-being' score (r=0.6383, p=0.0018) and the 'activities of daily living' score (r=0.5098, p=0.0182), showed a strong positive correlation with the improvement of the MusiQoL global index. This result shows significant direct association between the change of MusiQoL global index and the change in the above dimensions. The differences between MusiQoL groups for 'improved' versus 'worsened' patients were significant for all domains, except for the domains 'relationships with family' and 'coping' (figure 3).

In both the 'improved' and the 'worsened' groups, no correlation was found between the change from baseline in MusiQoL global index and the change in the EDSS score. There were no significant differences in the EDSS score change between the 'worsened' or 'improved' patients (Wilcoxon Mann-Whitney test). In the total natalizumab population, improvements in the Work Productivity and Activity Impairment (WPAI) presenteeism score (r=−0.5439, p=0.0294) and the MusiQoL sub scores, psychological well-being (r=0.4609, p=0.0053), symptoms (r=0.4279, p=0.0103), and sentimental and sexual life (r=0.4361, p=0.0088) were correlated with the improvement of the MusiQoL global index. This was consistent with the findings in the MusiQoL-improved patients showing that improvement in MusiQoL global index correlated with the score of the MSISQ-19 for primary causes of sexual dysfunction (r=−0.5157, p=0.0167), the FSMC total score (r=−0.6300, p=0.0022), and in the presenteeism WPAI score (r=−0.5862, p=0.0452) (figure 4, online supplemental table 4).

In addition, a negative association between the increase in the 'tertiary causes of sexual dysfunction' score and the improvement of the MusiQoL global index ('psychosocial causes' score, r=−0.4113, p=0.0640) was found. Finally, a negative association between the change from baseline to 1 year in the MusiQoL global index and the change in the Beck Depression Inventory-FS score in the 'improved' group was found (r=−0.4930, p=0.0619).

3.5 Safety/complications

No treatment-related SAEs were reported. Four patients experienced one or more SAEs, including acute hospitalisation with psychosis (n=1), mastitis and urinary tract infection (n=1), pregnancy (n=1) and severe MS relapses (n=2). In one patient a relapse occurred approximately 6 weeks, in another patient 6 months after initiating natalizumab treatment while still on therapy.

DISCUSSION

The primary PROTYS study looked at patients with RRMS treated with natalizumab for 1 year and aimed to assess correlations between changes in disability status and HRQoL; the post hoc analysis looked further at factors

Table 3 Baseline values for scores

	Baseline PP population (N=35)	Baseline MusiQoL index improved (n=21)	Baseline MusiQoL index worsened (n=14)
Sex (n (%)			
Male		7 (33.3)	7 (50.0)
Female		14 (66.7)	7 (50.0)
Education (n (%)			
Primary education (basic)		7 (33.3)	2 (14.3)
Secondary education (technical college)		9 (42.9)	11 (28.6)
Tertiary education (university)		5 (23.8)	1 (7.1)
MusiQoL index (N=35)	66.7±13.8	66.2±13.3	67.4±15.1
EDSS score (n=21)	3.04±1.19	2.83±1.22	3.36±1.12
ARR at baseline—all relapses (n=20)	0.9±0.7	1.2±0.7	0.5±0.5
ARR at baseline—relapses requiring steroid treatment (n=20)	0.6±0.7	0.9±0.7	0.3±0.3
FSMC total score (n=21)	57.7±23.6	54.3±23.2	63.2±24.1
BDI-FS (n=15)	2.6±2.9	2.7±3.2	2.3±2.6
SDMT (n=21)	49.6±12.1	53.1±10.6	44.3±12.6
MSISQ-19 total	38.7±15.3	36.1±14.6	42.6±16.0
MSISQ-19 primary causes of sexual dysfunction (n=21)	10.8±5.7	9.7±5.3	12.6±6.0
MSISQ-19 secondary causes of sexual dysfunction (n=21)	18.3±6.6	17.5±6.7	19.6±6.4
MSISQ-19 tertiary causes of sexual dysfunction (n=21)	9.5±5.1	9.0±5.3	10.4±4.9
EQ-5D index (n=21)	0.838±0.151	0.853±0.126	0.814±0.184
EQ-5D VAS (n=21)	70.3±22.5	69.7±19.0	71.3±27.6
WPAI presenteeism (n=12)	30.0±30.1	35.0±32.1	15.0±19.1
WPAI absenteeism (n=12)	16.4±34.9	21.8±39.2	0
WPAI productivity loss (n=12)	38.7±35.6	46.6±36.9	15.0±19.1
WPAI activity impairment (n=12)	35.6±27.6	40.8±27.8	20.0±23.1

The results are shown as mean±SD. PROs were secondary outcomes; not all values were available for all 35 patients, particularly BDI-FS and WPAI.
ARR, annualised relapse rate; BDI, Beck Depression Inventory; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQoL-5 Dimension; FSMC, Fatigue Scale of Motor and Cognitive Function; MSISQ, Multiple Sclerosis Intimacy and Sexuality Questionnaire-19; PRO, patient-reported outcome; SDMT, Symbol Digit Modalities Test; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment in MS.

that may influence QoL in patients with MS treated with natalizumab.

While there was no statistically significant difference in global HRQoL change (MusiQoL index score) between 'EDSS improved' and 'EDSS stable' groups of patients, natalizumab treatment did appear to improve several domains of HRQoL: fatigue, symptoms, overall health state, sexual dysfunction and work productivity, regardless of whether EDSS scores were stable or improved. Additional results and discussion regarding fatigue and work productivity are characterised in online supplemental information.

Table 4 Baseline (BL), EOS and change from Baseline to EOS for MusiQoL index: total, improved and worsened groups

	MusiQoL index total (N=35)	MusiQoL index improved (n=21)	MusiQoL Index worsened (n=14)
BL	66.7±13.8	66.2±13.3	67.4±15.1
EOS	69.9±16.4	75.9±14.6	60.9±15.1
Change from BL to EOS	3.3±11.1	9.8±8.1	−6.5±7.0

Scores are at BL and at month 12 (EOS). The results are shown as mean±SD 'Improved': change in the global MusiQoL index >0, 'worsened': change in the global MusiQoL index <0.
EOS, end of study; MusiQoL, Multiple Sclerosis International Quality of Life.

