CLINICAL STUDY REPORT

FINAL

Tracking number: GER-TYS-14-10626

Study Title: TRUST

TysabRi® Patient Management via a longitUdinal multi-dimensional STudy

A 3-year, non-interventional, prospective, multicenter study to investigate the impact of an integrated patient management including biomarkers, magnetic resonance imaging and expert advice on disease activity in relapsing remitting multiple sclerosis patients treated with Tysabri® over the last 12 months.

Start of Study Date:	20 August 2014 (first patient in)
End of Study Date:	12 December 2019 (last patient out)
Report Date:	21 January 2021 (Version 1.0)

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This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and all applicable local regulations.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Ab	Antibody
AE	Adverse event
ARR	Annualized Relapse Rate
CI	Confidence Interval
CL	Confidence Limit
CRF	Case Report Form
CRO	Contract Research Organization
DGN	Deutsche Gesellschaft für Neurologie (German Society of Neurology)
DMT	Disease-modifying Therapy
EC	Ethics committee
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EID	Extended interval dosing
FAS	Full Analysis Set
FSMC	Fatigue Scale for Motor and Cognitive functions
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	Interferon
IRIS	Immune reconstitution inflammatory syndrome
JCV	John Cunningham Virus
KKNMS	Krankheitsbezogenes Kompetenznetz Multiple Sklerose (Disease-related Competence Network Multiple Sclerosis)
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
$MSDS^{3D}$	Multiple Sclerosis Documentation System – 3D
MSFC	Multiple Sclerosis Functional Composite
MSIS	Multiple Sclerosis Impact Scale
NTZ	Natalizumab

OI	Opportunistic Infection
PML	Progressive Multifocal Leukoencephalopathy
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient Reported Outcomes
PSM	Propensity Score Matching
PT	Preferred Term
Q1/Q3	1st / 3rd Quartile
RRMS	Relapsing-remitting Multiple Sclerosis
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SID	Single interval dosing
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
TEAE	Treatment Emergent Adverse Events
TOP	Tysabri Observational Program
TRP	Treated patient set
TSQM	Treatment Satisfaction Questionnaire for Medication
UNL	Upper Normal Limit
WPAI	Work Productivity and Activity Impairment

2. PROTOCOL SYNOPSIS

The original observational protocol (version 1.0 of 08-April-2014) was amended twice. Amendment 1 (resulting in version 2.0 of 27-June-2014) entered into force before enrollment of the first patient.

Amendment 2 (resulting in version 3.0 of 19-November-2015) implemented the following changes: Deletion of biomarker collection (% CD62L expression on CD4+ T-lymphocytes); emphasis the possibility of requesting additional clinical and imaging expert advice (optional); trigger an alarm cascade in case of progressive multifocal leukoencephalopathy (PML) suspicion. The following observational synopsis summarizes protocol version 3.0 of 19-November-2015. The study design of TRUST has already been published (1):

Protocol number:	GER-TYS-14-10626
Protocol Title:	**T**ysab**R**i® Patient Management via a longit**U**dinal multi-dimensional **ST**udy A 3-year, non-interventional, prospective, multicenter study to investigate the impact of an integrated patient management including biomarkers, magnetic resonance imaging and expert advice on disease activity in relapsing remitting multiple sclerosis patients treated with Tysabri® over the last 12 months.
Version number:	3.0 (of 19-November-2015)
Rational and background:	Natalizumab provides rapid and high-efficacy control of multiple sclerosis disease activity with longterm stabilization. However, the benefits of the drug are countered by a risk of developing progressive multifocal leukoencephalopathy (PML) in patients infected with the John Cunningham Virus. Close monitoring is required in patients with increased progressive multifocal leukoencephalopathy risk receiving natalizumab in the long-term for an optimal benefit-risk evaluation. Standardized high-quality monitoring procedures may provide a superior basis for individual benefit and risk evaluation and thus improve treatment decisions. The non-interventional study TRUST was designed to capture natalizumab effectiveness under real-life conditions and to examine alternate approaches for clinical assessments, magnetic resonance imaging monitoring and use of biomarkers for progressive multifocal leukoencephalopathy risk stratification. It has been established that MS patients in general require close monitoring because of the increasing disability associated with this chronic disease and the need for long-term therapy. Close monitoring is especially important in natalizumab patients because of the PML risk. However, there is lack of too little data on diagnostic risk stratification in orders available to guide monitoring and treatment decision-making for natalizumab patients. To develop “customized” rather than “general” treatment modifications for each patient, long-term follow-up on a structured basis is essential. Tools and interments to evaluate MS patients on natalizumab therapy are already available. What matters is the implementation of these procedures in everyday clinical practice. The main tool used in the TRUST study for documentation of patient data in accordance with the Summary of Product Characteristics is the multidimensional Multiple Sclerosis Documentation System (MSDS3D) (2, 3).
Research question and objectives:	The aims of this registry-like study in RRMS patients with more than 12 months of exposure to natalizumab therapy are:

	• To collect and evaluate data on the course of the disease / disease activity (relapse rate, disability progression) over 36 months, in patients with sustained natalizumab therapy versus those who discontinue natalizumab treatment. • To assess the reasons and factors behind the decision to continue or discontinue natalizumab therapy. • To evaluate the use and effects of an integrated adaptive patient management approach, including multimodal monitoring and utilization of expert advice • To explore patient-centric outcomes in patients continuing versus discontinuing natalizumab treatment. • Data on treatment satisfaction (TSQM), life satisfaction (MSIS-29), cognition (SDMT), depression (HADS), fatigue (FSMC), and pharmacoeconomic impact (WPAI) is documented using electronic (tablet-based) patient questionnaires and compared between natalizumab patients and patients no longer using natalizumab.
Study design:	TRUST is a non-interventional, multicenter, prospective cohort study conducted at approximately 200 German neurological centers. The study is intended to enroll 1260 relapsing-remitting multiple sclerosis patients (RRMS) with ongoing natalizumab therapy for at least 12 months. Patients will be followed for a period of 3 years, irrespective of treatment changes after study start. Data on clinical, subclinical and patient-centric outcomes will be documented in order to compare the effectiveness of continuous versus discontinued natalizumab treatment. Furthermore, the type and frequency of clinical, magnetic resonance imaging and biomarker assessments, reasons for continuation or discontinuation of therapy and the safety profile of natalizumab will be collected to explore the impact of a systematic patient management approach and its potential impact on patient outcome.
Population:	TRUST will include a total of 1260 patients from approximately 200 centers in Germany who fulfill the following criteria: • At least 18 years of age at inclusion; • Diagnosis of RRMS according to McDonald criteria (2010 version); • Treatment with natalizumab according to prescription information for at least 12 months and informed consent prior to participating in the study. Patients with any of the following characteristics will be excluded from the study:

	• Progressive forms of MS; • Participation in the non-interventional Tysabri Observational Program (TOP) (patients included in the German REGIMS registry may participate); • Simultaneous therapy with another drug indicated for the treatment of RRMS or contraindications to natalizumab treatment according to prescription information.
Variable:	Demography, baseline MS characteristics and MS history, other baseline medical history (comorbidities, and concomitant medication), MS treatment (prior treatment before start of natalizumab, reason for initiating natalizumab, subsequent MS treatment after natalizumab discontinuation, if applicable). Natalizumab treatment: Natalizumab prior to and after study inclusion, number of natalizumab infusions, infusion intervals, time on natalizumab treatment, prognostic factors for natalizumab discontinuation. Effectiveness and other endpoints: Relapses and annualized relapse rates (ARR), Expanded Disability Status Scale (EDSS) score, symptoms of multiple sclerosis; John-Cunningham-Virus (JCV) test frequency, JCV antibody (Ab) status and JCV Ab-index; data density of magnetic resonance imaging (MRI) scans; Patient reported outcomes (PRO): Treatment Satisfaction Questionnaire for Medication (TSQM-9), Fatigue Scale for Motor and Cognitive functions (FSMC), Hospital Anxiety and Depression Scale (HADS), Multiple Sclerosis Impact Scale (MSIS-29), Work Productivity and Activity Index (WPAI), Symbol Digit Modalities Test (SDMT); safety (incidence of treatment-emergent adverse events).
Data sources:	Data are acquired using the MS patient management and documentation software package MSDS3D. A specific module of the MSDS3D software platform was developed for TRUST that can be used either as a local application or as an online web interface. • Patient data are documented using electronic reporting forms. Patient-centric outcomes are entered in paper or electronic standardized questionnaires. Neurologists who make use of clinical expert advice at any time during the study and radiologists seeking an MRI second opinion reading are asked to document such processes. Study procedures are intended explicitly to not interfere with or exert influence on therapeutic decisions made by the treating neurologist.

	On site monitoring and remote monitoring by phone is performed following a previously defined monitoring plan.
Study size:	No formal sample size estimation is performed, no hypothesis testing is planned. Due to the study design, a high level of drop out is expected. Hence, assuming a Poisson distribution and 3 years of follow-up, 1260 patients will be included in the study to adjust for study dropouts and patients restarting natalizumab treatment in order to detect differences with an alpha level of 0.05 (1). The participation of approximately 200 study centers is planned.
Data analysis:	All recorded data will be analyzed using descriptive statistics according to the recommendations for observational studies. Categorical data will be analyzed by presenting frequency tables (absolute and relative frequencies for non-missing data). For continuous data the sample statistics mean, standard deviation, median, minimum and maximum, and quartiles will be calculated. For incidence rates exact 95% confidence intervals will be presented, if appropriate. Data measured several times during the study will be analyzed by time point presenting absolute differences to baseline for continuous data and shift tables for categorical data. The scheduled visits as documented by the investigators will be used as time points (Note: the data management proved, that the scheduled intervals were adhered to). Time-to-event data (e.g. time on natalizumab) will be evaluated by Kaplan-Meier methods. ARR for patients treated with natalizumab during the complete follow-up period (36 months) and those with earlier discontinuation of natalizumab and subsequent alternative MS treatment will be calculated by a Negative Binomial Regression model. All PRO will be analyzed according to the usual score calculations. Yearly interim analyses are planned. Further explorative analysis and subgroups will be defined in a statistical analysis plan prior the database lock.
Milestones:	Start of data collection: Planned May 2014 Recruitment duration: 22 months Observation period per patient: 36 months regardless of any changes in treatment End of data collection: Planned for end of February 2019

2.1. Documentation schedule

Assessment documentation	**Visit 1**	**Visits 2-13 (until Month 36)**	
	Start of observation	**Every 3 months**	**Every 6 months**
Inclusion and exclusion criteria*	X		
Demographic data	X		
Date of data collection	X		
Demographic data/history	X		
MS disease data including history	X		
Comorbidities	X	X	
MS treatment including history	X		
Data on current MS treatment (including natalizumab treatment)	X	Changes to be documented on a continuous basis	
Relevant comedication	X	Changes to be documented on a continuous basis	
MS-related signs and symptoms	X	X	
MS relapses	X	X	
EDSS	X	X	
Opportunistic infections	X	X	X
MRI (if available)	X	X	
Lab values (if available)	X	X	
Anti-JCV Ab status (if available)	X	X	
Anti-JCV Ab index (if available)	X		X
Other biomarkers (if available)	X	X	
SAE/AE/pregnancy	Continuous		
TSQM-9**	X		X
FSMC**	X		X
HADS**	X		X
MSIS-29**	X		X
SDMT	X		X
WPAI**	X		X
Expert board	Continuous		

* Further documentation is only possible if the inclusion criteria are met and the exclusion criteria do not apply.
** If investigated in routine clinical practice

3. SUMMARY OF RESULTS AND CONCLUSIONS

Number of Subjects (Planned and Analyzed):

The study projection was for 1260 subjects to participate in the study (at approximately 200 study centers); 1264 subjects were enrolled (at 160 German study centers), and data from 1191 subjects (at 157 German study centers) were analyzed.

Criteria for Evaluation:

Demography, baseline MS characteristics and MS history, other baseline medical history (comorbidities, and concomitant medication), MS treatment (prior MS treatment before start of natalizumab, reason for initiating natalizumab, subsequent MS treatment after natalizumab discontinuation, if applicable).

Natalizumab treatment: Natalizumab prior to and after study inclusion, number of natalizumab infusions, infusion intervals, time on natalizumab treatment.

Effectiveness and other endpoints: Relapses and annualized relapse rates (ARR), Expanded Disability Status Scale (EDSS) score, symptoms of multiple sclerosis; John-Cunningham-Virus (JCV) test frequency, JCV antibody (Ab) status and JCV Ab index; data density of magnetic resonance imaging (MRI) scans;

Patient reported outcomes (PRO): Treatment Satisfaction Questionnaire for Medication (TSQM-9), Fatigue Scale for Motor and Cognitive functions (FSMC), Hospital Anxiety and Depression Scale (HADS), Multiple Sclerosis Impact Scale (MSIS-29), Work Productivity and Activity Index (WPAI), Symbol Digit Modalities Test (SDMT); safety (incidence of treatment-emergent adverse events).

Results: The first subject's first documentation was on 20 August 2014, the last subject's last documentation was on 12 December 2019.

Patient disposition and analysis sets

Treated patients (TRP) (N=1191) used for safety analyses: Comprised all patients who provided informed consent and had received at least one dose of natalizumab after enrolment.

- STAY cohort (N=698): Patients who continued natalizumab until the end of study at Month 36. SWITCH cohort (N=396): Patients who permanently discontinued natalizumab before the end of study at Month 36. INDETERMINABLE cohort (N=97 patient).

Full analysis set (FAS) (N=1189) used for effectiveness analyses: Comprised all TRP patients, with adherence to all selection criteria, and with at least one post-baseline visit documented (698 STAY, 396 SWITCH, and 95 INDETERMINABLE patients).

To address potential bias, a 1:1 **propensity score matched (PSM) (N=580)** subset of the FAS was used for selected effectiveness analyses (290 STAY, 290 SWITCH patients).

Overall, 396 patients (33.2%) of the TRP set **permanently discontinued natalizumab therapy at any time up to study end at Month 36**, the most common reasons were: "PML risk" (46.7%, 185 patients), "requested by patient" (13.4%, 53 patients), and "positive anti-JCV Ab test" (12.1%, 48 patients), "other clinical/medical reasons" (9.6%, 38 patients), "ineffectiveness" (8.6%, 34 patients), no reason was specified in 17.9% of patients (71 patients) (relative frequencies based on the number of patients who discontinued natalizumab).

The **observational time per patient** was mean ± SD 36.3 ± 1.8 months in the STAY cohort, 20.4 ± 9.8 months in SWITCH-ON patients (i.e., from baseline to natalizumab discontinuation; N=396), and

12.7 ± 10.7 months (median 11.2 months) in SWITCH-OFF patients (i.e., after natalizumab discontinuation; N=325).

FAS subgroups classified by **PML risk at baseline (based on the anti-JCV Ab index)**:

- Number of patients Total: No risk=703, low risk=61, intermediate risk=259, high risk=166.
- Number of patients STAY: No risk=494, low risk=32, intermediate risk=122, high risk=50.
- Number of patients SWITCH: No risk=143, low risk=22, intermediate risk=120, high risk=111.

Demography, MS diagnosis, and prior MS treatment

In the total TRP, the majority of patients were women (864, 72.5%) and patients' mean ± SD age was 39.1 ± 10.0 years (median 38.0 years ranging from 18.0 to 76.0 years).

Overall, the time interval between **the onset of the first MS symptoms and start of study** was median 10.2 years (Q1=5.5 years; Q3=15.4 years, range 1.1 to 42.3 years); likewise, the time between **first MS diagnosis and start of study** was median 9.0 years (Q1=4.4 years; Q3=13.8 years, range 1.1 to 35.3 years). The median value for the time between **onset of the first MS symptoms and first MS diagnosis** was 0.3 years (Q1=0.0 years; Q3=1.5 years).

Most patients in the TRP had received **previous MS treatment** before starting natalizumab (86.6%, 1031 patients), only 160 patients (13.4%) were MS treatment naïve at start of natalizumab. The mean ± SD **number of prior MS treatments** was 1.3 ± 0.9 treatments; median 1.0 treatments; range from 0 to 5 treatments, without remarkable differences between subcohorts. The most common previous MS treatments were: glatiramer acetate ("Copaxone", 34.5%), and interferons such as "Avonex" (31.2%), "Rebif" (30.8%) or "Betaferon/Extavia" (22.2%).

Natalizumab treatment prior to study inclusion

The **number of prior natalizumab infusions** as well as the **duration of prior natalizumab treatment before study inclusion** showed a very broad range across TRP patients: Overall, patients had received median 31.0 infusions of natalizumab prior to study inclusion (Q1=17.0 infusions; Q3=65.0 infusions; ranging from 9 to 122 infusion), corresponding to a median treatment duration of 36.1 months of prior natalizumab treatment (Q=17.2 months; Q3=76.5 months, ranging from 11.8 to 146.4 months).

The median **number of all natalizumab infusions / treatment duration before study inclusion** was slightly greater in the STAY cohort (median 32.0 infusions / 36.9 months) compared with the SWITCH cohort (median 29.5 infusions / 33.3 months) (TRP).

The number of **natalizumab infusions during the last 12 months before inclusion** into the study was median 12.0 infusions per patient (Q1=11.0 infusions; Q3=12.0 infusions). The **time since last infusion before study inclusion** was median 4.1 weeks (Q1=2.1 weeks; Q3=4.6 weeks) (TRP).

Natalizumab treatment after study inclusion:

The **number of natalizumab infusions after study start** widely ranged across patients of both cohorts. The mean ± SD number of infusions was 34.1 ± 5.3 infusions (median: 36.0, range from 4 to 43 infusions) in the STAY and 15.9 ± 9.5 infusions (median 15.0, range from 1 to 41 infusions) in the SWITCH cohort (total TRP: 26.5 ± 11.6 infusions; median 31.0 infusions).

Of the overall 30331 infusions intervals documented in this study, 36.5% (11058 intervals) were ≥4.5 weeks thereby pointing to a possible extended interval dosing (EID), with a minimally greater proportion among SWITCH patients (37.5%, 1209 intervals) compared with STAY patients (36.2%, 8360 intervals).