With respect to changes in EDSS within 1 year of natalizumab treatment, the majority (80.0%) of patients had stable EDSS scores, with all other patients (except for one with EDSS progression) showing sustained EDSS improvement. Long-term data from the 10 year real-world Tysabri Observational Programme (TOP) study revealed a 10-year cumulative probability of disability improvement of 33.1% and of worsening 27.8%.[16] Furthermore, in the TOP study which provides the real-world experience of 5384 patients, 23.9% (n=1287) had confirmed disability improvement.[17] In the PROTYS study, after 1 year of treatment with natalizumab 17.1% (6/35) of patients were assessed as 'EDSS improved,' 80% (28/35) of patients were 'EDSS stable' and 2.9% (1/35) of patients

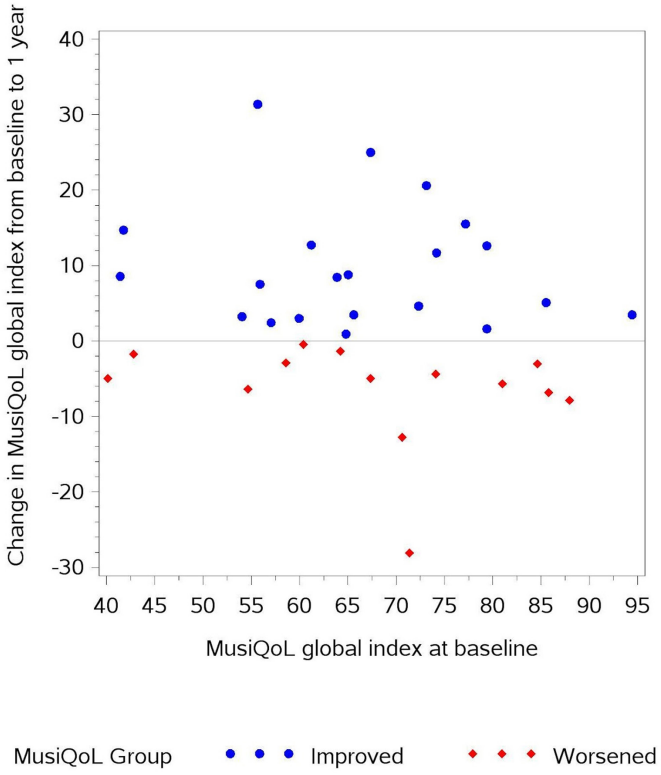


Figure 2 Scatter plot of MusiQoL global index at baseline versus change in MusiQoL global index, by MusiQoL change categories. MusiQoL, Multiple Sclerosis International Quality of Life.

were 'EDSS worsened'. These differing results may be due to the low study participant number in the PROTYS study (n=35), the different periods of analysis for EDSS (sustained for ≥12 week for PROTYS and sustained for ≥24 weeks for TOP), and differences in patient demographics (for PROTYS the median EDSS was 3.00 with a range of 1.00–5.50).[17]

Concerning changes in global HRQoL, we report a slight improvement in global HRQoL as measured by the MusiQoL index score. Planche *et al* reported a statistically

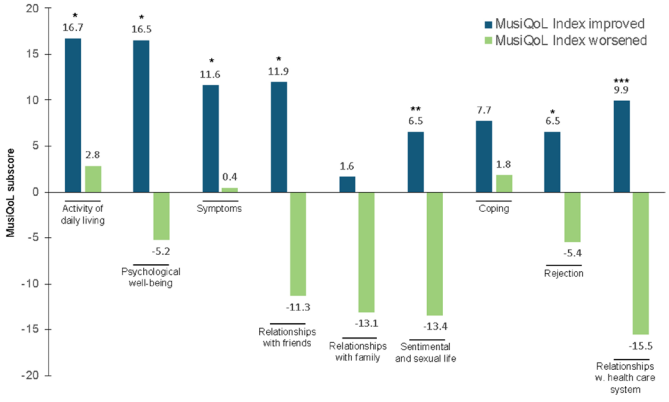


Figure 3 The change from baseline to EOS for MusiQoL Index improved (n=21) and worsened (n=14), Wilcoxon Mann-Whitney test, *p<0.05, **p<0.01, ***p<0.001. EOS, end of study; MusiQoL, Multiple Sclerosis International Quality of Life.

significant improvement in MusiQoL in a population of patients with RRMS treated with natalizumab (n=48).[28] Therein, the mean MusiQoL score increased from 58.6 at baseline to 68.1 at 1 year (p<0.001).[28] The increase in MusiQoL score was significant at 6 months after baseline and remained significant but did not increase beyond a score of 69.8 over 3 years.[28] It is difficult to make direct comparisons between the PROTYS study and the study of Planche *et al* because our analysis was restricted to comparisons between 'EDSS improved' and 'EDSS stable' groups of patients. Interestingly, mean HRQoL at baseline was higher in the PROTYS study compared with the study by Planche *et al*,[28] and the mean MusiQoL scores in both populations of patients in both studies were approximately 70 after 1 year of natalizumab treatment. Improvements in HRQoL with natalizumab treatment have also been reported by others using evaluations other than MusiQoL.[3 10] In Planche *et al* the HRQoL significantly improved within 6 months of treatment with natalizumab and this was sustained through 3 years of treatment.[28] It is therefore conceivable that we did not detect a statistically significant difference due to the small number of patients in each EDSS group, and the comparison being restricted to 'EDSS stable' and 'EDSS improved' groups of patients.

In the post hoc analysis, it was shown that improvements observed in MusiQoL global index after 1 year of natalizumab treatment correlated with improvements in the ability to cope with symptoms, in overall health, in primary causes of sexual dysfunction (MSISQ-19) and in presenteeism (WPAI). This suggests that improvements in patient psychological well-being, resolution of MS symptoms including fatigue and sexual dysfunction, and increases in workability may be important factors contributing to the increases in overall QoL.

Our results aligned with those of Planche *et al*, who reported that improvements in MusiQoL were mainly driven by the subparameters 'symptoms', 'activity of daily living', 'psychological well-being' and 'coping'.[28] The improvements in overall QoL over 1 year for patients initiating natalizumab in the PROTYS study are consistent with prior reports of natalizumab treatment effects on QoL.[3]

In a recent study—also on Swiss patients with MS—use of the EuroQol 5 Dimension (EQ-5D) and EQ-VAS showed that fatigue, depression and spasticity were important contributors to disease burden at a population level. For RRMS, the EQ-VAS was mostly impacted by balance problems, depression, dizziness and spasticity.[6] Although in the PROTYS study the 'EDSS improved' group had significantly greater improvements in EQ-VAS compared with the 'EDSS stable' group (mean change=14.5 vs −0.1, p=0.011), the post hoc analysis revealed no correlation between change of MusiQoL global index and changes of EQ-5D. Others have reported significant correlations between high EDSS scores and lower EQ-5D index scores.[29]