In the total TRP, the Kaplan-Meier estimated median **time on natalizumab from treatment start** was 10.3 years (95% CI: 10.0 years to 10.7 years); the median **time on natalizumab since study entry** was 3.6 years (95% CI: 3.6 years to 3.8 years) in the total TRP, and approx. 1.5 years in the SWITCH cohort.

With regard to PML risk at baseline, the estimated **time on natalizumab since treatment start / study entry** decreased with increasing PML risk; it was highest in the "no PML risk" subgroup (median about 12.0 years / median not estimable) and lowest in the "high PML risk" subgroup (median about 9.5 years / 2.1 years) (values graphically derived from Kaplan-Meier plot).

The cumulative incidence of discontinuations due to safety reasons (adjusted for non-safety reasons) was 0.9% after 2 years, and it increased to 4.7% after 3 years and to 11.1% after 5 years; after 10 years of natalizumab treatment it was 27.2%.

A logistic regression model including backward selection identified the following **prognostic factors for natalizumab discontinuation:** Patients were more likely to discontinue natalizumab with increasing **duration of exposure to natalizumab** (probably biased since treatment duration is inherently shorter in patients who discontinue natalizumab), patients with increasing **last EDSS score before discontinuation/end of study**, with increasing **PML risk at baseline**, and with **"not calculable EID"** (this finding might probably be biased since EID detection and assignment to a EID subgroup is only possible for patients with sufficiently long treatment duration).

The most frequent (≥10.0% of patients) **subsequent first DMTs after permanent discontinuation of natalizumab**, if applicable, were: "No subsequent therapy" (89 patients, 22.5%), "Gilenya" (82 patients, 20.7%), "Zinbryta/Daclizumab" (68 patients, 17.2%), "Ocrelizumab" (56 patients, 14.1%), and "Lemtrada" (40 patients, 10.1%).

Overall, 154 patients (12.9%) **discontinued natalizumab temporarily** during the study, the most frequent reason for was "(planned) pregnancy" and "other clinical/medical reasons" both with overall 3.4% (41 patients).

Number of MS relapses and ARR

- During **the last 12 months prior to initiating natalizumab,** only 8.1% (n=96) of the patients in the FAS were relapse-free with similar proportions in STAY (8.5%) and SWITCH (8.1%) cohorts. Patients with relapses within the last 12 months prior start of natalizumab were relatively equally distributed among the relapse frequency categories (1, 2, >2 relapses) with about 25–27% in each category, and comparable across STAY and SWITCH cohorts (FAS).
- **After start of natalizumab (**until study entry), the proportion of relapse-free patients markedly increased to nearly two thirds of patients across all cohorts (total 64.9%, n=771) (FAS).
- **From after study enrollment to natalizumab discontinuation**, overall 78.8% (n=937), and 79.5% (n=555) of patients in the STAY and 76.0% (n=301) in the SWITCH cohort were relapse-free (FAS).
- **After permanent discontinuation of natalizumab,** 78.5% (n=311) of patients in the SWITCH cohort remained relapse-free (FAS).

Table 2 summarizes **estimated ARRs** for different time periods including the 95% confidence intervals.

Table 2: Annualized relapse rates overall and by STAY vs. SWITCH cohorts (FAS and PSM)

Cohort	FAS		PSM	
Time interval	ARR estimate [a]	[95% CI]	ARR estimate [a]	[95% CI]
Total				
After NTZ start but prior to study entry	0.127	[0.099; 0.165]	0.150	[0.125; 0.180]
After study inclusion until NTZ discont.	0.100	[0.078; 0.130]	0.126	[0.103; 0.153]
After NTZ discontinuation	0.269	[0.193; 0.374]	0.308	[0.235; 0.403]
STAY				
After NTZ start but prior to study entry	0.131	[0.099; 0.175]	0.129	[0.099; 0.168]
After study inclusion until last visit	0.078	[0.058; 0.104]	0.081	[0.060; 0.110]
SWITCH				
After NTZ start but prior to study entry	0.133	[0.100; 0.177]	0.170	[0.137; 0.211]
After study inclusion until NTZ discont.	0.175	[0.131; 0.234]	0.198	[0.157; 0.251]
After NTZ discontinuation	0.274	[0.198; 0.380]	0.310	[0.237; 0.405]
INDETERMINABLE				
After NTZ start but prior to study entry	0.103	[0.066; 0.160]	-	-
After study inclusion until NTZ discont.	0.087	[0.049; 0.152]	-	-

ARR = Annualized Relapse Rate; CI = Confidence interval; NTZ = Natalizumab; FAS = Full Analysis Set; PSM = Propensity score matching.

a: Negative binomial regression including covariates: gender, baseline EDSS (<3 vs. ≥3), disease duration (<8 vs. ≥8 years), number of previous DMTs (0 vs. 1 vs. ≥2), and treatment duration (<3 vs. ≥3 years). Missing data were handled as separate category.

Course of EDSS

At start of natalizumab, the EDSS was (mean ± SD) 3.0 ± 1.5 in STAY and 3.2 ± 1.8 in SWITCH-ON patients (median: 3.0 in both cohorts) (retrospective documentation).

At study entry (baseline), EDSS was numerically lower in STAY compared with SWITCH-ON cohort (2.7 ± 1.6, median 2.5 vs. 3.1 ± 1.8, median 3.0, respectively).

During study course, no relevant mean or median changes from baseline were noted in either cohort throughout the study course. In the SWITCH-OFF subcohort, the last EDSS value before discontinuation of natalizumab was 3.1 ± 1.8 (median 3.0) (baseline for SWITCH-OFF).

The proportions of patients with an **EDSS worsening at any time point during the study** were numerically lower among STAY patients (6.6%, 38 patients) compared with SWITCH-ON (9.2%, 26 patients) or SWITCH-OFF (7.9%, 9 patients) cohorts.

MS symptoms during study

- Overall, 890 patients (74.9%) in the total FAS entered the study with **at least one symptom present at baseline** (STAY 73.5% and SWITCH 75.8%), and 651 patients (54.8%) had **more than one symptom present at baseline**, the proportion was lower in STAY (52.0%) compared with SWITCH (58.3%) patients.
- The most common MS symptoms present at baseline were “dys-/hyperesthesia” (31.4%, 373 patients), “other” (24.9%, 296 patients), “fatigue” (24.4%, 290 patients), “bladder/intestinal disorders” (22.8%, 271 patients).

- MS symptoms "fatigue" (23.5% STAY and 27.0% SWITCH patients), and "coordinative dysfunction" (16.0% STAY and 22.0% SWITCH patients) were more frequent in STAY than in SWITCH patients.
- Overall, in 306 patients (25.7%) of the total FAS **at least one MS symptom improved after study start** (STAY 26.1% and SWITCH 28.8%), and in overall 359 patients (30.2%) **at least one MS symptom worsened after study start** (STAY 27.9% and SWITCH 36.1%) (FAS).
- The most common MS symptoms which worsened after study start were "dys-/hyperesthesia" (total 8.3%, 99 patients), "other" (total 7.9%, 94 patients), and "fatigue" (total 7.5%, 89 patients), with constantly numerically lower percentages in STAY than in SWITCH patients.

JCV tests

- At baseline, a JCV test result (anti-JCV Ab index or status) was available in almost all patients (≥96.0% in STAY and SWITCH-ON cohort). In 49.0% of STAY patients and 60.9% of SWITCH-ON patients the anti-JCV Ab index was available.
- The mean **duration of the time interval between JCV tests** was similar across STAY, SWITCH-ON, and SWITCH-OFF of cohorts (mean values ranged from 5.2 to 5.7 months), whilst the median value was greater in the STAY cohort (median 5.2 months) than in SWITCH-ON (median 3.7 months) or SWITCH-OFF (median 3.2 months) cohorts.
- At baseline, the **anti-JCV Ab index** was mean ± SD 0.6 ± 0.9 (median 0.2; N=342) in STAY and 1.5 ± 1.3 (median 1.2; N = 241) in SWITCH-ON cohorts. The baseline value of the SWITCH-OFF cohort, i.e., when natalizumab discontinuation was first documented, was 2.4 ± 1.1 (median 2.6; N=103). Mean and median values of the anti-JCV Ab index did not relevantly change over time in STAY patients, whilst they mildly increased in SWITCH-ON, and mildly decreased in SWITCH-OFF cohorts: The last reported value was in the STAY cohort 0.8 ± 1.1 (median 0.2; N=510), in the SWITCH-ON cohort (2.0 ± 1.2) (median 2.1; N=314), and in the SWITCH-OFF cohort 2.1 ± 1.2 (median 1.3; N=52) (LOCF).
- At baseline, the **anti-JCV Ab status** was "positive in overall 441 FAS patients (37.1%), "negative" in 703 (59.1%) patients, and "missing" in 45 patients (3.8%).
- Of the 703 patients with a "negative" **anti-JCV Ab status** at baseline, 102 patients (8.6% of all FAS patients) were tested anti-JCV Ab "positive" at their last visit.

Data density of magnetic resonance imaging scans

Until natalizumab discontinuation, the **number of MRI scans per patient** was mean ± SD 5.4 ± 2.4, (median 5.0; Q1 = 4.0; Q3 = 7.0) MRI scans per patient in the STAY and 3.8 ± 2.0 (median 3.0; Q1 = 2.0; Q3 = 5.0) MRI scans per patient in the SWITCH cohort. The majority of patients in the STAY cohort had received 5–8 MRI scans (52.7%, 368 patients) whilst in the SWITCH cohort the majority of patients had received 2–4 MRI scans (60.9%, 241 patients).

The mean (± SD) and median **duration of the time interval between MRI check-ups** until natalizumab discontinuation was mildly greater among STAY (8.0 ± 6.4 months, median 6.3 months; N=3071 intervals) compared with SWITCH patients (7.0 ± 5.4 months, median 5.8 months; N=1096 intervals).

After natalizumab discontinuation, the **number of MRIs per patient** was mean ± SD 1.5 ± 1.5 (median 1.0; Q1 = 0.0; Q3 = 2.0) MRIs per patient in the SWITCH cohort. Patients of the SWITCH

cohort mostly had received either no MRI scans (32.8%, 130 patients) or 1 MRI scan (44.2%, 175 patients) after natalizumab discontinuation.

Patient reported outcomes

Generally, the PROs did not change remarkably over time in any of the cohorts (STAY, SWITCH-ON, or SWITCH-OFF), and nearly all PROs generally indicated relatively favorable patient's condition already at study entry. Nevertheless, distinctive individual changes in all PROs were noted during study course, deteriorations as well as improvements, in all cohorts.

Table 3 presents PRO summary statistics for baseline values, last documented value after baseline, and change from baseline to last documented value in the respective time period.

Table 3: Patient reported outcomes (FAS) – multipage table

PRO	STAY (N=698) Mean ± SD (median) [N]	SWITCH-ON (N=396) Mean ± SD (median) [N]	SWITCH-OFF (N=325) Mean ± SD (median) [N]
TSQM - Effectiveness			
Baseline	79.4 ± 27.3 (88.9) [637]	77.0 ± 28.2 (88.9) [356]	70.4 ± 32.1 (77.8) [64]
Last value	81.6 ± 25.6 (88.9) [656]	74.3 ± 29.5 (83.3) [312]	65.3 ± 27.9 (66.7) [116]
Change [a]	1.9 ± 35.1 (0.0) [621]	-3.3 ± 35.8 (0.0) [293]	-1.3 ± 38.4 (0.0) [44]
TSQM - Convenience			
Baseline	78.0 ± 17.2 (80.6) [636]	79.3 ± 17.1 (83.3) [358]	79.5 ± 17.8 (83.3) [64]
Last value	78.0 ± 17.6 (83.3) [656]	77.1 ± 18.5 (77.8) [310]	77.7 ± 19.6 (77.8) [116]
Change [a]	0.1 ± 16.5 (0.0) [619]	-2.5 ± 18.0 (0.0) [292]	-1.6 ± 19.1 (0.0) [44]
TSQM – Global satisfaction			
Baseline	84.4 ± 15.7 (85.7) [637]	82.1 ± 17.5 (85.7) [359]	72.3 ± 23.2 (71.4) [64]
Last value	84.7 ± 16.4 (85.7) [656]	78.6 ± 20.0 (82.9) [310]	69.4 ± 24.8 (78.6) [116]
Change [a]	0.2 ± 16.1 (0.0) [620]	-4.4 ± 19.0 (0.0) [293]	1.9 ± 26.3 (0.0) [44]
FSMC total			
Baseline	57.6 ± 20.3 (58.0) [588]	59.2 ± 19.5 (60.0) [313]	58.6 ± 19.7 (60.5) [60]
Last value	58.2 ± 21.2 (61.0) [644]	59.2 ± 20.3 (61.0) [288]	62.5 ± 20.0 (64.0) [111]
Change [a]	0.1 ± 11.9 (0.0) [567]	0.4 ± 10.8 (0.0) [243]	-0.1 ± 9.2 (0.0) [39]
HADS anxiety			
Baseline	6.1 ± 3.9 (6.0) [631]	6.3 ± 3.9 (6.0) [354]	5.6 ± 3.9 (5.0) [66]
Last value	5.8 ± 4.1 (5.0) [657]	6.0 ± 3.8 (6.0) [310]	6.0 ± 3.6 (6.0) [118]
Change [a]	-0.3 ± 3.1 (0.0) [617]	-0.2 ± 3.1 (0.0) [292]	-0.7 ± 2.7 (0.0) [47]
HADS depression			
Baseline	4.6 ± 3.9 (3.0) [629]	4.9 ± 3.9 (4.0) [353]	4.5 ± 4.0 (4.0) [66]
Last value	4.4 ± 4.1 (3.0) [657]	4.8 ± 4.1 (4.0) [310]	5.3 ± 4.0 (5.0) [118]
Change [a]	-0.2 ± 3.0 (0.0) [615]	-0.0 ± 3.0 (0.0) [291]	-0.2 ± 2.4 (0.0) [47]
MSIS-29			
Baseline	35.5 ± 13.0 (33.0) [628]	38.2 ± 14.7 (35.0) [359]	39.5 ± 15.9 (35.5) [66]
Last value	35.9 ± 13.6 (33.0) [657]	39.5 ± 15.6 (37.0) [314]	40.6 ± 15.0 (40.0) [117]
Change [a]	0.4 ± 8.5 (0.0) [612]	1.8 ± 9.1 (0.0) [296]	1.0 ± 8.4 (1.2) [46]

MSIS-29			
Baseline	17.4 ± 6.0 (17.0) [626]	18.0 ± 6.4 (17.0) [357]	17.7 ± 6.2 (17.0) [66]
Last value	17.1 ± 6.2 (16.0) [656]	17.8 ± 6.5 (17.0) [312]	18.6 ± 6.1 (18.0) [116]
Change [a]	-0.4 ± 4.8 (0.0) [610]	0.1 ± 5.0 (0.0) [292]	-0.9 ± 4.9 (-1.0) [45]
SDMT, symbols correct			
Baseline	46.7 ± 13.3 (48.0) [555]	47.0 ± 14.2 (47.0) [304]	52.0 ± 19.4 (52.0) [54]
Last value	52.6 ± 15.1 (52.0) [590]	49.1 ± 15.2 (50.0) [256]	52.2 ± 13.9 (52.0) [90]
Change [a]	6.1 ± 11.3 (5.0) [526]	2.1 ± 10.8 (3.0) [230]	-0.3 ± 10.0 (1.0) [34]
WPAI % work time missed due to MS			
Baseline	6.1 ± 19.1 (0.0) [329]	8.1 ± 23.1 (0.0) [181]	10.5 ± 29.5 (0.0) [32]
Last value	6.6 ± 21.5 (0.0) [458]	9.0 ± 23.9 (0.0) [185]	10.7 ± 25.6 (0.0) [59]
Change [a]	0.6 ± 25.1 (0.0) [313]	2.5 ± 28.0 (0.0) [140]	-3.6 ± 27.9 (0.0) [15]
WPAI % impairment while working due to MS			
Baseline	28.1 ± 22.0 (20.0) [357]	29.8 ± 24.6 (20.0) [194]	30.9 ± 23.1 (30.0) [33]
Last value	30.1 ± 23.5 (20.0) [477]	31.5 ± 22.3 (30.0) [201]	36.0 ± 26.4 (30.0) [63]
Change [a]	1.0 ± 20.8 (0.0) [334]	0.4 ± 18.0 (0.0) [151]	2.2 ± 15.6 (0.0) [18]
WPAI % overall work impairment due to MS			
Baseline	50.5 ± 22.5 (44.8) [48]	51.8 ± 24.3 (49.5) [27]	61.8 ± 6.1 (65.2) [3]
Last value	50.7 ± 22.6 (50.6) [114]	55.2 ± 20.3 (55.1) [50]	62.4 ± 19.6 (64.0) [14]
Change [a]	-2.8 ± 20.0 (-1.0) [30]	4.1 ± 22.7 (0.6) [12]	-0.2 ± n.a. (-0.2) [1]
WPAI % activity impairment due to MS			
Baseline	38.3 ± 24.7 (30.0) [624]	41.9 ± 26.7 (40.0) [348]	40.9 ± 24.3 (40.0) [64]
Last value	38.1 ± 24.8 (30.0) [655]	41.2 ± 25.5 (40.0) [306]	45.6 ± 26.3 (45.0) [116]
Change [a]	0.0 ± 21.0 (0.0) [607]	-0.1 ± 20.7 (0.0) [280]	-0.4 ± 18.7 (0.0) [45]

FAS= Full Analysis Set; FSMC = Fatigue Scale for Motor and Cognitive functions; HADS = Hospital Anxiety and Depression Scale; MS = Multiple Sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; PRO = Patient reported outcomes; Q1/Q3 = 1st/3rd Quartile; TSQM = Treatment Satisfaction Questionnaire for Medication; SDMT = Symbol Digit Modalities Test; SD = Standard deviation; WPAI = Work Productivity and Activity Impairment.
For SWITCH-OFF cohort, baseline, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
a: Change from baseline to last documented value in the respective time period
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
TSQM-9 subscales ranged from 0 to 100. Higher scores indicate greater satisfaction on that domain.
FSMC: The total sum score ranges from 20 to 100, the cognitive and physical subscores from 10 to 50 each. Higher scores indicated more pronounced fatigue.
The HADS anxiety and depression subscores range from 0 to 21 each. Higher scores indicated more pronounced depression / anxiety.
The MSIS-29 physical impact score ranges from 20 to 80, the psychological impact score from 9 to 36. Higher scores indicated worse disability.
WPAI outcomes are expressed as impairment percentage (ranging from 0% to 100%), with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.

Safety results

Table 4 provides an overall summary of the treatment emergent AE (TEAE) experience documented in the study. Please note that AEs starting before Visit 1 were not regarded as study events. This section and the following table summarize AEs occurring during participation in the TRUST study (i.e., starting at or after Visit 1) up to 90 days after last application of natalizumab. In addition, Biogen's drug safety department might have considered some events which occurred > 90 days after natalizumab discontinuation treatment emergent as well on an individual basis.

Table 4: Overview of treatment emergent adverse events (TRP)

Parameter	STAY (N=698) n (%) (95% CI)	SWITCH (N=396) n (%) (95% CI)	INDETERMI-NABLE (N=97) n (%) (95% CI)	Total (N=1191) n (%) (95% CI)
Any AE	542 (77.7) [74.4 - 80.7%]	286 (72.2) [67.5 - 76.6%]	54 (55.7) [45.2 - 65.8%]	882 (74.1) [71.5 - 76.5%]
Any AE possibly related to NTZ	265 (38.0) [34.4 - 41.7%]	149 (37.6) [32.8 - 42.6%]	20 (20.6) [13.1 - 30.0%]	434 (36.4) [33.7 - 39.2%]
Any AE leading to interruption or discontinuation of NTZ	43 (6.2) [4.5 - 8.2%]	89 (22.5) [18.5 - 26.9%]	5 (5.2) [1.7 - 11.6%]	137 (11.5) [9.7 - 13.5%]
Any SAE	155 (22.2) [19.2 - 25.5%]	99 (25.0) [20.8 - 29.6%]	19 (19.6) [12.2 - 28.9%]	273 (22.9) [20.6 - 25.4%]
Any SAE possibly related to natalizumab	42 (6.0) [4.4 - 8.0%]	45 (11.4) [8.4 - 14.9%]	9 (9.3) [4.3 - 16.9%]	96 (8.1) [6.6 - 9.8%]
Any SAE leading to interruption or discontinuation of NTZ	6 (0.9) [0.3 - 1.9%]	24 (6.1) [3.9 - 8.9%]	2 (2.1) [0.3 - 7.3%]	32 (2.7) [1.8 - 3.8%]
SAE category "Death"	0 (0.0) [0.0 - 0.5%]	3 (0.8) [0.2 - 2.2%]	2 (2.1) [0.3 - 7.3%]	5 (0.4) [0.1 - 1.0%]
Opportunistic infections	0 (0.0) [0.0 - 0.5%]	0 (0.0) [0.0 - 0.9%]	0 (0.0) [0.0 - 3.7%]	0 (0.0) [0.0 - 0.3%]
Serious infections	21 (3.0) [1.9 - 4.6%]	28 (7.1) [4.7 - 10.1%]	3 (3.1) [0.6 - 8.8%]	52 (4.4) [3.3 - 5.7%]
PML	0 (0.0) [0.0 - 0.5%]	8 (2.0) [0.9 - 3.9%]	1 (1.0) [0.0 - 5.6%]	9 (0.8) [0.3 - 1.4%]

AE = Adverse event; CI = Confidence interval; NTZ = Natalizumab; SAE = Serious adverse events; TRP = Treated patients.

Any AEs starting before Baseline (Visit 1) were not regarded as study events. Only AEs starting at or after Visit 1 up to 90 days after last application of NTZ were regarded treatment emergent in TRUST. In addition, Biogen's drug safety department might have considered some events which occurred > 90 days after NTZ discontinuation treatment emergent as well on an individual basis.

There were several numerical differences between STAY and SWITCH with regard to AE incidences, but these findings were presumably biased by differences in duration of observation (considerably longer in STAY compared with SWITCH patients), and more over by the definitions applicable for cohort assignment itself as AEs are a common reason to stop a drug therapy.

The 3 most common SOCs affected **by TEAEs** in the total TRP were “infections and infestations” (39.2%, 467 patients), “nervous system disorders” (37.6%, 448 patients), and “musculoskeletal and connective tissue disorders” (15.0%, 179 patients).

On a preferred term level, the most common **TEAEs** (overall ≥2.5% of patients) in the total TRP were “multiple sclerosis relapse” (22.2%, 264 patients), “nasopharyngitis” (21.7%, 259 patients), “vitamin D deficiency” (6.8%, 81 patients), “urinary tract infection” (6.0%, 72 patients), “headache” (5.2%, 62 patients), “depression” (4.5%, 53 patients), “fall” (3.1%, 37 patients), “sleep disorder” (3.1%, 37 patients), “dizziness” (3.0%, 36 patients), “diarrhoea” (3.0%, 36 patients), “fatigue” (2.9%, 35 patients), ”infection” (2.9%, 34 patients), “respiratory tract infection” (2.9%, 34 patients), “bronchitis” (2.7%, 32 patients), “sinusitis” (2.5%, 30 patients).

The 3 most common SOCs affected by **TEAEs possibly related to natalizumab** in the total TRP were “infections and infestations” (15.5%, 185 patients), “nervous system disorders” (13.3%, 158 patients), and “general disorders and administration site condition” (3.9%, 46 patients).

On a preferred term level, the most common **TEAEs possibly related to natalizumab** (reported in overall ≥1.0% of patients) in the total TRP were: “multiple sclerosis relapse” (8.4%, 100 patients), “nasopharyngitis” (6.6%, 79 patients), “urinary tract infection” (2.4%, 29 patients), “headache” (1.5%, 18 patients), “oral herpes” (1.2%, 14 patients), “depression” (1.0%, 12 patients), “gait disturbance” (1.0%, 12 patients), and “respiratory tract infection” (1.0%, 12 patients).

The most commonly documented SOCs for **serious TEAEs** (reported in overall ≥2.0% of patients) were “nervous system disorders” (9.1%, 108 patients), “infections and infestations” (4.4%, 52 patients), “injury, poisoning and procedural complications” (2.5%, 30 patients), and “psychiatric disorders” (2.2%, 26 patients).

The most frequent **serious TEAEs** preferred term were “multiple sclerosis relapse” (5.5%, 66 patients), “epilepsy” (0.8%, 9 patients), “progressive multifocal leukoencephalopathy” (0.8%, 9 patients), “depression” (0.8%, 9 patients), “fall” (0.7%, 8 patients), “gait disturbance” (0.7%, 8 patients), “abortion spontaneous” (0.6%, 7 patients), and “intervertebral disc protrusion” (0.5%, 6 patients), “multiple sclerosis” (0.5%, 6 patients), “Uhthoff's phenomenon” (0.5%, 6 patients).

Overall, 21 patients (1.8%) experience **serious TEAEs** pertaining to the primary SOC “neoplasms benign, malignant and unspecified (incl cysts and polyps)”.

Overall, there were 2 patients (0.3%) reported with preferred terms serious “liver function test increased”, and one patient (<0.1%) each with serious “alanine aminotransferase increased”, “blood bilirubin increased”, “gamma-glutamyltransferase increased”, “hepatic enzyme increased” (multiple responses per patient possible).

Overall, 5 (0.4%) **treatment emergent deaths** were reported, of which one case (“optic glioma”) was assessed as causally related to natalizumab, in two other cases the causality was assessed as “unknown” (preferred terms: “road traffic accident”; “death”, in the latter one related “progressive multifocal leukoencephalopathy” was additionally reported).

Overall, 9 patients (0.8%) had a **confirmed diagnosis of treatment emergent PML** (7 recovered, and 2 with PML outcome "not recovered". Of these two, one patient died later from an unspecified cause). Of the 9 confirmed PML, all but one (the causality of which was assessed as "unknown") were regarded as related to natalizumab treatment.

Treatment-emergent **serious infections** (defined as all serious TEAE pertaining to the MedDRA primary SOC "infections and infestations") occurred in overall 52 patients (4.4%) of the TRP.

The most frequent treatment-emergent **serious infections** (reported in overall ≥3 patients) on preferred term level were "progressive multifocal leukoencephalopathy" (0.8%, 9 patients), "appendicitis" (0.4%, 5 patients), "pneumonia" (0.4%, 5 patients), "infection" (0.3%, 4 patients), "urinary tract infection" (0.3%, 4 patients), "sepsis" (0.3%, 3 patients), and "urosepsis" (0.3%, 3 patients).

There was one patient (<0.1%) each reported with serious infections (preferred terms): "herpes zoster"; "ophthalmic herpes zoster", "tuberculosis"; "latent tuberculosis".

Conclusion(s): This non-interventional, observational, German, multicenter study included a large and heterogeneous sample of RRMS patients on ongoing treatment with natalizumab according to prescription information for at least 12 months.

- The patient sample broadly varied with regard to MS disease history, duration and exposure to previous natalizumab treatment before study enrollment. The majority of patients had longstanding MS disease (≥10 years) and more than 2 years natalizumab treatment duration at enrollment into TRUST. The Kaplan-Meier estimated median time on natalizumab from treatment start including the study period was 10.3 years.
- Almost all patients (≥96%) entered the study with an anti-JCV antibody test result (status or index) available at baseline, 37% of patients had a "positive" anti-JCV antibody status. The median duration of time intervals between anti-JCV tests was shorter among SWITCH compared with STAY patients.
- The MRI scans during natalizumab treatment were performed at approximately 6-month intervals (median duration between subsequent intervals).
- The proportion of relapse-free patients considerably increased after initiating natalizumab, was stable during study, and remained on the same level in the SWITCH cohort after discontinuation of natalizumab treatment, whilst ARR increased after permanent natalizumab discontinuation.
- The most frequent reason for permanent natalizumab discontinuation was PML risk.
- With the exception of the fatigue questionnaire and some WPAI scores, all PROs showed relatively favorable results and good patient's conditions already at study enrollment. Generally, neither the EDSS nor the PROs changed remarkably over time in any of the cohorts (STAY, SWITCH-ON/OFF)
- Overall 9 patients experienced confirmed PML during study participation.
- Evaluation of adverse events and the data generally supported the established safety profile of natalizumab. No new significant safety findings were noted and the benefit-risk profile of natalizumab remained positive.

4. ETHICS

4.1. Ethics Committees

The scientific expert presented the non-interventional study protocol along with the patient information and informed consent form to his competent ethics committee for review. Furthermore, each participating physician could seek advice from his competent ethics committee in line with professional legal obligations. For this purpose, it was possible to forward them the non-interventional study protocol along with the patient information and informed consent form. Ethics committee review was intended to ensure that patient rights were not compromised and that the non-interventional study was designed to gain knowledge. The details on the EC responsible for the scientific expert are included in Appendix A.

4.2. Patient Information and Consent

Written informed consent was obtained from each subject prior to evaluations performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Subjects were provided with a copy of the signed and dated informed consent form (ICF).

With respect of treatment decisions, no further information needed to be provided to patients that would go beyond the doctor's usual professional obligation to provide information.

Participating patients were informed about the collection and evaluation of data in this non-interventional study and they had to consent in participation in writing. Patients received a written copy of the patient information and a copy of the dated and signed consent form. The physician documented the patient's informed consent in the patient's medical records.

Patients were allowed to withdraw their consent to participation in the non-interventional study at any time at their own request and without giving any reasons. A withdrawal would not affect their further treatment.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

5.1. Investigators

A total of 171 neurology specialist study sites participated in the study (i.e., were enabled to enroll patients), a total of 160 study sites enrolled subjects. In addition, 172 imaging specialist study sites participated in the study. A list of all study sites that participated is located in the Sponsor’s study file (see Appendix B).

The scientific expert of the study was:

[redacted]

The signature of the scientific expert is provided in Appendix D.

5.2. Study Committees

5.2.1. Study Advisory Committee

The study advisory committee (steering committee) advised on study design and data analysis, reviewed and discussed the interim analyses, and provided scientific and medical advice.

The members of the study advisory committee are presented in Appendix B.

5.3. Vendors

A list of vendors and contractors that had responsibilities for study conduct, and data handling, analysis, and reporting are presented in Table 5.

Table 5: Vendors That Participated in Study GER-TYS-14-10626

Vendor Name	Vendor Address	Responsibilities
[redacted]	[redacted]	Study management / monitoring, statistical analysis, data evaluation, and report writing
[redacted]	[redacted]	eCRF provider, database and data collection, data management
[redacted]	[redacted]	MRI data processing

6. STATISTICAL ANALYSIS PLAN

The following information is taken from the Statistical Analysis Plan (SAP) (version 1.0 of 04 June 2020), which can be found in Appendix C.

The analyses were generated using the SAS software, version 9.2.

6.1. Analysis Populations

Only patients who provided informed consent were included into any analysis population. Two analysis populations were defined according to the SAP:

1. Analysis Set **"Treated patients" (TRP)** which was used for the safety analyses and was defined by:
    - Informed consent provided and
    - at least one dose of natalizumab after enrolment.
2. The **"Full analysis set" (FAS)** which was used for analyses of effectiveness and was defined by:
    - belonging to population "treated patients" (see above) and
    - adherence to all selection criteria (i.e., the three inclusion criteria, the four exclusion criteria, and the three criteria regarding patients informed consents),
    - at least one post-baseline visit documented.

A propensity score matched (PSM) subset of the FAS was used for selected effectiveness analyses (see section 6.2.2).

6.2. Statistical Methods for Study Endpoints

6.2.1. Descriptive analyses

Categorical data were analyzed by presenting frequency tables (absolute and relative frequencies for non-missing data). For continuous data the sample statistics mean, standard deviation, median, minimum and maximum, and quartiles were calculated. For incidence rates exact 95% confidence intervals were presented, if appropriate.

Data measured several times during the study were analyzed by time point presenting absolute differences to baseline for continuous data and shift tables for categorical data. The scheduled visits as documented by the investigators were used as time points (Note: the data management proved, that the scheduled intervals were adhered to).

Time-to-event data (e.g. time on natalizumab) were evaluated by Kaplan-Meier methods.

Annualized relapse rates (ARR) were calculated by a Negative Binomial Regression model (see section 6.2.9.1).

6.2.2. Propensity score matching

To address for possible confounding variables the patients were propensity score matched 1:1 for STAY versus SWITCH in an additional analysis for the outcome parameters ARR and Expanded Disability Status Scale (EDSS) worsening.

Matching was performed according to the greedy-method (using the widely-used SAS Macro %gmatch (Mayo Clinic, http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros): The closest SWITCH patient was selected on the basis of a logistic propensity model for natalizumab discontinuation using the characteristics:

- Disease duration,
- Number of MS relapses prior to natalizumab,

- Only for ARR analysis but not for EDSS (worsening) analysis: EDSS at study start,
- Region (by zip code of centers, pooling if necessary),
- Age,
- Gender,
- Number of prior MS therapies (before enrolment),
- Number of natalizumab infusions before study enrolment.

For the subset of matched STAY versus SWITCH patients the outcome measures ARR and EDSS worsening were displayed in addition.

6.2.3. Cohorts and subgroups

All data were presented separately (and in total) for the three cohorts "STAY" versus "SWITCH" versus "INDETERMINABLE".

The three cohorts were defined as follows:

STAY cohort: All patients who continued natalizumab therapy until the end of study at Month 36 or at least for 1000 days. In these patients no discontinuation of natalizumab or onset of subsequent MS medication was documented.

SWITCH cohort: All patients who discontinued natalizumab therapy at any time until the study end at Month 36.

INDETERMINABLE cohort: All patients without any natalizumab discontinuation documented who discontinued or dropped out from the study before day 1000 (approximately Month 33).

For the SWITCH cohort the periods **before versus after natalizumab discontinuation** were analyzed when data were displayed during the study course (called **SWITCH–ON** and **SWITCH–OFF**, respectively**)**. The baseline of the SWITCH-OFF period was the visit when natalizumab discontinuation was (first) reported.

Selected analysis tables were presented for the selected subgroups as described in the SAP (Appendix C).

6.2.3.1. Definition of PML risk groups

The Progressive Multifocal Leukoencephalopathy (PML) risk (at study enrolment) was classified as:

- **No risk**, if anti-(John Cunningham virus)JCV antibody status was negative
- **Low risk**, if anti-JCV antibody index between 0.4 and 0.9
- **High risk**, if anti-JCV antibody index ≥ 1.5 or positive JCV status in patient pretreated with immune suppressive therapies
- **Intermediate risk**, in all other cases (e.g. anti-JCV antibody status/index unknown or index between 0.9 and 1.5)

Before deriving these categories the data on JCV status were corrected according to 6.2.10.1.1.

6.2.3.2. Definition of extended interval dosing subgroups

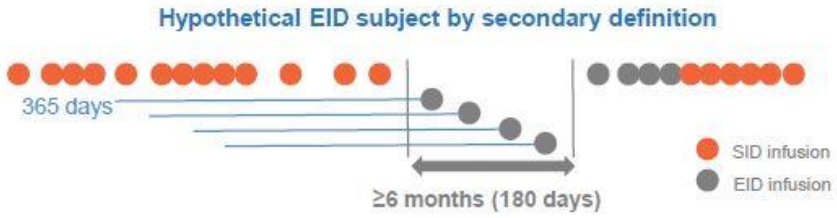
Extended interval dosing (EID) was derived according to (4) presented at ACTRIMS Forum 2018; San Diego, CA; February 1-3, 2018.

Three definitions of EID were used to capture different aspects of EID.