Even though in the PROTYS study significant correlations between MusiQoL global index and changes in

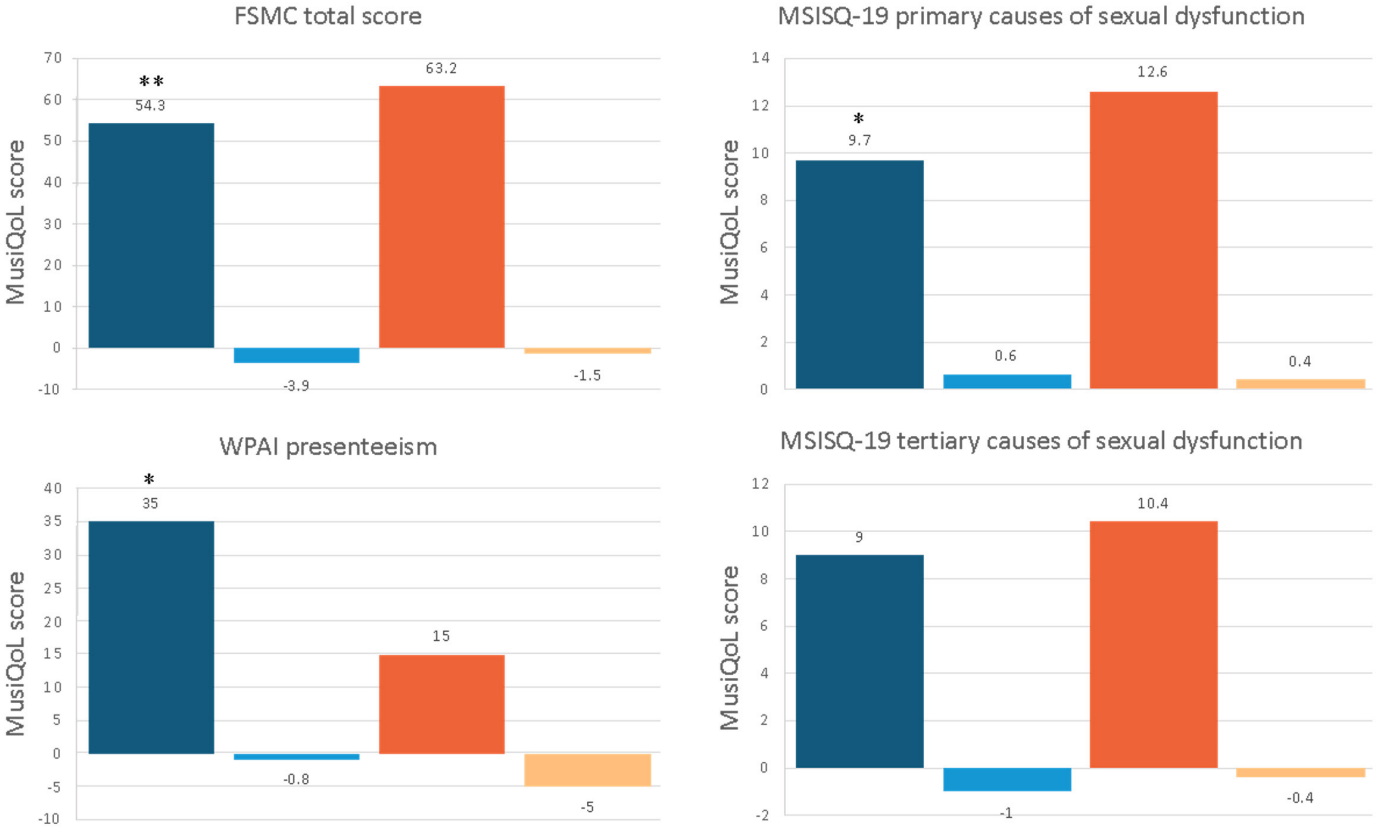


Figure 4 Correlation between change in global MusiQoL index after 1 year of natalizumab and the change from baseline to end of study (EOS) in the neurological symptoms and the PROs. Non-parametric Spearman's correlation coefficient. *p<0.05, **p<0.01. FSMC, Fatigue Scale of Motor and Cognitive Function; MSSIQ-19, Multiple Sclerosis Intimacy and Sexuality Questionnaire-19; MusiQoL, Multiple Sclerosis International Quality of Life; PROs, patient-reported outcomes; WPAI, Work Productivity and Activity Impairment.

EQ-5D were not found, the mean change of the 'EDSS improved' group may be clinically meaningful. A study by Kohn *et al* found the minimal clinical important difference (MCID) for the EQ-5D index scores to range from 0.050 to 0.084 with patients with severe disability having higher MCIDs than patients with mild-moderate disability.[30] However, the study is limited in this aspect by the fact that these MIDs were not considered during study design, and thus this is an area where future research would be useful.

As regards sexual dysfunction, it has been shown that tertiary sexual dysfunction increases as HRQoL decreases.[31] We found that the MSISQ-19 subparameter 'tertiary' was significantly more improved in the 'EDSS improved' group compared with the 'EDSS stable' group (mean change=-3.5 vs −0.1, p=0.029. Furthermore, the post hoc analysis showed that improvements in sexual life were correlated with the improvement of the MusiQoL global index. This was consistent with the findings in the 'MusiQoL improved' patients showing that improvement in MusiQoL global index correlated with the score of the MSISQ-19 for primary causes of sexual dysfunction. In addition, a negative association between the increase in 'tertiary causes of sexual dysfunction' score and the improvement of the MusiQoL global index was found (online supplemental tables 3,4). Significant improvements in sexual dysfunction (based on MSISQ-19) within 24 weeks of starting natalizumab treatment have also been shown in another study.[32] Given that mental health aspects of HRQoL have been shown to be detrimentally impacted by sexual dysfunction,[33] and that our results suggest that resolution of MS symptoms such as sexual dysfunction may be an important factor contributing to the increases in overall QoL, aspects of sexual dysfunction in patients with RRMS treated with natalizumab should be further investigated in larger studies.

This study had several limitations; slow recruitment, which led to small numbers of patients and meant that the original recruitment goals were not met, risk stratification strategies that precluded treatment with natalizumab in patients positive for JCV antibodies, and some sites reported low number of patients having disease activity enough to fulfil natalizumab indications according to the local prescribing information. This may have been affected by new MS therapies, fingolimod, alemtuzumab, teriflunomide and dimethyl fumarate, which were entering the market prior to or at the time of recruitment. The study duration was also limited to 1 year, which may have been too short to observe significant changes in some of the domains of HRQoL. Finally, the EDSS was limited to fully ambulatory patients (EDSS up to 3.5) and

therefore we cannot assess impact of higher degrees of disability on HRQoL.