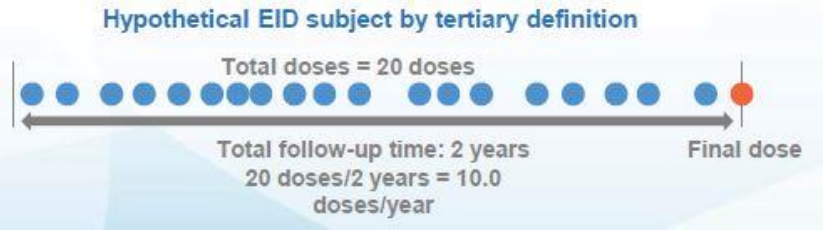
All definitions included known anti-JCV antibody positive patients and excluded patients with dosing gap (>12 weeks) or overdose (<3 weeks).

- Primary definition: tests whether dosing history in the last 18 months of natalizumab treatment affects PML risk
  - EID was defined as ≤15 infusions in the last 18 months (548 days)
  - Standard interval dosing (SID) was defined by >15 infusions in the last 18 months (548 days)

- Secondary definition: tests whether an EID period occurring anytime in the dosing history affects PML risk
  - An EID infusion was an infusion with ≤10 doses occurring in the prior 365 days
  - EID patients were defined as those who had consecutive EID infusions for ≥6 months after the first EID infusion
  - SID was defined as >10 doses over 365 days prior to any infusion



- Tertiary definition: tests whether a primarily EID dosing history affects PML risk
  - EID was defined as ≤10 infusions/year when considering the total number of infusions divided by total follow-up time
  - SID was defined as >10 infusions/year when considering the total number of infusions divided by total follow-up time



The tertiary EID definition was chosen as most meaningful definition when additional subgroup comparisons were performed.

6.2.4. Analysis of longitudinal data

The clinical data EDSS, MS symptoms, Magnetic Resonance Imaging (MRI), monitoring of laboratory values should be documented approximately every 3 months. Patient reported outcomes (TSQM-9, FSMC, HADS, MSIS-29, WPAI-MS) and the SDMT were scheduled approximately every 6 months. During data management the adherence to the scheduled intervals was checked. Thus, for longitudinal data frequency tables respectively sample statistics are displayed at the scheduled time points.

For continuous data, changes from baseline (i.e. start of study) were presented in addition.

6.2.5. Handling of implausible values

Although great efforts were taken by data management to check and clean the documented data some values may be implausible or contradictory.

Therefore, data correction was performed when the analysis data was derived from the raw data. During this step not only data corrections but also calculation of sum scores, setting of analysis markers and replacement of incomplete dates were done. By comparison of raw versus analysis data all modifications were traceable. All data modifications of this step might be described in a separate document, if required.

6.2.6. Handling of missing values

In general, missing values were not replaced for this analysis except incomplete dates.

Incomplete dates were replaced by the mid of month or year (15^{th} for missing days, June for missing months).

For EDSS, missing scores, which were expected in a relevant amount due to the fact that in practice the EDSS assessment would not take place every 3 months, were replaced by the last available EDSS score (=last observation carried forward [LOCF] method). Replacement of missing EDSS scores was only done for visits which took place but not for future visits or when the patient was withdrawn from the study.

For anti-JCV antibody analysis, missing values were replaced by the last observation carried forward (LOCF method).

In the logistic regression model to identify prognostic factors for natalizumab discontinuation (see section 6.2.8.2), missing continuous values were replaced by multiple imputation (seed=2020, k=5 imputations), while missing values in categorical variables were handled as separate category.

For analyses of ARR (see section 6.2.9.1), missing continuous values (including the no. of MS relapses prior to natalizumab, disease duration, treatment duration) were replaced by multiple imputation (seed=2019, k=5 imputations), while missing values in categorical variables were handled as separate category.

For patient reported outcomes the respective questionnaire instructions were used to account for missing values (see section 6.2.11). Here the scores were calculated (averaged) from the non-missing items. The number of missing items was restricted to 1, 0, 1 per subscale or respectively 50% for TSQM-9, FSMC, HADS, or MSIS-29.

6.2.7. Analysis of demographic and anamnestic parameters

Demographic, anamnestic and disease characteristic data were analyzed descriptively by frequency tables and/or sample statistics as appropriate (see SAP, Appendix C).

6.2.7.1. Comorbidities

Frequencies for patients with at least one comorbidity, at least one comorbidity in the respective Medical Dictionary for Regulatory Affairs (MedDRA) system organ class (SOC) and at least one comorbidity in the respective MedDRA preferred term (PT) (within SOC) were calculated.

Comorbidities were to be documented as pre-specified terms (drop-down-list in eCRF), the pre-specified terms were: Depression; hypertension; thyroid dysfunction; muscle disorder/ joint disorder; nervous (system) disorder; allergy; gastrointestinal disorder; adiposity; diabetes mellitus; eye disorder; dermal symptoms; autoimmune disease; cardiac insufficiency; urinary tract infection; cardiac arrhythmia; oncological disease; renal dysfunction; lymphatic system disorder; fungal infection; hair loss; hepatitis; herpes infection; opportunistic infection; human immunodeficiency virus (HIV); liver cirrhosis; PML; pancreatitis; pneumonia; tuberculosis. For the category “other” a free text entry was possible. Both, the free text entry and the pre-specified terms were coded according to MedDRA (for details on coding of pre-specified terms please refer to Appendix C, SAP).

6.2.7.2. Opportunistic infections

Opportunistic infections were documented as free text entries. These verbatim terms were coded according to MedDRA (current version). Because ≤20 opportunistic infections were documented, they were listed only.

6.2.8. Analysis of natalizumab discontinuation

The time on natalizumab (from treatment start as well as from study start) was analyzed by Kaplan-Meier estimates and curve. Patients for whom no natalizumab discontinuation was reported (e.g., patients who stayed on natalizumab or who were lost-to-follow up) were censored with the date of their last visit. Programming details to derive natalizumab discontinuation and exposure are provided in the SAP.

6.2.8.1. Competing risk analysis for natalizumab discontinuation due to safety reasons

The risk of discontinuing natalizumab for safety reasons (i.e., positive anti-JCV antibody test, PML risk, or adverse events) was curtailed due to the competing risk that a patient was discontinued due to non-safety reasons (i.e. reasons other than mentioned before, which includes

not specified reasons). To adjust the risk for natalizumab discontinuation due to safety reasons for the incidence of competing events, the cumulative incidence function was calculated by a competing risk analysis.

Proc lifetest with the option eventcode=1 of SAS v9.4 was used. The Summary of failure outcomes, CIF graph and estimates for specific time points were presented.

6.2.8.2. Prognostic factors for natalizumab discontinuation

The logistic regression model to identify prognostic factors for natalizumab discontinuation included the following factors:

- PML risk categories at baseline (no risk; low risk; intermediate risk; high risk)
- Duration of exposure to natalizumab in days (including time before study start)
- Duration of disease in years (since diagnosis)
- Prior immunosuppressive treatment (no versus yes)
- Number of MS relapses during natalizumab treatment (0; 1; ≥2 relapses)
- Time since last relapse before discontinuation/end of study in days
- Last EDSS value before discontinuation/end of study (handled as continuous parameter)
- Last treatment satisfaction/TSQM) value before discontinuation/end of study
- EID according to tertiary definition (yes; no; not calculable)

No interaction terms were considered. A logistic regression model including all of these parameters was calculated as well as a model with backward parameter selection.

Missing continuous values were replaced by multiple imputation (seed=2020, k=5 imputations), while missing values in categorical variables were handled as separate category.

The dependent variable was natalizumab discontinuation or persistence. Type 3 sum of squares were considered.

6.2.9. Analysis of clinical efficacy endpoints

6.2.9.1. Annualized relapse rates (ARR)

The number of relapses prior to natalizumab and after natalizumab start but before study inclusion were analyzed by patient with a frequency table (n, percentages) and overall by total numbers. The corresponding observational times (patient-years) were displayed by sample statistics and the total value.

Annualized relapse rates for natalizumab therapy respective for follow-up medication were estimated for three periods (1. Prior to study; 2. After enrolment until natalizumab discontinuation; and 3. After natalizumab discontinuation) using a negative binomial regression model with independent correlation.

Covariates were the following baseline data: sex, EDSS total score (<3 vs. ≥3), disease duration (<8 vs. ≥8), number of previous DMTs (0 vs. 1 vs. ≥2) and treatment duration (<3 vs. ≥3). The offset variable was the log of the respective observational period in years.

The estimated ARRs and the associated 95% CIs were reported. ARRs were calculated in total as well as for STAY, SWITCH-ON and SWITCH-OFF cohorts. If mentioned in the SAP, ARRs were also calculated for selected subgroups.

6.2.9.2. Total Expanded Disability Status Scale (EDSS) score

The EDSS score was documented by the investigators as a total score (one value) and/or as individual scores of the individual functional systems (multiple values). When both versions were documented, the score resulting from individual functional systems was used for analysis.

The total EDSS score was displayed by sample statistics and frequency tables for the following time points:

Time point	STAY	SWITCH-ON	SWITCH-OFF
Start of natalizumab (retrospectively collected)	X	X	Not applicable
Baseline	Start of study	Start of study	Last value before natalizumab discontinuation
Month 3, and all subsequent visits at 3 months intervals	X	X	X
Last value	Last value after baseline	Last value after baseline before natalizumab discontinuation	Last value after natalizumab discontinuation

Changes were calculated as differences from baseline to Month 3 (and to subsequent visits up to month 36), and to the last value and displayed by sample statistics. In addition, the time between first and last EDSS assessment was analyzed by sample statistics. The EDSS course during study was graphically displayed by boxplots.

<u>EDSS Worsening</u>

An EDSS worsening was defined by:

- if baseline EDSS was >5.5 and change from baseline to last value was > 0.5 points
- if baseline EDSS was > 0 and ≤5.5 and change from baseline to last value was > 1 point
- if baseline EDSS was =0 and change from baseline to last value was ≥ 1.5 points

The incidence of EDSS worsening was displayed for STAY, SWITCH-ON and SWITCH-OFF.

If mentioned in the SAP incidences for EDSS worsening were also calculated for subgroups.

Frequency of EDSS worsening was additionally presented for the SWITCH vs. STAY subcohorts after propensity-score matching to address possible confounding variables in this analysis (see 6.2.2).

6.2.9.3. Symptoms of multiple sclerosis

A frequency table was provided analyzing how many patients were suffering at study start (STAY and SWITCH) from at least one MS symptom, respectively from the unique symptoms.

This table was similarly repeated for the symptoms which improved/worsened or newly occurred at any time during the study after baseline.

6.2.10. Analysis of other endpoints

6.2.10.1. JCV antibody status and index

6.2.10.1.1. Standardization / data correction

To standardize the JCV statuses according to the anti-JCV antibody indices the following data corrections were performed:

- If anti-JCV antibody index < 0.4 then JCV status was corrected into negative.
- If anti-JCV antibody index ≥ 0.4 then JCV status was corrected into positive.

6.2.10.1.2. Handling of missing values

It was expected that not at each visit the anti-JCV antibody status respectively the anti-JCV antibody index would be measured. Therefore, missing values were replaced by the last available value. This method is known as LOCF.

6.2.10.1.3. Frequency of JCV tests

For each visit the kind of JCV test was displayed, using the JCV data “as observed” but not the data completed by LOCF:

- Anti-JCV antibody index was available
- Anti-JCV antibody status index was available only
- No information on anti-JCV antibody status available

6.2.10.1.4. Intervals between JCV tests

The duration of intervals between JCV tests was displayed by sample statistics. N was here not the number of patients but the number of intervals.

6.2.10.1.5. Change of anti-JCV antibody index

The values (completed by LOCF) were displayed by sample statistics for the following time points:

- Baseline, i.e. start of study for STAY and SWITCH-ON respectively last value before natalizumab discontinuation for SWITCH-OFF

- Month 3, 6, and every 3 months thereafter up to month 36
- Last value after baseline. This means, if no post-baseline value existed (especially for SWITCH-OFF) “last value” and the “change to last value” were not available.

The change between baseline and last anti-JCV antibody status (replaced by LOCF) was displayed by a shift table for negative versus positive cases.

6.2.10.1.6. Biomarker

Analysis of biomarkers was omitted because only few data were available and this objective was assessed of minor relevance by the study steering committee.

6.2.11. Analysis of patient reported outcomes (PRO)

The (sub)scores of the patient reported outcomes were analyzed separately by sample statistics and/or frequency tables according to the categories which are described below. Each visit was displayed separately for the cohorts STAY and SWITCH, with the cohort SWITCH being split into SWITCH-ON and SWITCH-OFF groups by visit.

To display changes from baseline the intra-individual differences between the last available value after baseline and the baseline score (=start of study) were calculated. The changes from baseline could only be calculated when post-baseline values were available.

6.2.11.1. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

In this study the German TSQM-9 was used. The TSQM-9 is an abbreviated 9-item questionnaire which was derived from the TSQM Version 1.4 by omitting the five items of the “side effects” domain.

The 9-item-scale was scored on Likert-scales as follows: 1 (extremely dissatisfied) to 7 (extremely satisfied) for all items except 7 and 8, which were scored from 1 (extreme dissatisfied) to 5 (extremely satisfied). The scores of each domain were summed and an algorithm was used to create a score of 0 to 100. Higher scores indicated greater satisfaction on that domain.

The scales of the TSQM-9 included the effectiveness scale (questions 1 to 3), the convenience scale (questions 4 to 6) and the global satisfaction scale (questions 7 to 9).

TSQM-9 scale raw scores were computed by adding the items loading on each factor.

The TSQM-9 scales were standardized to 0–100 range as follows:

(Raw-score – lowest possible raw score) divided by greatest possible range of raw scores. This provided a transformed score between 0 and 1 that should be multiplied by greatest possible value for the new score (=by 100) as described below.

If more than one item was missing in any of the subscales, this subscale was considered invalid for that respondent (more details on calculation are provided in the SAP, Appendix C).

The 3 subscale scores were analyzed separately by sample statistics. Each visit was displayed and intra-individual differences between last available and baseline score were analyzed. For the first interim analysis only baseline (=visit 1) values were displayed.

6.2.11.2. Fatigue Scale for Motor and Cognitive Functions (FSMC)

This 20-item FSMC scale (5) was scored on 5-point-Likert-scales (ranging from "does not apply at all" to "applies completely") producing a score between 1 and 5 for each scored question.

The FSMC comprises 2 subscales:

The **cognitive** subscale: Item 1, 4, 7, 8, 11, 13, 15, 17, 18, and 20

The **motor** subscale: Item 2, 3, 5, 6, 9, 10, 12, 14, 16, and 19

The FSMC total score was the sum score over all 20 items and ranges from minimum 20 ("no fatigue at all") to maximum 100 ("severest grade of fatigue").

According to the calculation guidelines, the total score or the subscores were not calculated if one or more contributing items were missing.

The FSMC total score as well as both subscales (cognitive and motor fatigue) could categorized by severity of fatigue as follows:

FSMC total score (range 20 – 100)	No fatigue (20 to 42) Mild fatigue (43 to 52) Moderate fatigue (53 to 62) Severe fatigue (≥ 63)
FSMC cognitive subscore (range 10 – 50)	No cognitive fatigue (10 to 21) Mild cognitive fatigue (22 to 27) Moderate cognitive fatigue (28 to 33) Severe cognitive fatigue (≥ 34)
FSMC motor subscore (range 10 – 50)	No motor fatigue (10 to 21) Mild motor fatigue (22 to 26) Moderate motor fatigue (27 to 31) Severe motor fatigue (≥ 32)

6.2.11.3. Hospital Anxiety and Depression Scale (HADS)

The HADS consisted of 14 questions forming two subscales "anxiety" (HADS-A) and "depression" (HADS-D).

HADS-A (anxiety score) was calculated as sum of scores for questions 1, 3, 5, 7, 9, 11, and 13. Most questions were scored as 3–2–1–0 points, only questions 7 and 9 were scored as 0–1–2–3. Higher score values indicated more pronounced anxiety.

HADS-D (depression score) was calculated as sum of scores for questions 2, 4, 6, 8, 10, 12, and 14. The questions (2, 4, 12 and 14) were scored as 3–2–1–0 points. The remaining questions (6, 8, and 10) were scored as 0-1–2–3. Higher scored values indicated more pronounced depression.

The HADS-A and HADS-D could only be calculated as long as only one question per subscale was missing. In this case the average of the remaining 6 questions of the subscale rounded up was used to impute the missing value. Both subscores, HADS-A and HADS-D, ranged from 0 to

21. Even though HADS-A and HADS-D were ordinal scaled, sample statistics were presented because sample statistics were also presented in literature.

6.2.11.4. Multiple Sclerosis Impact Scale-29 items (MSIS-29)

The MSIS-29 questionnaire in its second version (version 2) was used and the MSIS-29 scores were calculated according to Hobart (6-8).

Responses used a 4-point-Likert scale ranging from 1 (not at all) to 4 (extremely). The two subscales, **physical impact** scale (items 1-20) and **psychological impact** scale (items 21-29), were calculated by summing individual items. Scores on the physical impact scale ranged from 20 to 80, those of the psychological impact scale from 9 to 36, with lower scores indicating less impact of MS and higher scores indicating greater impact.

In case of missing items, each score was calculated if at least 50% of the items were completed. Then, a respondent-specific mean score from the completed items was calculated. If more than half of the items were missing the score was not calculated.

6.2.11.5. Work productivity and activity impairment questionnaire (WPAI)

In this study the WPAI-MS, version 2.0 was used (9, 10).

The WPAI yielded four types of scores: 1. Absenteeism (work time missed). 2. Presenteesism (impairment at work / reduced on-the-job effectiveness). 3. Work productivity loss (overall work impairment / absenteeism plus presenteeism). 4. Activity Impairment.

The WPAI outcomes were expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes and calculated as follows

Questions (Q):

Q1 = currently employed; Q2 = hours missed due to health problems; Q3 = hours missed other reasons; 4 = hours actually worked; Q5 = degree health affected productivity while working; Q6 = degree health affected regular activities.