CONCLUSIONS

In conclusion, we report that 1 year of natalizumab treatment resulted in sustained EDSS improvement in 17.1% of patients and stable EDSS in 80% of patients. While there was no statistically significant difference in global HRQoL change (MusiQoL index score) between 'EDSS improved' and 'EDSS stable' groups of patients, natalizumab treatment did appear to improve several domains of HRQoL: fatigue, symptoms, overall health state, sexual dysfunction and work productivity, regardless of whether EDSS scores were stable or improved. The results of the post hoc analysis suggest that improvements in patient psychological well-being, resolution of MS symptoms including fatigue and sexual dysfunction, and increases in workability may be important factors contributing to the increases in overall QoL.

Author affiliations
[1]Department of Neurology, Cantonal Hospital Aarau, Aarau, Switzerland
[2]Department of Neurology, Multiple Sclerosis Center (MSC), Neurocenter of Southern Switzerland, Lugano, Switzerland
[3]Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland
[4]Neurocenter, Cantonal Hospital Lucerne, Luzern, Switzerland
[5]Department of Neurology, Inselspital, University Hospital Bern and University of Bern, Bern, Switzerland
[6]Department of Neurology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
[7]Multiple Sclerosis Centre, Neurology, Departments of Head, Spine and Neuromedicine, Biomedicine and Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland
[8]Neurology Clinic, University Hospital Zurich & University of Zurich, Zurich, Switzerland
[9]Biogen Switzerland AG, Zug, Switzerland

Acknowledgements The authors thank Dr R. Mähler (Neuropraxis Wohlen, Wohlen, Switzerland), Dr P. Stellmes (Neurologie am Löwenplatz, Lucerne, Switzerland) and Dr Anke Salmen (Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland) for their participation in the study as investigators. Katharina Bruppacher (Biogen Switzerland AG, Baar, Switzerland), for her help with the protocol and regulatory submissions, Melanie Barth and Melinda Farkas (Biogen Switzerland AG, Baar, Switzerland), for operational support. The authors also thank Dr Mea Holm and Lyndsey Kostadinov CMPP of Medicalwriters.com (Zurich, Switzerland) for providing medical writing support (writing and editing the manuscript) funded by Biogen Switzerland (Baar, Switzerland).

Contributors LA wrote and worked on the study protocol; was principal investigator of the study, recruited and cared for patients during the study, evaluated and interpreted data, and worked on the manuscript. CZ interpreted data and reviewed the data analysis and the manuscript. OF was involved in patient recruitment, drafting the manuscript, and interpretation of data conception and design of study. CPK was involved in patient recruitment, interpreted data, and reviewed the data analysis and the manuscript. SM worked on the study protocol, evaluated, and interpreted data, and worked on manuscript. JK, AL, CG and CV interpreted data and reviewed the data analysis and the manuscript. EV-B designed the protocol, interpreted the data, and reviewed the data analysis and the manuscript. KN wrote and worked on the study protocol, evaluated, and interpreted data, and worked on the manuscript.

Funding This study was funded by Biogen Switzerland (CHE-TYS-12-10341).

Competing interests LA has received speaker honoraria and/or travel compensation for activities with Biogen, Novartis, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche, Celgene and the Swiss MS Society (SMSG). CZ received honoraria for speaking, consulting fees, grants or travel compensation from Abbvie, Almirall, Biogen Idec, Celgene, Genzyme, Lilly, Merck Serono, Novartis, Roche, Teva Pharma. OF has received honoraria for lectures and advisory boards as well as research and travel support from Biogen, Novartis, Almirall, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche and the Swiss MS Society (SMSG). CPK has received honoraria for lectures as well as research support from Biogen, Novartis, Almirall, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche, Celgene and the Swiss MS Society (SMSG). SM received speaker honoraria and/or travel compensation for activities with Bayer Schweiz AG, Biogen, Celgene, Teva, Merck-Serono, Sanofi Genzyme, Novartis, Roche and Almirall and the Swiss MS Society (SMSG).J. Kuhle received speaker fees, research support, travel support from, and/or served on advisory boards for Swiss MS Society, Swiss National Research Foundation (320030_189140/1), University of Basel, Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, Roche, and Sanofi. AL received financial compensation and/or travel support for lectures and advice from Almirall, Biogen Idec, Bayer, Celgene, Genzyme, Merck Serono, Novartis, Roche Teva. A Lutterotti is a co-founder of Cellerys and co-inventor on a patent held by the University of Zurich on the use of peptide-coupled cells for treatment of MS.C. Gobbi received honoraria for speaking, consulting fees, grants or travel compensation from Abbvie, Almirall, Biogen Idec, Celgene, Genzyme, Lilly, Merck Serono, Novartis, Roche, Teva Pharma. CV was an employee of Biogen Switzerland at the time of the study. EV-B is an employee of Biogen International. KN has served on advisory boards for Biogen, Novartis, Bayer Schweiz AG, Teva, Merck, Sanofi Genzyme, Roche, Celgene and the Swiss MS Society (SMSG).

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethikkommission Nordwest- und Zentralschweiz: EKNZ 2014-327 Participants. gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

REFERENCES

1 Zwibel HL. Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. *Adv Ther* 2009;26:1043–57.
2 Højsgaard Chow H, Schreiber K, Magyari M, *et al*. Progressive multiple sclerosis, cognitive function, and quality of life. *Brain Behav* 2018;8:e00875.
3 Rudick RA, Miller D, Hass S, *et al*. Health-related quality of life in multiple sclerosis: effects of natalizumab. *Ann Neurol* 2007;62:335–46.
4 Mitchell AJ, Benito-León J, González J-MM, *et al*. Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *Lancet Neurol* 2005;4:556–66.
5 Baumstarck K, Pelletier J, Butzkueven H, *et al*. Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. *Eur J Neurol* 2013;20:907–79.
6 Barin L, Salmen A, Disanto G, *et al*. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–21.
7 Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* 2010;33:1061–7.
8 Lecat M, Decavel P, Magnin E, *et al*. Multiple sclerosis and clinical gait analysis before and after fampridine: a systematic review. *Eur Neurol* 2017;78:272–86.