The following scores (WPAI:MS) were derived:

- Percent work time missed due to health: Q2/(Q2+Q4)
- Percent impairment while working due to health: Q5/10
- Percent overall work impairment due to health: Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)*(Q5/10)]
- Percent activity impairment due to health: Q6/10

The scores were multiplied by 100 to express in percentages.

6.2.12. Analysis of adverse events

Treatment emergent AEs were defined as AEs starting between subject's start of the study and 90 days after end of subject's natalizumab therapy. In addition, Biogen might have considered some other events which occurred after 90 days of discontinuing natalizumab therapy treatment emergent as well. The analyses for treatment emergent AEs were described in more detail in the SAP.

AEs were coded and checked by the department of pharmacovigilance of Biogen. These data were provided separately and they were the basis for the AE evaluation.

6.3. Interim Analyses

Annual interim analyses were performed (overall: 6 interim analyses (11-15)). The results had no consequences on the study conduct or the final analysis of the study. Therefore, and due to the descriptive nature of the study, no multiplicity adjustment of significance level was needed.

6.4. Determination of Sample Size

No hypothesis was planned to be tested. There was no formal sample size determination performed.

Due to the study design, a high level of drop out was expected. Hence, assuming a Poisson distribution and 3 years of follow-up, 1260 patients were planned to be included in the study to adjust for study dropouts and patients restarting natalizumab treatment in order to detect differences with an alpha level of 0.05 (1). The participation of approximately 200 study centers was planned.

7. STUDY SUBJECTS

7.1. Subject Accountability

7.1.1. Study centers / subjects and study period

This study was conducted from 20 August 2014 (first subject in) to 12 December 2019 (last subject out) (post-text Table 1.2). A total of 1264 subjects were enrolled at 160 study centers, of whom 1227 subjects gave informed consent and 1215 subjects received at least one dose of natalizumab (post-text Table 1.1a).

Of the 1264 subjects enrolled, 1191 subjects (enrolled at 157 study centers) fulfilled the definition criteria for the **TRP** set (IC provided and received at least one dose of natalizumab after enrolment), 698 of whom were classified as belonging to the STAY cohort, 396 to the SWITCH cohort, and 97 to the INDETERMINABLE cohort (post-text Table 1.1b and post-text Table 1.3.2), for cohort definitions see section 6.2.3. The mean (SD) number of subjects enrolled per center was 7.6 (11.2) subjects, 1st quartile (Q1) 3.0 subject, median 4.0 subjects, 3rd quartile (Q3) 8.0 subjects, and ranging from a minimum of 1 subject to a maximum of 110 subject (post-text Table 1.1b).

All subjects of the TRP with adherence to all selection criteria (i.e., the three inclusion and the four exclusion criteria) and with at least one post-baseline visit documented contributed to the **FAS**. Two (2) subjects were excluded from the FAS, both were in the INDETERMINABLE cohort, because they violated one of the inclusion criteria (“study diagnosis” in 1 subject, and at least “12-month pretreatment” with natalizumab in another subject). Thus, the FAS comprised 1189 subjects (698 STAY cohort, 396 SWITCH cohort, and 95 INDETERMINABLE cohort) (post-text Table 1.1c, post-text Table 1.3.2 and Table 1.3.3).

As described in section 6.2.2, the FAS patients were additionally **propensity score matched** (PSM) for STAY versus SWITCH for the outcome parameters ARR and EDSS worsening. After 1:1 matching, 290 SWITCH patients could be matched to 290 patients of the STAY cohort.

The patient disposition is shown in Table 6.

Table 6: Patient disposition

Number of patients	STAY	SWITCH	INDETERMI-NABLE	Total
Enrolled	712	412	140	1264
Gave informed consent	698	404	125	1227
Received at least one dose of NTZ	712	404	99	1215
Included in TRP [a]	698	396	97	1191
Included in FAS [b]	698	396	95	1189
Included in PSM [c]	290	290	0	580

FAS = Full Analysis Set; NTZ = Natalizumab; PSM = Propensity Score Matched; TRP = Treated patients.
a: TRP, if informed consent was provided and patient received at least on dose of natalizumab after enrolment.
b: FAS, if TRP and adherence to all selection criteria and at least one post-baseline visit documented
c: 1:1 PSM matching between STAY and SWITCH patients of the FAS population. Baseline parameters included into the propensity score model are described in the Statistical Analysis Plan.
Source: Post-text Table 1.3.2

The reasons (including frequencies) for (first) **natalizumab discontinuation** are presented in post-text Table 1.4.2a (TRP) and 1.4.2b (PSM), in addition, they are summarized in Table 7. Patients who discontinued natalizumab before regular end of study at month 36 were not discontinued from study at once; they continued study data collection on subsequent treatment.

Overall, 396 patients (33.2%) of the TRP set discontinued natalizumab therapy at any time up to study end at Month 36. The most common reasons (≥10.0%) were “PML risk” in 185 patients (46.7%), “no reason specified” in 71 patients (17.9%), “requested by patient” 53 patients (13.4%), and “positive JCV antibody test” 48 patients (12.1%).

In the PSM, reasons and relative frequencies for (first) natalizumab discontinuation were similar to those in the total TRP; the most common were “PML risk” (44.8%), “no reason specified” (19.0%), “request by patient (11.4%)”, and “positive JCV test” (12.4%).

Table 7: Frequency and reasons for natalizumab discontinuation

Parameter	Total	
	TRP (N=1191)	**PSM (N=580)**
Natalizumab discontinuation, n (%)		
No	795 (66.8)	290 (50.0)
Yes	396 (33.2)	290 (50.0)
Reason(s) for first NTZ discontinuation, n (%) [a]		
Ineffectiveness	34 (8.6)	26 (9.0)
Adverse events/side effects	3 (0.8)	3 (1.0)
(Planned) pregnancy	6 (1.5)	5 (1.7)
Positive JCV antibody test	48 (12.1)	36 (12.4)
Requested by patient	53 (13.4)	33 (11.4)
Informed consent withdrawn	2 (0.5)	2 (0.7)
Non-compliance	1 (0.3)	0 (0.0)
PML risk	185 (46.7)	130 (44.8)
Other clinical/medical reasons	38 (9.6)	26 (9.0)
No reason specified	71 (17.9)	55 (19.0)

JCV = John-Cunningham virus; NTZ = Natalizumab; PML = Progressive multifocal leukoencephalopathy; PSM = Propensity score matching; TRP = Treated patients
a: Relative frequencies are based on the number of patients who discontinued natalizumab.
Source: Post-text Table 1.4.2a and Table 1.4.2b

The reasons (including frequencies) for **premature study discontinuation** are presented in post-text Table 1.5.1a and Table 1.5.2a **for TRP**, in addition, they are summarized in Table 8.

Overall, a total of 233 patients (19.6%) prematurely discontinued from study for any reason, the most common reasons (≥3.0%) were “other reason” with 64 patients (5.4%), “patient lost to follow-up” with 42 patients (3.5%), “switch to other physician” with 41 patients (3.4%), and “inclusion in other study” with 41 patients (3.4%).

The drop-out rate was higher among the SWITCH patients (35.9%, 142 patients) compared with STAY patients (1.6%, 11 patients), and highest in the INDETERMINABLE cohort (82.5%, 80 patients), what can be explained by the definition of this cohort (which was also resulting from cohort definitions).

The reasons (including frequencies) for **premature study discontinuation** in the **PSM** are presented in post-text Table 1.5.1b and Table 1.5.2b (PSM).

The overall drop-out rate in the total PSM (N=580) was 19.8% (115 patients), 2.1% (12 patients) completed the study, in 78.1% (453 patients) completion status was unknown.

The most common reasons (≥3.0%) for premature study discontinuation in total PSM were: “Other reason” with 28 patients (4.8%), “patient lost to follow-up” with 27 patients (4.7%), “informed consent withdrawn” with 23 patients (4.0%), and “inclusion in other study” with 24 patients (4.1%) (post-text 1.5.2b).

Again, the drop-out rate was higher among the SWITCH patients (38.6%, 112 patients) compared with STAY patients (1.0%, 3 patients) (post-text 1.5.1b).

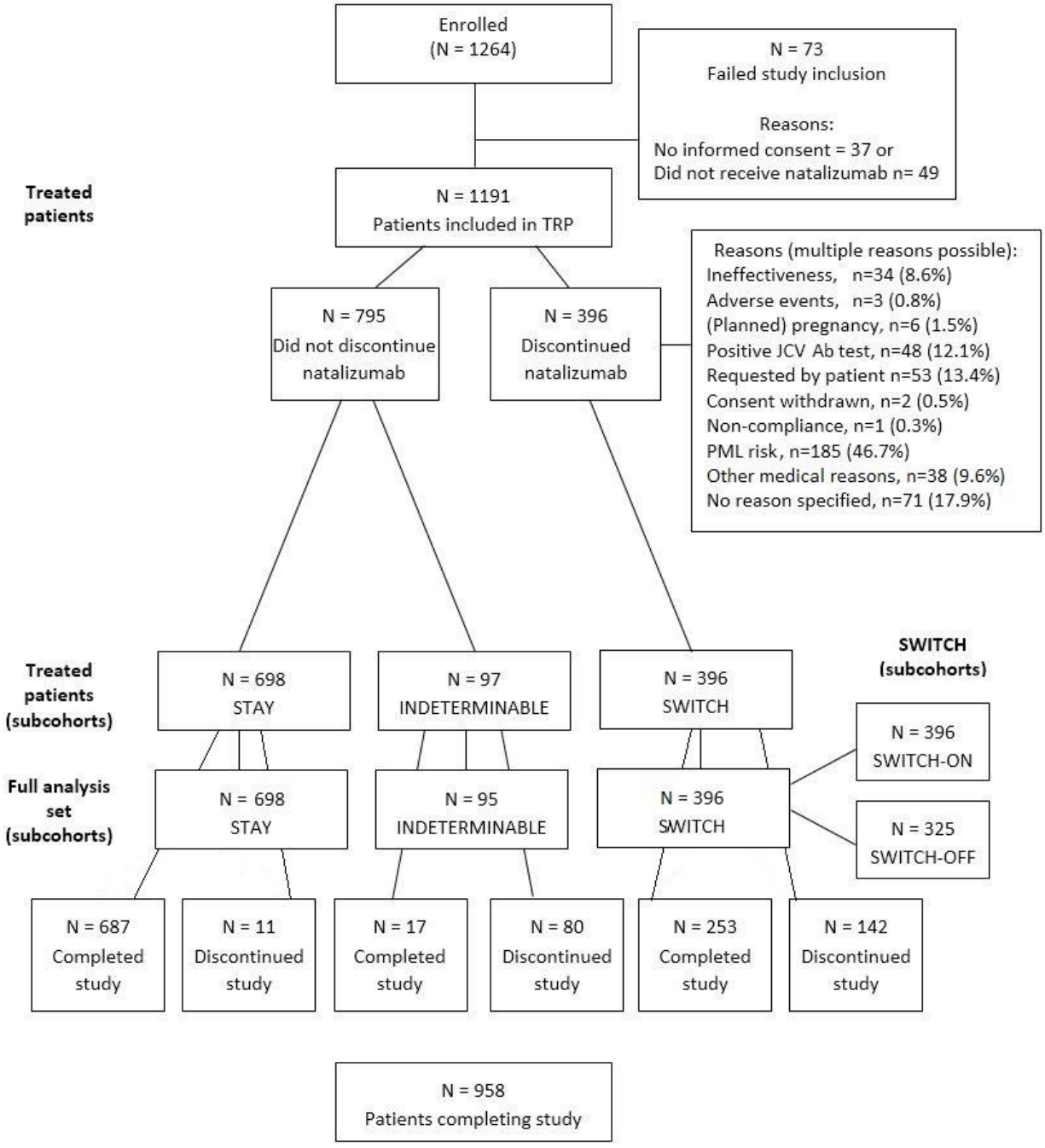
Table 8: Premature study discontinuation

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Study discontinued prematurely, n (%)				
No (completer)	5 (0.7)	14 (3.5)	0 (0.0)	19 (1.6)
Yes (drop-out)	11 (1.6)	142 (35.9)	80 (82.5)	233 (19.6)
Unknown	682 (97.7)	240 (60.6)	17 (17.5)	939 (78.8)
Reason(s) for premature study discontinuation, n (%) [a]				
Any reason	**11 (1.6)**	**142 (35.9)**	**80 (82.5)**	**233 (19.6)**
Screening failure	0 (0.0)	0 (0.0)	2 (2.1)	2 (0.2)
Adverse events/drug reaction	0 (0.0)	8 (2.0)	0 (0.0)	8 (0.7)
Switch to another physician	2 (0.3)	12 (3.0)	27 (27.8)	41 (3.4)
Physician's decision	0 (0.0)	17 (4.3)	7 (7.2)	24 (2.0)
Patient lost to follow-up	2 (0.3)	28 (7.1)	12 (12.4)	42 (3.5)
Informed consent withdrawn	0 (0.0)	27 (6.8)	7 (7.2)	34 (2.9)
Progression of MS	0 (0.0)	6 (1.5)	0 (0.0)	6 (0.5)
Other reasons	6 (0.9)	34 (8.6)	24 (24.7)	64 (5.4)
Inclusion in another study	1 (0.1)	31 (7.8)	9 (9.3)	41 (3.4)

MS = Multiple Sclerosis; TRP = Treated patients
a: Relative frequencies are based on the number of patients who discontinued study.
Source: Post-text Table 1.5.1a and Table 1.5.2a

Post-text Table 1.4.1a (TRP) and Table 1.4.1b (PSM) show summary statistics for the observational time per patient before and after matching, the results are additionally presented in Table 9.

Figure 1: Disposition of Patients by Study Population



Source: Post-text Table 1.3.2, Table 1.4.2a, Table 1.4.2b, Table 1.5.1a and Table 1.5.2a.
N = Number of patients.

7.1.2. Observational time and study periods

As described in section 6.2.3, when data were analyzed during the study course, the SWITCH cohort was split into two subsets representing the periods before versus after natalizumab discontinuation (called SWITCH–ON and SWITCH–OFF set, respectively).

The **observational time per patient** (defined as the interval between first and last visit) in the TRP was mean ± SD 36.3 ± 1.8 months in the STAY cohort (N=698); in patients who switched treatment the observational time per patient was mean ± SD 20.4 ± 9.8 months **before** natalizumab discontinuation (SWITCH-ON; N=396), and 12.7 ± 10.7 months **after** natalizumab discontinuation (SWITCH-OFF; N=325).

After matching (PSM), results obtained for the observational time per patient in the STAY cohort were almost identical to pre-matching value, observational time for SWITCH-ON patients was minimally shorter (19.6 ± 9.8 months), whilst it was minimally longer for SWITCH-OFF patients (13.6 ± 11.2 months) compared with TRP (see Table 9).

Table 9: Observational time

Interval between first and last visit (months)	**STAY**	**SWITCH-ON**	**SWITCH-OFF**
		TRP	
	N=698	N=396	N=325
N	698	396	325
Mean ± SD	36.3 ± 1.8	20.4 ± 9.8	12.7 ± 10.7
Median (Q1; Q3)	36.1 (35.4; 37.0)	20.2 (12.2; 28.2)	11.2 (2.4; 22.1)
Min; Max	30.1; 43.3	2.3; 45.1	0.0; 37.9
		PSM	
	N=290	N=290	N=235
N	290	290	235
Mean ± SD	36.3 ± 1.9	19.6 ± 9.8	13.6 ± 11.2
Median (Q1; Q3)	36.1 (35.4; 37.0)	18.7 (12.0; 27.1)	13.3 (2.3; 23.0)
Min; Max	30.6; 43.3	2.3; 45.1	0.0; 37.9

PSM = Propensity score matching; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Source: Post-text Table 1.4.1a and Table 1.4.1b

In addition, Table 10 shows the specific important time intervals in the FAS (e.g., for calculation of the ARRs) by subcohort.

The mean ± SD duration between **start of natalizumab and start of study** (=visit 1) was 3.9 ± 2.6 years in the total FAS with only minor differences between the different subcohorts.

The mean ± SD **duration between start of study (=visit 1) and natalizumab discontinuation** (or last visit, if patient was still exposed to natalizumab at last visit) was 3.0 ± 0.2 years in the STAY cohort (which corresponds to the planned individual observational period) and 1.6 ± 0.8 years in the SWITCH cohort.

The mean ± SD **duration between natalizumab discontinuation and last visit** was 1.1 ± 0.9 years (applicable for SWITCH patients only).

Table 10: Important study specific time intervals (FAS)

Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Time between start of NTZ and start of study (=visit 1) (years)				
N	698	396	95	1189
Mean ± SD	3.9 ± 2.6	3.8 ± 2.7	3.6 ± 2.3	3.9 ± 2.6
Median (Q1; Q3)	3.1 (1.4; 6.5)	2.8 (1.4; 6.3)	3.0 (1.7; 5.2)	3.0 (1.4; 6.4)
Min; Max	1.0; 12.2	1.0; 10.1	1.0; 8.8	1.0; 12.2
Time between start of study (=visit 1) and NTZ discontinuation / last visit (years)				
N	698	396	95	1189
Mean ± SD	3.0 ± 0.2	1.6 ± 0.8	1.6 ± 0.7	2.4 ± 0.9
Median (Q1; Q3)	3.0 (3.0; 3.1)	1.6 (0.9; 2.3)	1.5 (1.1; 2.3)	2.9 (1.8; 3.0)
Min; Max	2.5; 3.6	0.1; 3.8	0.2; 3.5	0.1; 3.8
Time between NTZ discontinuation and last visit (years)				
N	0	325	0	325
Mean ± SD	-	1.1 ± 0.9	-	1.1 ± 0.9
Median (Q1; Q3)	-	1.0 (0.3; 1.9)	-	1.0 (0.3; 1.9)
Min; Max	-	0.0; 3.2	-	0.0; 3.2

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; FAS = Full analysis set
Source: Post-text Table 5.1.1

7.2. Demographics

Table 11 summarizes the demographic characteristics at baseline of the TRP patients. In the total TRP (N=1191), the majority (864, 72.5%) of patients were women and patients' mean ± SD age was 39.1 ± 10.0 years (median 38.0 years ranging from 18.0 to 76.0 years). Mean ± SD body weight was 73.1 ± 16.7 kg (median 70.0 kg ranging from 35.0 to 157.0 kg). Mean ± SD body mass index was 24.8 ± 5.1 kg/m^2 (median 23.8 kg/m^2 ranging from 12.9 to 55.5 kg/m^2).

There was a marked preponderance of females across all cohorts. Demographic data differed between STAY and SWITCH cohorts, with a greater proportion of women (74.2% vs. 69.9%) and slightly lower patients' age (mean ± SD 38.7 ± 9.9 years vs. 40.3 ± 10.2 years) in STAY compared with SWITCH cohort.

Table 12 summarizes demographic data of patients matched by propensity score for the STAY and SWITCH cohorts. After matching, these gender distribution and mean age approximated each other in the subcohorts (73.4% women vs. 70.0% women and 39.6 ± 10.0 years vs. 39.9 ± 10.2 years; STAY vs. SWITCH, respectively) (PSM).

Table 11: Demographic data at baseline (TRP)

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Gender, n (%)				
Male	180 (25.8)	119 (30.1)	28 (28.9)	327 (27.5)
Female	518 (74.2)	277 (69.9)	69 (71.1)	864 (72.5)
Age (years)				
N	698	396	97	1191
Mean ± SD	38.7 ± 9.9	40.3 ± 10.2	37.5 ± 9.9	39.1 ± 10.0
Median (Q1; Q3)	38.0 (31.0; 46.0)	40.0 (33.0; 48.0)	36.0 (30.0; 45.0)	38.0 (31.0; 47.0)
Min; Max	18.0; 76.0	19.0; 65.0	19.0; 61.0	18.0; 76.0
Height (cm)				
N	687	392	93	1172
Mean ± SD	171.1 ± 8.8	171.9 ± 8.8	171.6 ± 9.0	171.4 ± 8.8
Median (Q1; Q3)	170.0 (165.0; 176.0)	170.0 (165.0; 178.0)	170.0 (167.0; 175.0)	170.0 (165.0; 177.0)
Min; Max	150.0; 201.0	150.0; 196.0	155.0; 198.0	150.0; 201.0
Weight (kg)				
N	686	393	92	1171
Mean ± SD	72.3 ± 16.6	74.1 ± 17.2	73.7 ± 14.8	73.1 ± 16.7
Median (Q1; Q3)	70.0 (60.0; 80.0)	71.0 (62.0; 82.0)	71.0 (62.0; 85.0)	70.0 (61.0; 82.0)
Min; Max	40.0; 157.0	35.0; 145.0	44.0; 115.0	35.0; 157.0
Body mass index (kg/m^2)				
N	686	392	92	1170
Mean ± SD	24.6 ± 5.1	25.0 ± 5.3	25.1 ± 4.8	24.8 ± 5.1
Median (Q1; Q3)	23.5 (21.2; 26.7)	24.0 (21.6; 26.8)	24.3 (21.6; 27.8)	23.8 (21.3; 26.8)
Min; Max	15.2; 55.5	12.9; 51.4	14.5; 40.7	12.9; 55.5

Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Source: Post-text Table 2.1a

The school education and vocational education as well as occupational status of the TRP patients is summarized (by German terms) in Post-Text Table 2.1a. Overall, with regards to school education the 3 most commonly specified categories were, “Mittlere Reife” [secondary education] in 434 patients (36.5%), “Abitur/Fachhochschulreife” [upper secondary education; qualification for university entrance] in 339 patients (28.5%), and “Hauptschulabschluss” [lower secondary education] in 149 patients (12.5%).

Overall, the 3 most commonly specified occupation categories (excluding the category "unknown", 6.2%) were “voll berufstätig” [employed full-time] with 412 patients (34.6%), “Teilzeit” [employed part-time] with 225 patients (18.9%), and “berentet-EU” [retired-disabled] with 215 patients (18.1%).

The school education and vocational education as well as occupational status of the PSM patients is summarized (by German terms) in Post-Text Table 2.1b.

Table 12: Post-matching: Demographic data at baseline (PSM)

	STAY (N=290)	SWITCH (N=290)
Gender, n (%)		
Male	77 (26.6)	87 (30.0)
Female	213 (73.4)	203 (70.0)
Age (years)		
N	290	290
Mean (SD)	39.6 ± 10.0	39.9 ± 10.2
Median (Q1; Q3)	40.0 (32.0; 48.0)	39.0 (32.0; 49.0)
Min; Max	18.0; 64.0	19.0; 65.0
Weight (kg)		
N	288	289
Mean (SD)	72.3 ± 16.1	74.2 ± 17.7
Median (Q1; Q3)	70.0 (60.0; 81.5)	70.0 (62.0; 83.0)
Min; Max	44.0; 140.0	35.0; 137.0
Body mass index (kg/m^2)		
N	288	288
Mean (SD)	24.6 (4.9)	25.1 (5.5)
Median (Q1; Q3)	23.6 (21.0; 27.0)	23.9 (21.5; 26.9)
Min; Max	17.1	12.9

PSM = Propensity score matching; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
Source: Post-text Table 2.1b

7.3. Baseline MS Characteristics

Overall, the time interval between the **onset of the first MS symptoms and start of study** showed a very broad range across TRP patients (1.1 to 42.3 years); the median was 10.2 years (Q1=5.5 years; Q3=15.4 years); likewise the **time between first MS diagnosis and start of study** varied broadly (1.1 to 35.3 years), the median was 9.0 years (Q1=4.4 years; Q3=13.8 years). The median value for the **time between onset of the first MS symptoms and first MS diagnosis** was 0.3 years (Q1=0.0 years; Q3=1.5 years), the maximum value was 29.0 years which had been confirmed by a DM query (see Table 13).

There were no notable differences between the STAY and SWITCH cohorts, with regard to time since first MS symptoms or first MS diagnosis and study entry.

Nevertheless, patients of the SWITCH cohort were 1:1 propensity score matched to patients in the STAY cohorts, the results are presented in Table 13. After propensity sore matching, STAY and SWITCH patients were still comparable regarding time between first MS symptoms / MS diagnosis and study entry.

Table 13: Time since first symptoms / first MS diagnosis (TRP)

Parameter	TRP [a]			PSM	
Time between…	**STAY (N=698)**	**SWITCH (N=396)**	**Total (N=1191)**	**STAY (N=290)**	**SWITCH (N=290)**
First MS symptoms and study start (years)					
N	652	364	1102	276	274
Mean ± SD	11.4 ± 7.0	11.3 ± 7.2	11.2 ± 7.1	11.0 ± 7.0	11.2 ± 7.3
Median (Q1; Q3)	10.5 (5.8; 15.8)	10.7 (5.5; 15.2)	10.2 (5.5; 15.4)	10.1 (5.5; 15.4)	10.8 (5.3; 15.3)
Min; Max	1.2; 38.1	1.1; 42.3	1.1; 42.3	1.2; 35.1	1.2; 42.3
First MS diagnosis and study start (years)					
N	686	389	1169	290	290
Mean ± SD	9.9 ± 6.3	9.9 ± 6.5	9.8 ± 6.3	9.4 ± 6.1	9.8 ± 6.6
Median (Q1; Q3)	9.1 (4.9; 14.1)	9.1 (4.1; 13.7)	9.0 (4.4; 13.8)	8.8 (4.2; 13.4)	9.1 (3.9; 13.7)
Min; Max	1.1; 35.3	1.1; 35.2	1.1; 35.3	1.1; 27.4	1.1; 30.1
First MS symptoms and first MS diagnosis (years)					
N	638	360	1083	273	271
Mean ± SD	1.6 ± 3.2	1.6 ± 3.4	1.6 ± 3.3	1.7 ± 3.4	1.6 ± 3.2
Median (Q1; Q3)	0.2 (0.0; 1.5)	0.3 (0.0; 1.5)	0.3 (0.0; 1.5)	0.3 (0.0; 1.9)	0.3 (0.0; 1.4)
Min; Max	0.0; 22.2	0.0; 29.0	0.0; 29.0	0.0; 20.4	0.0; 28.7

Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; PSM = Propensity score matched; TRP = Treated patients

a: In the INDETERMINABLE cohort (N=97), the time between first MS symptoms and study start (mean ± SD: 9.6 ± 6.3 years, median 9.2 years) as well as the time between MS diagnosis and study start (mean ± SD: 8.1 ± 5.2 years, median 7.4 years) was numerically smaller compared with the STAY and SWITCH cohorts. The time between first MS symptoms and MS diagnosis was similar (mean ± SD: 1.9 ± 3.3 years, median 0.3 years), summary statistics is fully tabulated in the post-text tables.

Source: Post-text Table 2.2a and Table 2.2b

Furthermore, Table 14 summarizes the patients´ systems that were affected at **first symptoms of MS** as well at **first diagnosis of MS** (multiple answers were possible). In the totals TRP set, in 975 out of 1191 patients (81.9%) at least one affected system was documented **at first symptoms of MS**. Overall, the most commonly specified systems (≥10.0%) were, "sensory" with 578 patients (48.5%), "visual" with 328 patients (27.5%), and "pyramidal" with 218 patients (18.3%). In about a quarter of patients (27.8%, 331 patients) MS affected more than one body system.

Before matching, individual proportions within the systems affected **at first symptoms of MS** differed slightly between the two cohorts of the TRP, with a greater proportion of STAY compared with SWITCH patients with:

- any system affected (83.2% vs. 80.8%),
- with "cerebellar" system affected (10.0% vs. 5.3%),

- with “brain stem” affected (8.3% vs. 6.1%),
- with “sensory” system affected (49.0% vs. 47.0%),
- and with more than one system affected (28.9% vs. 25.0%).

After propensity score matching (PSM), these proportions of patients were:

- any system affected (83.4% vs. 84.5%),
- with “cerebellar” system affected (9.7% vs. 5.9%),
- with “brain stem” affected (7.6% vs. 7.6%),
- with “sensory” system affected (46.6% vs. 47.6%),
- and with more than one system affected (28.3% vs. 27.2%).

With regard to system(s) affected **at first diagnosis of MS**, 996 out of 1191 patients (83.6%) in the totals TRP set had at least one affected system documented. Overall, the most commonly (≥10.0%) specified systems were, “sensory” with 635 patients (53.3%), “visual” with 324 patients (27.2%), “pyramidal” with 291 patients (24.4%), and “cerebellar” with 128 patients (10.7%). In more than one third of patients (35.6%, 424 patients) MS affected more than one body system at first diagnosis.

Before matching (TRP set), individual measures within the systems affected **at first diagnosis of MS** differed numerically between the two cohorts, with a smaller proportion of STAY patients with “pyramidal” system affected (23.1% vs. 26.5%), and a numerically greater proportion of STAY patients (compared with SWITCH patients):

- with “cerebellar” system affected (11.9% vs. 8.8%),
- with “sensory” system affected (53.4 vs. 50.8%),
- with “visual” system affected (29.5% vs. 25.8%),
- and with more than one system affected (36.2% vs. 34.6%).

After propensity score matching (PSM), these proportions of patients were (STAY vs. SWITCH):

- with “pyramidal” system affected (23.4% vs. 29.3%),
- with “cerebellar” system affected (12.4% vs. 10.7%),
- with “sensory” system affected (52.8% vs. 51.0%),
- with “visual” system affected (29.7% vs. 28.3%),
- and with more than one system affected (36.6% vs. 37.2%).

Table 14: Body systems affected by multiple sclerosis

System affected	TRP [a]			PSM	
	STAY (N=698)	SWITCH (N=396)	Total (N=1191)	STAY (N=290)	SWITCH (N=290)
First symptoms, n (%)					
Any system affected	**581 (83.2)**	**320 (80.8)**	**975 (81.9)**	**242 (83.4)**	**245 (84.5)**
Pyramidal	125 (17.9)	72 (18.2)	218 (18.3)	55 (19.0)	57 (19.7)
Cerebellar	70 (10.0)	21 (5.3)	99 (8.3)	28 (9.7)	17 (5.9)
Brain stem	58 (8.3)	24 (6.1)	90 (7.6)	22 (7.6)	22 (7.6)
Sensory	342 (49.0)	186 (47.0)	578 (48.5)	135 (46.6)	138 (47.6)
Bowel and bladder function	20 (2.9)	13 (3.3)	36 (3.0)	8 (2.8)	12 (4.1)
Visual	197 (28.2)	112 (28.3)	328 (27.5)	81 (27.9)	90 (31.0)
Mental	19 (2.7)	13 (3.3)	38 (3.2)	9 (3.1)	10 (3.4)
Other	41 (5.9)	14 (3.5)	59 (5.0)	14 (4.8)	9 (3.1)
Unknown	**113 (16.2)**	**72 (18.2)**	**205 (17.2)**	**48 (16.6)**	**43 (14.8)**
Missing values	**4 (0.6)**	**4 (1.0)**	**11 (0.9)**	**0 (0.0)**	**2 (0.7)**
More than one system affected	**202 (28.9)**	**99 (25.0)**	**331 (27.8)**	**82 (28.3)**	**79 (27.2)**
First MS diagnosis, n (%)					
Any system affected	**589 (84.4)**	**332 (83.8)**	**996 (83.6)**	**249 (85.9)**	**254 (87.6)**
Pyramidal	161 (23.1)	105 (26.5)	291 (24.4)	68 (23.4)	85 (29.3)
Cerebellar	83 (11.9)	35 (8.8)	128 (10.7)	36 (12.4)	31 (10.7)
Brain stem	66 (9.5)	32 (8.1)	103 (8.6)	29 (10.0)	29 (10.0)
Sensory	373 (53.4)	201 (50.8)	635 (53.3)	153 (52.8)	148 (51.0)
Bowel and bladder function	30 (4.3)	19 (4.8)	55 (4.6)	12 (4.1)	15 (5.2)
Visual	206 (29.5)	102 (25.8)	324 (27.2)	86 (29.7)	82 (28.3)
Mental	27 (3.9)	21 (5.3)	57 (4.8)	12 (4.1)	16 (5.5)
Other	26 (3.7)	20 (5.1)	48 (4.0)	9 (3.1)	14 (4.8)
Unknown	**105 (15.0)**	**62 (15.7)**	**186 (15.6)**	**41 (14.1)**	**35 (12.1)**
Missing values	**4 (0.6)**	**2 (0.5)**	**9 (0.8)**	**0 (0.0)**	**1 (0.3)**
More than one system affected	**253 (36.2)**	**137 (34.6)**	**424 (35.6)**	**106 (36.6)**	**108 (37.2)**

PSM = Propensity score matched; TRP = Treated patients
a: Results for the INDETERMINABLE (N=97) cohort were similar and can be found in the post-text Tables.
Source: Post-text Table 2.3.1a, Table 2.3.1b, Table 2.3.2a, and Table 2.3.2b

Post-text Table 2.4.1 (TRP) tabulates all opportunistic infections (OI) which occurred prior to start of natalizumab, post-text Table 2.4.2 (TRP) presents all OIs which occurred during

natalizumab therapy but prior to start of study as a by-patient listing (including JCV status at time of infection).

A total of 10 patients were documented having 13 OIs **prior to start of natalizumab** therapy. Patient's JCV status was negative at the time of occurrence of 8 OIs (in 8 patients), and positive for 2 OIs (both documented as "herpes zoster") arising in 1 patient each (JCV status was missing in 3 OIs).

The MedDRA preferred terms for the OIs were: 3 events "herpes zoster"; 2 events "bronchitis"; 1 event each "otitis media", "nasopharyngitis", "cystitis", "gastrointestinal infection", "herpes simplex", "sepsis", "unknown", "viral infection".

None of the MedDRA terms for OI matched the Sponsor's OI Catalog (version MedDRA 18.1).

A total of 14 patients were documented having 17 OIs **during natalizumab therapy but prior to start of study**. Patient's JCV status was negative at the time of occurrence of 8 OIs (in 8 patients), and positive for 6 opportunistic infections (1 "ophthalmic herpes zoster", 1 "respiratory tract infection", 4 "herpes zoster") arising in 6 patients (JCV status missing 3 OIs).

The MedDRA preferred terms for opportunistic infections were: 7 events "herpes zoster"; 2 events "respiratory tract infection" and "urinary tract infection"; and 1 event each "viral infection", "seborrhoeic dermatitis", "ophthalmic herpes zoster", "bronchitis", "febrile infection", "nasopharyngitis".

None of the MedDRA terms for opportunistic infections matched the Sponsor's OI Catalog (version MedDRA 18.1).

7.4. Baseline Medical History

7.4.1. Comorbidities

The concomitant diseases at the time of study entry are fully summarized in post-text Table 3.1.1. Generally, the reported concomitant diseases covered a broad spectrum of neurological and non-neurological conditions. Overall, 680 TRP patients (57.1%) – 415 (59.5%) of the STAY cohort, 212 (53.5%) of the SWITCH, and 53 (54.6%) of the INDETERMINABLE cohort – suffered from any comorbidity, and the highest incidences (≥5% in either group) were referring to the following MedDRA SOCs (Table 15, for preferred terms see post-Text Table 3.1.1):

- **"Psychiatric disorders" (total 24.3%; 24.8% STAY and 21.5% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either group) were: "Depression" (19.8%; 19.6% and 18.2%), and "sleep disorder" (1.8%; 2.0% and 1.8%) (total; STAY and SWITCH, respectively).
- **"Nervous system disorder" (total 14.7%; 16.3% STAY and 11.9% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either group) were: "Migraine" (4.0%; 4.6% and 3.3%), "nervous system disorder" (3.2% 3.9% and 2.3%), and "muscle spasticity" (0.9%; 1.3% and 0.5%) (total; STAY and SWITCH, respectively).
- **"Metabolism and nutrition disorders" (total 14.1%; 15.3% STAY and 13.9% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either

group) were: “Vitamin D deficiency” (8.5%; 9.0% and 8.6%), “obesity” (2.2%; 2.4% and 2.0%), diabetes mellitus (1.8%; 2.0% and 1.5%), and “vitamin B12 deficiency” (1.2% 1.3% and 1.3%) (total; STAY and SWITCH, respectively).