9 Jongen PJ. Health-Related quality of life in patients with multiple sclerosis: impact of disease-modifying drugs. *CNS Drugs* 2017;31:585–602.
10 Foley JF, Nair KV, Vollmer T, *et al*. Long-term natalizumab treatment is associated with sustained improvements in quality of life in patients with multiple sclerosis. *Patient Prefer Adherence* 2017;11:1035–48.
11 Hersh C, Kieseier B, De Moor C. *Impact of natalizumab on quality of life in a real-world cohort of patients with multiple sclerosis: results from MS paths. MS virtual 2020, 8th joint ACTRIMS-ECTRIMS meeting; virtual*, 2020.
12 Nair KV, Foley FW, Stephenson JJ. Physical aspects of quality of life (QOL) over 3 years in patients with multiple sclerosis (MS) initiating natalizumab treatment earlier versus later in the course of disease (P3.276). *Neurology* 2015;84:276.
13 Stephenson JJ, Kern DM, Agarwal SS, *et al*. Impact of natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study. *Health Qual Life Outcomes* 2012;10:155.
14 Perumal J, Fox RJ, Balabanov R, *et al*. *Natalizumab is associated with no evidence of disease activity and improved cognitive function and health-related quality of life in anti-JC virus seronegative patients with early relapsing-remitting multiple sclerosis: a 3-year analysis of STRIVE. ECTRIMS 2018*. Berlin, Germany: ECTRIMS Online Library, 2018.
15 Freedman MS, Jeffery D, Miller AE. *The impact of natalizumab on health-related quality of life in patients with secondary-progressive multiple sclerosis*. New Orleans, Louisiana: 2017 Annual Meeting of the Consortium of Multiple Sclerosis Centers, 2017.
16 Butzkueven H, Kappos L, Wiendl H, *et al*. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri observational program (top). *J Neurol Neurosurg Psychiatry* 2020;91:660–8.
17 Wiendl H, Spelman T, Butzkueven H, *et al*. Real-world disability improvement in patients with relapsing-remitting multiple sclerosis treated with natalizumab in the Tysabri observational program. *Mult Scler* 2021;27:719–28.
18 Phillips JT, Giovannoni G, Lublin FD, *et al*. Sustained improvement in expanded disability status scale as a new efficacy measure of neurological change in multiple sclerosis: treatment effects with natalizumab in patients with relapsing multiple sclerosis. *Mult Scler* 2011;17:970–9.
19 Butzkueven H, Kappos L, Pellegrini F, *et al*. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. *J Neurol Neurosurg Psychiatry* 2014;85:1190–7.
20 Mazdeh M, Hosseini S, Taheri M, *et al*. The effect of natalizumab on disability score and relapse rate of multiple sclerosis patients: a prospective cohort study. *Clin Transl Med* 2018;7:38.
21 Perumal J, Fox RJ, Balabanov R, *et al*. Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE. *BMC Neurol* 2019;19:116.
22 Trojano M, Butzkueven H, Kappos L, *et al*. Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting. *Mult Scler Relat Disord* 2018;24:11–19.
23 Penner I-K, Sivertsdotter EC, Celius EG, *et al*. Improvement in fatigue during natalizumab treatment is linked to improvement in depression and Day-Time sleepiness. *Front Neurol* 2015;6:18.
24 Svenningsson A, Falk E, Celius EG, *et al*. Natalizumab treatment reduces fatigue in multiple sclerosis. results from the TYNERGY trial; a study in the real life setting. *PLoS One* 2013;8:e58643.
25 Balcer LJ, Galetta SL, Calabresi PA, *et al*. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 2007;68:1299–304.
26 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.
27 Simeoni M, Auquier P, Fernandez O, *et al*. Validation of the multiple sclerosis International quality of life questionnaire. *Mult Scler* 2008;14:219–30.
28 Planche V, Moisset X, Morello R, *et al*. Improvement of quality of life and its relationship with neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with natalizumab: a 3-year follow-up multicentric study. *J Neurol Sci* 2017;382:148–54.
29 Reese JP, Wienemann G, John A, *et al*. Preference-based health status in a German outpatient cohort with multiple sclerosis. *Health Qual Life Outcomes* 2013;11:162.
30 Kohn CG, Sidovar MF, Kaur K, *et al*. Estimating a minimal clinically important difference for the EuroQol 5-Dimension health status index in persons with multiple sclerosis. *Health Qual Life Outcomes* 2014;12:66.
31 Domingo S, Kinzy T, Thompson N, *et al*. Factors associated with sexual dysfunction in individuals with multiple sclerosis: implications for assessment and treatment. *Int J MS Care* 2018;20:191–7.
32 Robertson D, Aungst A, Collier R, *et al*. Patient perceived changes in sexual dysfunction after initiation of natalizumab for multiple sclerosis. *Mult Scler J Exp Transl Clin* 2018;4:2055217318781989:20 5521731878198.
33 Schairer LC, Foley FW, Zemon V, *et al*. The impact of sexual dysfunction on health-related quality of life in people with multiple sclerosis. *Mult Scler* 2014;20:610–6.

Lutz Achtnichts [1,*], Chiara Zecca [2,3], Oliver Findling [1,*], Christian P. Kamm [4,5], Stefanie Müller [6], Jens Kuhle [7], Andreas Lutterotti [8], Claudio Gobbi [2,3], Camille Viviani [9], Emanuela Villiger-Borter [9], Krassen Nedeltchev [1], on behalf of the PROTYS investigators

Supplementary Information

Supplementary methods

Study design of the PROTYS study

Study design included:

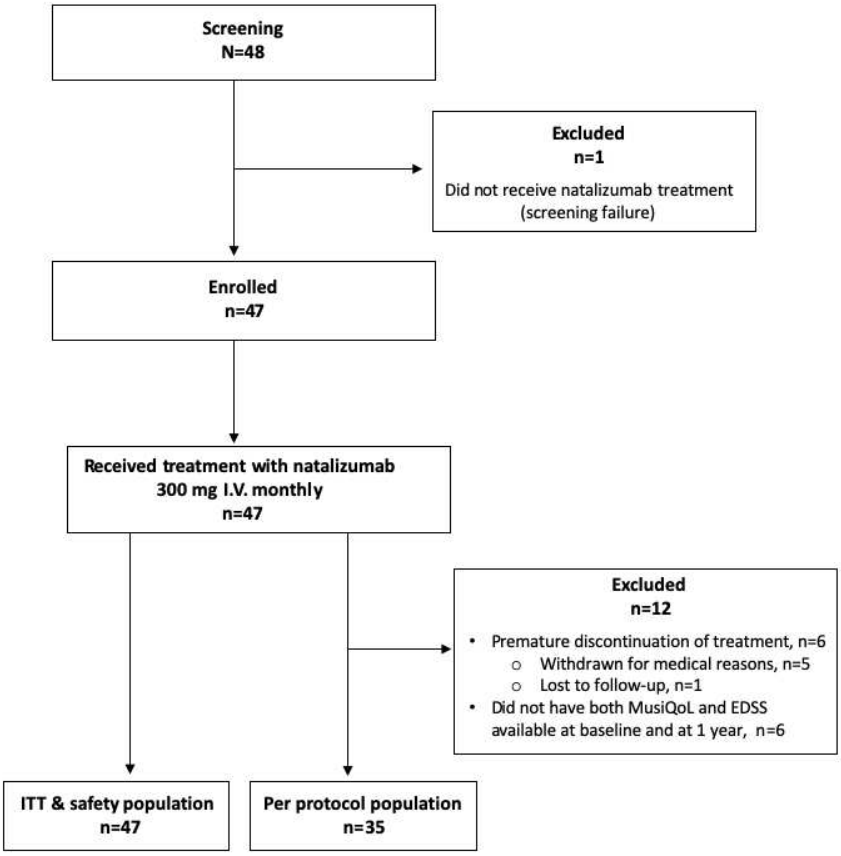
Supplementary Table 1: Inclusion and exclusion criteria for study participation.

Inclusion	Exclusion

• Aged 18-65 years old, inclusive, at the time of the informed consent
• Able to understand the purpose and risks of the study
• Confirmed diagnosis of RRMS, as per the 2010 revised McDonald criteria **[1]**
• EDSS score of 2.0-5.5, inclusive
• Natalizumab-naïve patients satisfying the therapeutic indication of natalizumab, as described in the Swiss product label and confirmed by the Investigator
  ○ Decision for treatment with natalizumab was made before screening
  ○ Patients with previous treatment with natalizumab were also considered to be eligible, if the last natalizumab infusion was at least one year before screening
	• Diagnosed co-existing brain pathology other than MS, which in the judgement of the investigator impacts the value of EDSS or QoL
	• Pure spinal manifestation of demyelination
	• Diagnosis of primary or secondary progressive MS
	• Any change in concomitant medication known to affect cognition or bladder function within 4 weeks prior to the baseline visit
	• A history of severe depressive disorder and/or suicidality, seizure, drug or alcohol abuse, as assessed by the investigator
	• Insufficient understanding of the local language
	• Unwillingness or inability to comply with requirements of the protocol, including the presence of any condition (physical, mental or social) that is likely to affect the patient"s ability to comply with the protocol

EDSS, Expanded Disability Status Scale; RRMS, relapsing–remitting multiple sclerosis; MS, multiple sclerosis; QoL, quality of life.

Supplementary Figure 1: Study flow diagram.



The intention to treat (ITT) and safety population received at least one infusion of 300 mg natalizumab intravenously (I.V.). The per protocol population were treated with natalizumab for at least one year, received 8 or more natalizumab infusions, and had both Multiple Sclerosis Quality of Life (MusiQoL) and Expanded Disability Status Scale (EDSS) scores available at baseline and at one year.

Secondary objectives of the PROTYS study

Secondary objectives included:

- Assessment of the cumulative probability of sustained disability (EDSS) changes at one year compared to baseline.

- Evaluation of the associations between disability (EDSS), fatigue, sexual dysfunction, depression and neurocognitive function with scores on the Euro-QoL questionnaire (EQ-5D) at three to six-months intervals up to one year compared to baseline.
- Evaluation of the relationship between clinical disease-free status (no confirmed EDSS worsening of ≥1.0 point and no relapse) and HRQoL (MusiQoL) at one year compared to baseline.
- Assessment of changes in work impairment at three-month intervals up to one year after initiation of natalizumab treatment.
- Assessment of any change in the percentage of disability pension, work productivity and activity impairment and change in occupation after one year of natalizumab treatment.
- Rates of clinical relapses and relapses requiring steroid treatment at 3-month intervals up to one year after initiation of natalizumab treatment.
- Incidence and number of SAEs during the duration of the study.

Further information on self-administered tests and questionnaires

The MSISQ-19 is a 19-item questionnaire, scored on a scale of 19-95, and designed to assess sexual dysfunctional in MS patients. It is divided into three sub-scales: primary (dysfunction due to direct neurological damage involving the genitalia), secondary (dysfunction due to MS symptoms unrelated to the genitalia), and tertiary (dysfunction due to cultural, emotional and psychosocial aspects).[2] The EuroQoL-5D is a standardised questionnaire of health-related quality of life and consists of two parts, index and visual analogue scale (VAS), giving an overall score of health status.[3] The FSMC consists of 20 items on two sub-scales for cognitive and motor fatigue, giving an overall score of 20 (no fatigue) to 100 (severe fatigue).[4] The SDMT is a self-administered test of cognitive processing speed where participants match pairs of symbols and digits over 90 seconds and receive an overall score of processing speed between 0-110.[5] The BDI-FS estimates the severity of depression on a scale of 0-21, with a score of ≥4 representing depression.[6] The WPAI-MS

measures impairments in paid and unpaid work due to MS, expressed as percentage impairment.[7]

Supplementary Table 2: HRQoL assessments.

Instrument	No. of items	Domains assessed	Scoring
MusiQoL **[8]**	31	Physical (8), symptoms (4), psychological (8), self-esteem (4), relationship/friends (3), relationships/family (4)	Total score (0-100) with 0 being worst and 100 best possible level of QoL
MSISQ-19**[2]**	19	Primary (sexual dysfunction due to direct neurological damage involving genitalia), secondary (sexual dysfunction due to MS symptoms unrelated to the genitalia), tertiary (sexual dysfunction due to cultural, emotional and psychosocial aspects)	Total score(19-95) with higher score indicating more sexual dysfunction
EQ-5D **[3]**	5	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression	5-digit health state profile describing the patient's health state across the 5 dimensions of health
EQ-VAS **[3]**	1	Patient's self-rated health	Total score (0-100) with 0 being the worst health you can imagine and 100 being the best health you can imagine
FSMC **[4]**	20	Cognitive (10) and motor fatigue (10)	Total score (20-100) with 20 being no fatigue and 100 being severe fatigue
SDMT **[5]**	120 symbols to be paired	Cognitive impairment/disorder	Total score (0-110) with higher scores indicating higher number of correct pairings and better cognitive function
BDI-FS **[6]**	7	Dysphoria, anhedonia, suicidal ideation, and cognitive-related symptoms	Total score (0-21) with score of ≥4 representing depressive symptoms
WPAI-MS **[7]**	6	Absenteeisim, presenteeism, productivity loss and activity impairment	Percent absenteeism, presenteeism, productivity loss due to health, and activity impairment due to health. Higher percentages indicating greater impairment and less productivity

BDI-FS, Beck Depression Inventory-Fast Screen; EQ-5D, EuroQoL-5D; EQ-VAS, EuroQoL-Visual Analogue Scale, FSMC, Fatigue Scale of Motor and Cognitive Function; HRQoL, health-related QoL; MusiQoL, Multiple Sclerosis International QoL; MS, multiple sclerosis; MSISQ-19, MS Intimacy and Sexuality Questionnaire-19; QoL, quality of life; SDMT, Symbol Digit Modalities Test; WPAI-MS, Work Productivity and Activity Impairment in MS.