- **“Vascular disorders” (total 7.9%; 7.2% STAY and 9.1% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: “hypertension” (total 7.3%; 6.9% STAY and 8.1% SWITCH).
- **“Endocrine disorder” (total 7.7%; 7.7% STAY and 7.8% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: “thyroid dysfunction” (total 7.1%; 6.9% STAY and 7.3% SWITCH).
- **“Musculoskeletal and connective tissue disorders” (total 7.2; 7.6% STAY and 6.1% SWITCH);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: “Muscle disorder/joint disorder” (total 3.6%; 3.6% STAY and 3.0% SWITCH).

Table 15: Comorbidities present at study start (TRP)

MedDRA Primary system organ class	STAY (N=698) n (%)	SWITCH (N=396) n (%)	Total [a] (N=1191) n (%)
Any comorbidity present at study start	**415 (59.5)**	**212 (53.5)**	**680 (57.1)**
Psychiatric disorders	173 (24.8)	85 (21.5)	289 (24.3)
Nervous system disorders	114 (16.3)	47 (11.9)	175 (14.7)
Metabolism and nutrition disorders	107 (15.3)	55 (13.9)	168 (14.1)
Vascular disorders	50 (7.2)	36 (9.1)	94 (7.9)
Endocrine disorders	54 (7.7)	31 (7.8)	92 (7.7)
Musculoskeletal and connective tissue disorders	53 (7.6)	24 (6.1)	86 (7.2)
Immune system disorders	34 (4.9)	19 (4.8)	56 (4.7)
Gastrointestinal disorders	28 (4.0)	12 (3.0)	46 (3.9)
General disorders and administration site conditions	18 (2.6)	12 (3.0)	32 (2.7)
Skin and subcutaneous tissue disorders	19 (2.7)	13 (3.3)	32 (2.7)
Renal and urinary disorders	16 (2.3)	13 (3.3)	30 (2.5)
Respiratory, thoracic and mediastinal disorders	20 (2.9)	7 (1.8)	28 (2.4)
Cardiac disorders	15 (2.1)	12 (3.0)	27 (2.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15 (2.1)	10 (2.5)	27 (2.3)
Blood and lymphatic system disorders	14 (2.0)	9 (2.3)	24 (2.0)
Infections and infestations	14 (2.0)	8 (2.0)	24 (2.0)
Surgical and medical procedures	12 (1.7)	9 (2.3)	21 (1.8)
Eye disorders	7 (1.0)	9 (2.3)	18 (1.5)
Congenital, familial and genetic disorders	9 (1.3)	5 (1.3)	16 (1.3)
Reproductive system and breast disorders	9 (1.3)	7 (1.8)	16 (1.3)
Ear and labyrinth disorders	5 (0.7)	3 (0.8)	8 (0.7)

Injury, poisoning and procedural complications	5 (0.7)	3 (0.8)	8 (0.7)
Hepatobiliary disorders	4 (0.6)	3 (0.8)	7 (0.6)
Investigations	4 (0.6)	0 (0.0)	5 (0.4)
Social circumstances	1 (0.1)	1 (0.3)	2 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0 (0.0)	1 (<0.1)
Not specified	1 (0.1)	0 (0.0)	1 (<0.1)

MedDRA = Medical Dictionary for Drug Regulatory Activities; TRP = Treated patients
a: In the INDETERMINABLE (N=97) cohort, 53 patients (54.6%) presented with any comorbidity present at study start, the most common comorbidities present at study start were "psychiatric disorders" with 31 patients (32.0%) and "nervous system disorders" with 14 patients (14.4%); all results for the INDETERMINABLE cohort can be found in the post-text Table.
Source: Post-text Table 3.1.1.

The **concomitant diseases present at study start that required drug treatment** are fully summarized in post-text Table 3.1.2. Overall, 484 TRP patients (40.6%) –292 (41.8%) of the STAY cohort, 150 (37.9%) of the SWITCH cohort, and 42 (43.3%) of the INDETERMINABLE cohort– suffered from any comorbidity, and the highest incidences (>5% in either group) were referring to the following MedDRA SOCs (see Table 16):

- **"Psychiatric disorders" (total 16.8%; STAY 16.2% and SWITCH 15.9%);** within this SOC the highest prevalence based on PT-level (>1% in either group) were: depression (14.7%; 13.9% and 14.6%), and sleep disorder (1.4%; 1.4% and 1.5%) (total; STAY and SWITCH, respectively).
- **"Metabolism and nutrition disorders" (total 10.2%; STAY 11.7% and SWITCH 9.1%);** within this SOC the highest prevalence based on PT-level (>1% in either group) were: vitamin D deficiency (7.0%; 7.6% and 6.8%), diabetes mellitus (1.4%; 1.9% and 0.8%), and vitamin B12 deficiency (0.8%; 1.1% and 0.5%) (total; STAY and SWITCH, respectively).
- **"Nervous system disorder" (total 8.4%; STAY 9.7% and SWITCH 6.3%);** within this SOC the highest prevalence based on PT-level (>1% in either group) were: migraine (2.4%; 3.2% and 1.3%), nervous system disorder (2.1%; 2.3% and 1.8%), and muscle spasticity (0.9% 1.3% and 0.5%) (STAY and SWITCH, respectively).
- **"Endocrine disorder" (total 6.2% STAY 6.3% and SWITCH 6.3%);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: thyroid dysfunction (total 6.0%; 5.9% STAY and 6.3% SWITCH).
- **"Vascular disorders" (total 5.7%; STAY 5.0% and SWITCH 6.6%);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: hypertension (total 5.7% STAY and 6.6% SWITCH).

Relevant concomitant diseases appearing during study period are fully summarized in post-text Table 3.2. Overall, 454 TRP patients (38.1%) –280 (40.1%) of the STAY cohort, 153 (38.6%) of the SWITCH cohort, and 21 (21.6%) of the INDETERMINABLE cohort– suffered from any relevant concomitant diseases appearing during study period, and the highest incidences (≥5% in either group) were referring to the following MedDRA SOCs (see Table 16):

- **"Infections and infestations" (total 16.4%; STAY 16.0% and SWITCH 17.9%);** within this SOC the highest prevalence based on PT-level (≥1% in either group) was: "Nasopharyngitis" (total 6.4%; with STAY 6.2% and 7.3% SWITCH).
- **"Nervous system disorders" (total 6.6%; STAY 6.9% and SWITCH 7.3%);** within this SOC the highest prevalence based on PT-level (≥1% in either group) were: "Nervous (system) disorder" (1.2%; 1.4% and 1.0%) and "headache" (1.0%; with 0.7% and 1.8%) (total; STAY and SWITCH, respectively). Within this SOC, there were also 4 patients documented with "progressive multifocal leukoencephalopathy", full information on PML is found in section 9.2.2.3.
- **"Musculoskeletal and connective tissue disorders" (total 6.3%; STAY 6.9% and SWITCH 7.3%);** within this SOC the highest prevalence based on PT-level (≥1% in either group) was: "Muscle disorder/joint disorder" (3.9; 4.3% and 4.0%) (total; STAY and SWITCH, respectively).
- **"Psychiatric disorders" (total 6.0%; STAY 6.2% and SWITCH 6.1%);** within this SOC the highest prevalence based on PT-level (≥1% in either group) were: "Depression" (3.9%, 3.7% and 4.5%) and "sleep disorder" depression" (1.0%; 1.0% and 1.0%) (total; STAY and SWITCH, respectively).
- **"Metabolism and nutrition disorders" (total 5.1%; STAY 5.7% and SWITCH 5.1%);** within this SOC the highest prevalence based on PT-level (>1% in either group) was: "Vitamin D deficiency" (3.6%; STAY 4.0% STAY and 3.8% SWITCH).

Table 16: Relevant concomitant diseases appearing during study period (TRP)

MedDRA Primary system organ class	STAY (N=698) n (%)	SWITCH (N=396) n (%)	Total [a] (N=1191) n (%)
Any disease appearing during study period	**280 (40.1)**	**153 (38.6)**	**454 (38.1)**
Infections and infestations	112 (16.0)	71 (17.9)	195 (16.4)
Nervous system disorders	48 (6.9)	29 (7.3)	79 (6.6)
Musculoskeletal and connective tissue disorders	48 (6.9)	27 (6.8)	75 (6.3)
Psychiatric disorders	43 (6.2)	24 (6.1)	71 (6.0)
Metabolism and nutrition disorders	40 (5.7)	20 (5.1)	61 (5.1)
Gastrointestinal disorders	36 (5.2)	13 (3.3)	51 (4.3)
Skin and subcutaneous tissue disorders	22 (3.2)	15 (3.8)	38 (3.2)
General disorders and administration site conditions	12 (1.7)	12 (3.0)	24 (2.0)
Endocrine disorders	15 (2.1)	8 (2.0)	23 (1.9)
Injury, poisoning and procedural complications	8 (1.1)	8 (2.0)	18 (1.5)
Vascular disorders	7 (1.0)	10 (2.5)	17 (1.4)
Respiratory, thoracic and mediastinal disorders	6 (0.9)	7 (1.8)	15 (1.3)
Blood and lymphatic system disorders	1 (0.1)	12 (3.0)	14 (1.2)
Immune system disorders	9 (1.3)	4 (1.0)	14 (1.2)
Eye disorders	8 (1.1)	4 (1.0)	12 (1.0)

MedDRA Primary system organ class	STAY (N=698) n (%)	SWITCH (N=396) n (%)	Total [a] (N=1191) n (%)
Investigations	8 (1.1)	4 (1.0)	12 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1.1)	1 (0.3)	10 (0.8)
Renal and urinary disorders	6 (0.9)	3 (0.8)	9 (0.8)
Reproductive system and breast disorders	6 (0.9)	3 (0.8)	9 (0.8)
Ear and labyrinth disorders	4 (0.6)	3 (0.8)	7 (0.6)
Cardiac disorders	4 (0.6)	2 (0.5)	6 (0.5)
Congenital, familial and genetic disorders	3 (0.4)	1 (0.3)	4 (0.3)
Surgical and medical procedures	3 (0.4)	0 (0.0)	3 (0.3)
Hepatobiliary disorders	1 (0.1)	1 (0.3)	2 (0.2)

MedDRA = Medical Dictionary for Drug Regulatory Activities; TRP = Treated patients
a: In the INDETERMINABLE (N=97) cohort, 21 patients (21.6%) were documented with any relevant comorbidity appearing during study period, the most common once were "infections and infestations" with 12 patients (12.4%), "psychiatric disorders" with 4 patients (4.1%); all results for the INDETERMINABLE cohort can be found in the post-text Table.
Source: Post-text Table 3.2

7.4.2. Concomitant medications

Concomitant medications **present at study start** are fully summarized in Post-Text Table 4.3.4. Overall, 724 TRP patients (60.8%) received any concomitant medication at study start, 427 (61.2%) STAY cohort, 232 (58.6%) of the SWITCH cohort, and 65 (67.0%) of the INDETERMINABLE cohort.

Most commonly (>10% in either cohort), concomitant medication present at study start referred to (WHO-DD ATC level 1):

- **Nervous system (total 37.0%; STAY 36.0% and SWITCH 37.4%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) were: fampridine (total 10.0%; 8.6% and 12.4%), citalopram (total 6.4%; 6.2% and 6.3%), and pregabalin (total 4.5%; 3.4% and 5.3%) (STAY and SWITCH, respectively).
- **Alimentary tract and metabolism (total 20.4%; STAY 21.1% and SWITCH 19.9%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) was: colecalciferol (total 15.3%; 15.6% STAY and 15.4% SWITCH).
- **Musculo-skeletal system (total 16.1%; STAY 16.5% and SWITCH 16.7%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) were: baclofen (total 7.3%; 7.4% and 7.3%) and ibuprofen (total 6.1%; 6.3% and 6.6%) (STAY and SWITCH, respectively).

- **Genito urinary system and sex hormones (total 10.9%; STAY 11.5% and SWITCH 9.8%);** within this ATC class the highest prevalence based on preferred name level was: trospium chloride (total 1.9%; 2.0% STAY and 1.8% SWITCH).

Concomitant medications **started at/after study start** are summarized in Table 17 and are fully tabulated in Post-Text Table 4.3.5.

Overall, 799 TRP patients (67.1%) received any concomitant medication started at/after study start, 467 (66.9%) of the STAY cohort, 290 (73.2%) of the SWITCH cohort, and 42 (43.3%) of the INDETERMINABLE cohort.

Most commonly (>10% in either cohort), concomitant medications started at/after study start referred to (WHO-DD ATC level 1):

- **Nervous system (total 39.1%; STAY 36.7% and SWITCH 46.0%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) were: fampridine (total 5.0%; 3.6% and 8.6%) and pregabalin (total 5.0%; 4.4% and 6.1%), and Sativex (total 5.0%; 5.6% and 4.5) (STAY and SWITCH, respectively).
- **Alimentary tract and metabolism (total 29.7%; STAY 28.7% and SWITCH 35.1%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) was: colecalciferol (total 19.1%; 19.8% STAY and 19.2% SWITCH) and pantoprazole (total 5.0%; 4.0% and 8.1%).
- **Systemic hormonal preparations, excl. sex hormones and insulins (total 24.1%; STAY 19.3% and SWITCH 36.1%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) was: methylprednisolone (total 11.3%, with 9.0% STAY and 17.2% SWITCH) and prednisolone (total 5.0%, 3.7% and 7.6%).
- **Musculo-skeletal system (total 18.1%; STAY 17.6% and SWITCH 20.5%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) were: ibuprofen (total 8.6%; 8.3% and 9.8%) and baclofen (total 7.0%; 6.7% and 8.3%) (STAY and SWITCH, respectively).
- **Antiinfectives for systemic use (total 17.0; STAY 16.5% and SWITCH 20.7%);** within this ATC class the highest prevalence based on preferred name level was: aciclovir (total 3.4%; 1.9% STAY and 6.6% SWITCH).

Furthermore, numerical differences between the subcohorts STAY and SWITCH with regard to the incidence of concomitant medications started at/after study start were also seen in the WHO-DD ATC level 1 classes:

- **Antineoplastic and immunomodulating agents (total 5.0%; STAY 0.4% and SWITCH 14.4%);** within this ATC class the highest prevalence based on preferred name level was fingolimod (total 2.0%; with 0.0% STAY and 6.1% SWITCH).
- **Respiratory system (total 7.6%; STAY 4.0% and SWITCH 15.2%);** within this ATC class the highest prevalence based on preferred name level (>5% in either group) were: desloratadine (total 1.9%; with 0.0% STAY and 5.8% SWITCH).

In the STAY cohort, 3 patients (0.4%) received medications of the "antineoplastic and immunomodulating agents" WHO-DD ATC level 1 classes besides natalizumab therapy, the preferred names were rituximab, glatiramer acetate, carboplatin, docetaxel, pertuzumab documented in 1 patient each (multiple medications per patient possible).

Table 17: Concomitant medication which started after/at study start and most common (>5% in either cohort or most frequent preferred name) preferred names (TRP) – multipage table

WHO-DD ATC level 1 WHO-DD Preferred name	STAY (N=698) n (%)	SWITCH (N=396) n (%)	Total [a] (N=1191) n (%)
Any concomitant medication which started after/at study start	**467 (66.9)**	**290 (73.2)**	**799 (67.1)**
Nervous system	**256 (36.7)**	**182 (46.0)**	**466 (39.1)**
Fampridine	25 (3.6)	34 (8.6)	60 (5.0)
Pregabalin	31 (4.4)	24 (6.1)	60 (5.0)
Sativex	39 (5.6)	18 (4.5)	59 (5.0)
Paracetamol	11 (1.6)	35 (8.8)	48 (4.0)
Zopiclone	16 (2.3)	21 (5.3)	38 (3.2)
Alimentary tract and metabolism	**200 (28.7)**	**139 (35.1)**	**354 (29.7)**
Colecalciferol	138 (19.8)	76 (19.2)	228 (19.1)
Pantoprazole	28 (4.0)	32 (8.1)	60 (5.0)
Systemic hormonal preparations, excl. sex hormones and insulins	**135 (19.3)**	**143 (36.1)**	**287 (24.1)**
Methylprednisolone	63 (9.0)	68 (17.2)	135 (11.3)
Prednisolone	26 (3.7)	30 (7.6)	59 (5.0)
Methylprednisolone sodium succinate	22 (3.2)	32 (8.1)	55 (4.6)
Prednisolone sodium succinate	9 (1.3)	24 (6.1)	36 (3.0)
Musculo-skeletal system	**123 (17.6)**	**81 (20.5)**	**215 (18.1)**
Ibuprofen	58 (8.3)	39 (9.8)	102 (8.6)
Baclofen	47 (6.7)	33 (8.3)	83 (7.0)
Antiinfectives for systemic use	**115 (16.5)**	**82 (20.7)**	**203 (17.0)**
Aciclovir	13 (1.9)	26 (6.6)	40 (3.4)
Antibiotics	20 (2.9)	16 (4.0)	38 (3.2)
Genito urinary system and sex hormones	**67 (9.6)**	**38 (9.6)**	**107 (9.0)**
Blood and blood forming organs	**55 (7.9)**	**41 (10.4)**	**99 (8.3)**
Respiratory system	**28 (4.0)**	**60 (15.2)**	**91 (7.6)**
Desloratadine	-	23 (5.8)	23 (1.9)
Antineoplastic and immunomodulating agents [b]	**3 (0.4)**	**57 (14.4)**	**60 (5.0)**
Fingolimod hydrochloride	-	24 (6.1)	24 (2.0)
Alemtuzumab	-	15 (3.8)	15 (1.3)
Daclizumab	-	14 (3.5)	14 (1.2)
Ocrelizumab	-	9 (2.3)	9 (0.8)

Cladribine	-	3 (0.8)	3 (0.3)
Rituximab	1 (0.1)	2 (0.5)	3 (0.3)
Glatiramer acetate	1 (0.1)	1 (0.3)	2 (0.2)
Azathioprine	-	1 (0.3)	1 (<0.1)
Carboplatin	1 (0.1)	-	1 (<0.1)
Docetaxel	1 (0.1)	-	1 (<0.1)
Peginterferon beta-1a	-	1 (0.3)	1 (<0.1)
Pertuzumab	1 (0.1)	-	1 (<0.1)
Various	**27 (3.9)**	**30 (7.6)**	**57 (4.8)**
Cannabis sativa	7 (1.0)	2 (0.5)	9 (0.8)
Cardiovascular system	**22 (3.2)**	**18 (4.5)**	**41 (3.4)**
Dermatologicals	**21 (3.0)**	**14 (3.5)**	**36 (3.0)**
Aciclovir	5 (0.7)	4 (1.0)	9 (0.8)
Sensory organs	**11 (1.6)**	**5 (1.3)**	**18 (1.5)**
Ofloxacin	3 (0.4)	2 (0.5)	6 (0.5)
Antiparasitic products, insecticides and repellents	**1 (0.1)**	**2 (0.5)**	**3 (0.3)**
Mefloquine hydrochloride	-	2 (0.5)	2 (0.2)

MedDRA = Medical Dictionary for Drug Regulatory Activities; TRP = Treated patients
a: In the INDETERMINABLE (N=97) cohort, 42 patients (43.3%) presented with any comorbidity present at study start, the most common comorbidities present at study start were "nervous system disorders" with 28 patients (28.9%) and "alimentary tract and metabolism" with 15 patients (15.5%); all results for the INDETERMINABLE cohort can be found in the post-text Table.
b: All preferred names are presented.
Source: Post-text Table 4.3.5.