Post hoc analysis statistical endpoints

For the purpose of this additional *post hoc* analysis, the statistical endpoint is the assessment of the correlation between the following endpoints:

- Change from baseline to EOS in the nine sub-scores of the MusiQoL questionnaire
- Change from baseline to EOS (visit of the last EDSS report) in the EDSS value
- Change from baseline to EOS in the FSMC total score
- Change from baseline to EOS in the WPAI outcomes (absenteeism, presenteeism, productivity loss and activity impairment)
- Change from baseline to EOS in the MSISQ-19 scores (primary, secondary and tertiary causes of sexual dysfunction)
- Change from baseline to EOS in the SDMT score
- Change from baseline to EOS in the EQ-5D index and VAS
- Change from baseline to EOS in the BDI-FS score
- Change from baseline to EOS in the ARR
- Change from baseline to EOS in the ARR of relapses requiring steroid treatment
- Gender, educational level

and the change after 1 year of natalizumab treatment in the global MusiQoL index (categorised as improved or worsened after 1 year), on the complete study population of the per protocol population.

Supplementary results

PROTYS study

Relapses

At one year after initiation of natalizumab treatment, the mean change from baseline in number of relapses requiring corticosteroid treatment was -0.2 ± 1.1 for the EDSS improved group, and -0.4 ± 0.6 for the EDSS stable group.

Post hoc analysis results

Negative or no correlations

Supplementary Table 3: Changes from baseline (BL) to month 12 (EOS). The results are shown as mean ± SD. r = non-parametric Spearman's correlation coefficient was used to investigate relationships between the change in the MusiQoL global index at 1 year and the change in the questionnaires scores in each group (improved, worsened), *The changes from baseline to 1 year in the score of each questionnaire were compared between “worsened” or “improved” patients using the Wilcoxon Mann–Whitney test. Negative correlations or associations are bolded.

	MusiQoL Index improved					**MusiQoL Index worsened**					
	n	Baseline	Change from baseline to EOS	correlation		n	Baseline	Change from baseline to EOS	correlation		Difference between MusiQoL groups improved vs. worsened* (p-value)
				r	p-value				r	p-value	
EDSS score	21	2.83±1.22	-0.38±0.84	-0.0877	0.7053	14	3.36±1.12	-0.25	-0.1847	0.5274	0.5652
ARR - all relapses	20	1.2±0.7	-0.9±0.9	0.3385	0.1444	14	0.5±0.5	-0.5±0.5	-0.1020	0.7262	0.0653
FSMC total score	21	54.3±23.2	-3.9±15.4	**-0.6300**	**0.0022**	13	63.2±24.1	-1.5±14.3	0.4437	0.1458	1.0000
BDI-FS	15	2.7±3.2	0.2±1.4	**-0.4930**	**0.0619**	6	2.3±2.6	0.2±1.3	-0.1518	0.7741	0.4875
SDMT	21	53.1±10.6	2.8±4.9	0.2097	0.3617	14	44.3±12.6	1.6±5.3	0.313	0.2759	0.4274
MSISQ-19 primary causes of sexual dysfunction	21	9.7±5.3	0.6±4.3	**-0.5157**	**0.0167**	14	12.6±6.0	0.4±1.7	0.0023	0.9938	0.3780
MSISQ-19 secondary causes of sexual dysfunction	21	17.5±6.7	-1.1±4.4	0.0176	0.9395	14	19.6±6.4	0.6±4.9	0.0734	0.8030	0.6713

MSISQ-19 tertiary causes of sexual dysfunction	21	9.0±5.3	-1.0±3.7	**-0.4113**	**0.0640**	14	10.4±4.9	-0.4±3.0	0.179	0.5404	0.6939
EQ-5D index	21	0.853±0.126	0.024±0.147	0.1935	0.4007	14	0.814±0.184	0.004±0.148	-0.1213	0.6796	0.4893
EQ-5D VAS	21	69.7±19.0	4.8±13.0	0.3511	0.1186	14	71.3±27.6	-1.4±12.6	0.1645	0.5743	0.2497
WPAI presenteeism	12	35.0±32.1	-0.8±39.4	**-0.5862**	**0.0452**	4	15.0±19.1	-5.0±10.0	0.2582	0.7418	0.6162

Supplementary Table 3.

See Supplementary Table 3.

- Change in MusiQoL global index and change in EDSS score: No correlation
- Change in FSMC total score and MusiQoL global index: strong negative correlation in “improved” group (r=-0.6300, p=0.0022)
- Presenteeism score (WPAI) and MusiQoL global index: strong negative correlation in “improved” patients (r=-0.5862, p=0.0452)
- MSISQ-19 and MusiQoL global index: strong negative correlation in “improved” patients (increase in “primary causes of sexual dysfunction” score, “direct physical causes” score, r=-0.5157, p=0.0167)
- Negative association between the increase in the “tertiary causes of sexual dysfunction” score and the improvement of the MusiQoL global index (“psychosocial causes” score, r=-0.4113, p=0.0640)
- Change in SDMT total score and MusiQoL global index: no correlation (both groups)
- Change in EQ-5D index and VAS and MusiQoL global index: no correlation (both groups)
- Change in BDI-FS and MusiQoL global index: moderate negative association in “improved” patients (r=-0.4930, p=0.0619)

- Change in ARR and MusiQoL global index: no correlation (both groups)

FSMC

A decrease in total fatigue (FSMC score) after one year of treatment with natalizumab was noted in both the “EDSS improved” and “EDSS stable” groups; the decrease was more pronounced in the “EDSS improved” group, although the difference in fatigue scores between the groups was not significant. Additionally, in the *post hoc* analysis, a strong negative correlation between the change from baseline to 1 year in the FSMC total score and the MusiQoL global index was found (r=-0.6300, p=0.0022) in improved patients. In a larger study on 195 RRMS patients treated with natalizumab for one year,[9] a statistically significant improvement in overall fatigue within one year of natalizumab treatment was also found.[9] It should be noted that in the PROTYS study patients were pre-treated mainly with interferons which could have impacted FSMC scores.

WPAI

Patients with MS are also known to face challenges in their work lives, and work productivity impacts the economic burden of MS.[10] In a previous study, natalizumab treatment was shown to significantly increase work productivity after 50 weeks of treatment.[11] In our study, an improvement in work productivity was seen among the EDSS improved and stable groups within one year of natalizumab treatment. The *post hoc* analysis revealed a strong negative correlation in “MusiQoL improved” patients in the presenteeism score, which reflects an increase in workability. Although these preliminary findings remain to be confirmed in larger studies, this still has importance given patients with low EDSS are already significantly restricted in their ability to work at an age when full working capacity is important.[12]

Supplementary Table 4: Correlation between change in global MusiQoL index after 1 year of natalizumab and the change from baseline to end of study (EOS) in the neurological symptoms and the PROs. The results are shown as mean ± SD. “Improved”: change in the global MusiQoL index >0, “worsened”: change in the global MusiQoL index <0.

	MusiQoL Index improved		**MusiQoL Index worsened**	
	Baseline for MusiQoL index improved	**Change from Baseline to EOS**	**Baseline for MusiQoL index worsened**	**Change from Baseline to EOS**
EDSS score	2.83 ± 1.22	-0.38 ± 0.84	3.36 ± 1.12	-0.25 ± 0
ARR - all relapses	1.2 ± 0.7	-0.9 ± 0.9	0.5 ± 0.5	-0.5 ± 0.5
ARR - relapses requiring steroid treatment	0.9 ± 0.7	-0.6 ± 0.9	0.3 ± 0.3	-0.2 ± 0.4
FSMC total score	54.3 ± 23.2	-3.9 ± 15.4	63.2 ± 24.1	-1.5 ± 14.3
BDI-FS	2.7 ± 3.2	0.2 ± 1.4	2.3 ± 2.6	0.2 ± 1.3
SDMT	53.1 ± 10.6	2.8 ± 4.9	44.3 ± 12.6	1.6 ± 5.3
MSISQ-19 primary causes of sexual dysfunction	9.7 ± 5.3	0.6 ± 4.3	12.6 ± 6.0	0.4 ± 1.7
MSISQ-19 secondary causes of sexual dysfunction	17.5 ± 6.7	-1.1 ± 4.4	19.6 ± 6.4	0.6 ± 4.9
MSISQ-19 tertiary causes of sexual dysfunction	9.0 ± 5.3	-1.0 ± 3.7	10.4 ± 4.9	-0.4 ± 3.0
EQ-5D index	0.853 ± 0.126	0.024 ± 0.147	0.814 ± 0.184	0.004 ± 0.148
EQ-5D VAS	69.7 ± 19	4.8 ± 13	71.3 ± 27.6	-1.4 ± 12.6
WPAI presenteeism	35 ± 32.1	-0.8 ± 39.4	15 ± 19.1	-5 ± 10
WPAI absenteeism	21.8 ± 39.2	-3.2 ± 33.9	0 ± 0	0 ± 0
WPAI productivity loss	46.6 ± 36.9	-9 ± 31.2	15 ± 19.1	-5 ± 10
WPAI activity impairment	40.8 ± 27.8	-9.2 ± 23.1	20 ± 23.1	0 ± 16.3

List of abbreviations

ANOVA: one-way analysis of variance
BDI-FS: Beck Depression Inventory
DMT: disease modifying therapy
eCRF: electronic case report form
EDSS: expanded disability status scale
EOS: end of study
EQ-5D: Euro-QoL questionnaire
EQ-VAS: EQ-5D visual analogue scale
FSMC: Fatigue scale of Motor and Cognitive Function
GCP: good clinical practice
HRQoL: health-related quality of life
IV: intravenously
ICH: International Council for Harmonisation
ITT: intention to treat
JCV: John Cunningham virus
LOCF: last observation carried forward
MSIS-29: Multiple Sclerosis Impact Scale
MSISQ-19: Multiple Sclerosis Intimacy and Sexuality Questionnaire-19
MusiQoL; Multiple Sclerosis International Quality of Life questionnaire
RRMS: relapsing-remitting multiple sclerosis
SAE: serious adverse event
SD: standard deviation
SDMT: Symbol Digit Modalities Test
SF-12: Short Form 12
SF-36: Short Form 36
SMSG: Swiss MS Society
VAS: Visual Analogue Scale
WPAI-MS: Work Productivity and Activity Impairment in MS

References

1. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of neurology. 2011;69(2):292-302.
2. Sanders ASF, F.W.; LaRocca, N.G. The Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19). Sexuality and Disability. 2000;18(3):23.
3. Jones KH, Ford DV, Jones PA, John A, Middleton RM, Lockhart-Jones H, et al. How people with multiple sclerosis rate their quality of life: an EQ-5D survey via the UK MS register. PLoS One. 2013;8(6):e65640.
4. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. Mult Scler. 2009;15(12):1509-17.
5. Smith A. Symbol Digit Modalities Test. Los Angeles: Western Psychological Services. 1982.
6. Beck AT, Steer, R.A, Brown, G.K. Beck Depressions-Inventar – FS, Deutsche Bearbeitung. Pearson. 2013.
7. Glanz BI, Degano IR, Rintell DJ, Chitnis T, Weiner HL, Healy BC. Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(8):1029-35.
8. Simeoni M, Auquier P, Fernandez O, Flachenecker P, Stecchi S, Constantinescu C, et al. Validation of the Multiple Sclerosis International Quality of Life questionnaire. Mult Scler. 2008;14(2):219-30.
9. Penner IK, Sivertsdotter EC, Celius EG, Fuchs S, Schreiber K, Berko S, et al. Improvement in Fatigue during Natalizumab Treatment is Linked to Improvement in Depression and Day-Time Sleepiness. Frontiers in neurology. 2015;6:18.
10. Vijayasingham L, Mairami FF. Employment of patients with multiple sclerosis: the influence of psychosocial-structural coping and context. Degener Neurol Neuromuscul Dis. 2018;8:15-24.
11. Olofsson S, Wickstrom A, Hager Glenngard A, Persson U, Svenningsson A. Effect of treatment with natalizumab on ability to work in people with multiple sclerosis: productivity gain based on direct measurement of work capacity before and after 1 year of treatment. BioDrugs. 2011;25(5):299-306.
12. Findling O, Baltisberger M, Jung S, Kamm CP, Mattle HP, Sellner J. Variables related to working capability among Swiss patients with multiple sclerosis--a cohort study. PLoS One. 2015;10(4):e0121856.