7.5. Multiple Sclerosis Therapy

7.5.1. Prior Multiple Sclerosis treatment before start of natalizumab

Table 18 presents data on the number of prior MS treatments (other than natalizumab) before start of natalizumab therapy. Most patients in the TRP had received previous treatment due to MS, only 160 patients (13.4%) had not received any prior MS treatment before start of natalizumab. More than half of the patients in the TRP (52.6%, 626 patients) had received 1 prior MS treatment, further 25.1% (299 patients) had received 2 prior treatments, and 106 patients (8.9%) had received ≥3 prior treatments.

The proportions of patients without any prior MS treatment and with ≥2 prior MS treatments were smaller in the STAY cohort compared with the SWITCH cohort (0 prior MS treatments 12.3% vs. 14.9% and ≥2 prior MS treatments 32.5% vs. 36.1%, STAY vs. SWITCH, respectively).

Overall, the TRP patients had received mean ± SD 1.3 ± 0.9 prior MS therapies (median 1.0 treatments range from 0 to 5 treatments), without remarkable differences between subcohorts.

Table 18: Number of previous MS treatments before start of natalizumab (TRP)

Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Number of prior treatments [a], n (%)				
0	86 (12.3)	59 (14.9)	15 (15.5)	160 (13.4)
1	385 (55.2)	194 (49.0)	47 (48.5)	626 (52.6)
2	172 (24.6)	100 (25.3)	27 (27.8)	299 (25.1)
3	49 (7.0)	32 (8.1)	7 (7.2)	88 (7.4)
4	6 (0.9)	9 (2.3)	0 (0.0)	15 (1.3)
5	0 (0.0)	2 (0.5)	1 (1.0)	3 (0.3)
Number of prior treatments [a]				
N	698	396	97	1191
Mean ± SD	1.3 ± 0.8	1.4 ± 0.9	1.3 ± 0.9	1.3 ± 0.9
Median (Q1; Q3)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)
Min; Max	0.0; 4.0	0.0; 5.0	0.0; 5.0	0.0; 5.0

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
a: The three interferon categories were counted as one type of prior treatment.
Source: Post-text Table 4.3.2

The documentation of previous **MS treatments before start of natalizumab** was done by selecting pre-specified therapy classes in the eCRF, these comprised: Copaxone, Avonex, Rebif, Betaferon/ Extavia, Gilenya, Tecfidera, Novantron/Onkotrone, Gamunex/Octagam, Aubagio, MabThera, Plegridy, Bendatrexat/Lantarel/Metex, Endoxan, Fampyra, Lemtrada, Ocrelizumab, Zinbryta, Other. Table 19 presents data on the specific prior MS treatments before start of natalizumab.

Overall, TRP patients were most commonly previously treated with glatiramer acetate (Copaxone, 411 patients, 34.5%), with interferons such as Avonex (371 patients, 31.2%), Rebif (367 patients, 30.8%) or Betaferon/Extavia (264 patients, 22.2%), and with fingolimod (Gilenya, 118 patients, 9.9%). Proportions of patients with a specific previous treatment specified were mostly comparable across STAY and SWITCH subcohort, the only exception was Gilenya with 7.9% (55 patients) in the STAY and 13.1% (52 patients) in the SWITCH cohort.

In parallel, **last prior MS treatment before initializing natalizumab** was most commonly glatiramer acetate (Copaxone, 252 patients, 24.4%, relative frequencies based on the number of patients with any previous treatment) and/or interferons like Avonex (205 patients, 19.9%), (Rebif 200 patients, 19.4%), or Betaferon/Extavia (130 patient, 12.6%), and fingolimod (Gilenya, 104 patients, 10.1%).

Again, proportions of patients with a specific last previous treatment specified were mostly comparable across STAY and SWITCH subcohorts, the only exception was Gilenya with 7.7% (47 patients) in the STAY and 13.6% (46 patients) in the SWITCH cohort.

Table 19: Previous MS treatment before start of natalizumab (TRP)

Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Any prior treatment other than NTZ	**612 (87.7)**	**337 (85.1)**	**82 (84.5)**	**1031 (86.6)**
Copaxone	235 (33.7)	134 (33.8)	42 (43.3)	411 (34.5)
Avonex	227 (32.5)	119 (30.1)	25 (25.8)	371 (31.2)
Rebif	217 (31.1)	117 (29.5)	33 (34.0)	367 (30.8)
Betaferon/Extavia	155 (22.2)	93 (23.5)	16 (16.5)	264 (22.2)
Gilenya	55 (7.9)	52 (13.1)	11 (11.3)	118 (9.9)
Other [a]	42 (6.0)	37 (9.3)	6 (6.2)	85 (7.1)
Tecfidera	26 (3.7)	17 (4.3)	1 (1.0)	44 (3.7)
Novantron/Onkotrone	24 (3.4)	9 (2.3)	2 (2.1)	35 (2.9)
Gamunex/Octagam	17 (2.4)	7 (1.8)	1 (1.0)	25 (2.1)
Aubagio	9 (1.3)	4 (1.0)	0 (0.0)	13 (1.1)
MabThera	1 (0.1)	2 (0.5)	0 (0.0)	3 (0.3)
Endoxan	1 (0.1)	0 (0.0)	1 (1.0)	2 (0.2)
Plegridy	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)
Bendatrexat/Lantarel/Metex	1 (0.1)	0 (0.0)	0 (0.0)	1 (<0.1)
Fampyra	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lemtrada	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ocrelizumab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Zinbryta	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Last prior treatment before NTZ [b]				
Copaxone	143 (23.4)	81 (24.0)	28 (34.1)	252 (24.4)
Avonex	128 (20.9)	63 (18.7)	14 (17.1)	205 (19.9)
Rebif	124 (20.3)	59 (17.5)	17 (20.7)	200 (19.4)
Betaferon/Extavia	79 (12.9)	45 (13.4)	6 (7.3)	130 (12.6)
Gilenya	47 (7.7)	46 (13.6)	11 (13.4)	104 (10.1)
Tecfidera	24 (3.9)	12 (3.6)	1 (1.2)	37 (3.6)
Other	18 (2.9)	12 (3.6)	3 (3.7)	33 (3.2)
Unknown	16 (2.6)	5 (1.5)	0 (0.0)	21 (2.0)
Novantron/Onkotrone	11 (1.8)	5 (1.5)	1 (1.2)	17 (1.6)
Gamunex/Octagam	10 (1.6)	4 (1.2)	0 (0.0)	14 (1.4)
Aubagio	9 (1.5)	3 (0.9)	0 (0.0)	12 (1.2)
MabThera	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.2)
Plegridy	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)
Bendatrexat/Lantarel/Metex	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Endoxan	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.1)

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
a: "Other" than the pre-specified CRF categories, no specification for "other" was requested.
b: Percentages based on the number of pre-treated patients.
Source: Post-text Table 4.3.1, Table 4.3.3

7.5.2. Multiple sclerosis treatment after discontinuation of natalizumab

Table 20 presents data on DMTs received after discontinuation of natalizumab in the SWITCH cohort (N=396).

The most frequent (≥10.0% of patients) subsequent **first DMTs after natalizumab discontinuation** were: “No subsequent therapy” in 89 patients (22.5%), “Gilenya” in 82 patients (20.7%), „Zinbryta/Daclizumab“ in 68 patients (17.2%), “Ocrelizumab” in 56 patients (14.1%), and “Lemtrada” in 40 patients (10.1%).

Similar proportions were seen in the PSM.

With regard to **any DMTs received after natalizumab discontinuation**, the most frequent (≥10.0% of patients) once were: “Gilenya” in 102 patients (25.8%), “Ocrelizumab” in 86 patients (21.7%), „Zinbryta/Daclizumab“ in 83 patients (21.0%), and “Lemtrada” in 54 patients (13.6%).

Similar proportions were seen in the PSM.

Table 20: Disease modifying therapies after discontinuation of natalizumab

	TRP	PSM
Parameter	**SWITCH, (N=396)**	**SWITCH, (N=290)**
First DMT after NTZ discontinuation, n (%)		
No subsequent therapy	89 (22.5)	70 (24.1)
Gilenya	82 (20.7)	61 (21.0)
Zinbryta/Daclizumab	68 (17.2)	50 (17.2)
Ocrelizumab	56 (14.1)	38 (13.1)
Lemtrada	40 (10.1)	26 (9.0)
Tecfidera	16 (4.0)	14 (4.8)
Other [a]	14 (3.5)	11 (3.8)
Copaxone	10 (2.5)	6 (2.1)
MabThera	7 (1.8)	5 (1.7)
Aubagio	6 (1.5)	3 (1.0)
Plegridy	2 (0.5)	2 (0.7)
Rebif	2 (0.5)	1 (0.3)
Avonex	1 (0.3)	0 (0.0)
Betaferon/Extavia	1 (0.3)	1 (0.3)
Gamunex/Octagam	1 (0.3)	1 (0.3)
Novantron/Onkotrone	1 (0.3)	1 (0.3)
All DMTs after NTZ discontinuation, n (%)		
Gilenya	102 (25.8)	74 (25.5)
Ocrelizumab	86 (21.7)	59 (20.3)
Zinbryta/Daclizumab	83 (21.0)	63 (21.7)
Lemtrada	54 (13.6)	38 (13.1)
Other [a]	32 (8.1)	27 (9.3)
Tecfidera	25 (6.3)	22 (7.6)
Copaxone	12 (3.0)	8 (2.8)
MabThera	11 (2.8)	9 (3.1)
Aubagio	8 (2.0)	4 (1.4)
Novantron/Onkotrone	3 (0.8)	3 (1.0)
Plegridy	3 (0.8)	2 (0.7)
Gamunex/Octagam	2 (0.5)	2 (0.7)
Rebif	2 (0.5)	1 (0.3)
Avonex	1 (0.3)	0 (0.0)
Betaferon/Extavia	1 (0.3)	1 (0.3)

DMT = Disease modifying therapy; NTZ = Natalizumab; PSM = Propensity score matching; TRP = Treated patients
Note: None of the patients received Bendatrexat/Lantarel/Metex, Endoxan, or Fampyra as subsequent treatment.
a: "Other" than the pre-specified CRF categories, no specification for "other" was requested.
Source: Post-text Table 1.4.3a, Table 1.4.3b, Table 1.4.4a, and Table 1.4.4b

7.6. Study-Specific Subgroup(s)

Study specific cohorts and subgroups were generated according to the definition provided in section 6.2.3.

As described in section 7.1, patients were classified based on the decision to stay on natalizumab treatment (STAY cohort) or switch to another treatment (SWITCH cohort) during the observational study period; patients who could not be assigned to one of these two cohorts were assigned to the INDETERMINABLE cohort, see Table 21.

Table 21: Number of patients in study specific cohorts

Analysis set	STAY	SWITCH	INDETERMI-NABLE	Total
TRP	698	396	97	1191
FAS	698	396	95	1189
PSM	290	290	0	580
PSM2	326	326	0	652

FAS = Full Analysis Set; PSM = Propensity score matching; TRP = Treated patients
The PSM2 (used for EDSS-analysis) was derived from propensity score matching without considering the baseline EDSS value. Thus, more values could be matched pairwise compared with the PSM because there were fewer missing values.
Source: Post-text Table 1.3.1 and Table 5.3.6a

In addition, subgroups by PML risk at study inclusion (see section 6.2.3.1 for details on risk definition) and by EID (see section 6.2.3.2 for details on EID definition) were generated, the number of patients assigned to each subgroups are presented in Table 22.

Table 22: Number of patients in subgroups by PML risk or by EID

Analysis set/Cohort	No PML risk	Low PML risk	Intermediate PML risk	High PML risk
FAS (N=1189)	703	61	259	166
PSM (N=580)	341	34	153	124
STAY (N=698)	494	32	122	50
SWITCH (N=396)	143	22	120	111
	EID no	**EID yes**	**EID not calculable**	**-**
FAS (N=1189)	696	69	424	-
PSM2 (N=652)	352	42	258	-

EID = Extended Interval Dosing; FAS = Full Analysis Set; PML = Progressive Multifocal Leukoencephalopathy; PSM = Propensity score matching; TRP = Treated patients
The PSM2 (used for EDSS-analysis) was derived from propensity score matching without considering the baseline EDSS value. This population ensures independence from the dependent variable “worsening in EDSS”.
Source: Post-text Table 4.1.1c, 4.1.1d, Table 5.3.5b, Table 5.3.5c, Table 5.3.6b, and Table 5.3.6c

8. STUDY RESULTS

8.1. Natalizumab treatment

As per eligibility criteria, patients should have received natalizumab treatment for at least 12 months as per the therapeutic indications and contraindications given in the Summary of Product Characteristics (SmPC). The observational time per patient was 36 months regardless of any changes in treatment.

8.1.1. Natalizumab treatment prior to study inclusion

Table 23 summarizes natalizumab treatment prior to study inclusion **for the TRP**.

The number of prior natalizumab infusions as well as the duration of prior natalizumab treatment before study inclusion showed a very broad range across TRP patients (9 to 122 prior infusions corresponding to a prior natalizumab treatment duration of 11.8 to 146.4 months).

Overall, in the total TRP, patients had received median 31.0 infusions (Q1=17.0 infusions; Q3=65.0 infusions) of natalizumab prior to study inclusion, corresponding to a median treatment duration of 36.1 months (Q=17.2 months; Q3=76.5 months).

The number of natalizumab infusions during the last 12 months before inclusion into the study was median 12.0 infusions (Q1=11.0 infusions; Q3=12.0 infusions) per patient. The time since last infusion before study inclusion was median 4.1 weeks (Q1=2.1 weeks; Q3=4.6 weeks).

The number of all natalizumab infusions before study inclusion was slightly greater in the STAY cohort (median 32.0 infusions) compared with the SWITCH cohort (median 29.5 infusions), and also the duration of prior natalizumab treatment was also longer in the STAY cohort (median 36.9 months vs. 33.3 months).

Table 24 summarizes natalizumab treatment prior to study inclusion **for the PSM**.

After propensity score matching (PSM), the number of all natalizumab infusions before study inclusion was similar in STAY and SWITCH cohorts but slightly lower (median 27.0 infusions for both cohorts) than in the TRP. In parallel, the duration of natalizumab treatment before study inclusion was similar in both cohorts (STAY median 27.9 months, SWITCH median 28.5 months) but also shorter compared with the TRP.

No relevant differences were observed between STAY and SWITCH patients regarding the number of natalizumab infusions within the last 12 months before study inclusion (median 12.0 in both cohorts) or the time since last infusion before study inclusion (median 4.1 weeks in both cohorts, neither before (TRP) nor after matching (PSM).

Table 23: Natalizumab treatment prior to study inclusion (TRP)

Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Number of all NTZ infusions before study inclusion				
N	653	372	90	1115
Mean ± SD	43.3 ± 29.6	41.9 ± 30.5	40.1 ± 25.0	42.6 ± 29.6
Median (Q1; Q3)	32.0 (17.0; 69.0)	29.5 (16.0; 63.5)	32.5 (20.0; 54.0)	31.0 (17.0; 65.0)
Min; Max	9.0; 114.0	10.0; 122.0	12.0; 104.0	9.0; 122.0
Duration of NTZ prior to study inclusion (months prior to V1)				
N	698	396	97	1191
Mean ± SD	47.1 ± 31.6	45.8 ± 32.1	43.2 ± 27.4	46.3 ± 31.4
Median (Q1; Q3)	36.9 (16.7; 78.3)	33.3 (17.3; 75.5)	34.8 (19.8; 61.5)	36.1 (17.2; 76.5)
Min; Max	12.0; 146.4	12.0; 120.8	11.8; 105.5	11.8; 146.4
Number of NTZ infusions during last 12 months before study inclusion				
N	698	396	97	1191
Mean ± SD	11.6 ± 1.9	11.6 ± 2.1	12.0 ± 4.1	11.6 ± 2.2
Median (Q1; Q3)	12.0 (11.0; 12.0)	12.0 (11.0; 12.0)	12.0 (11.0; 12.0)	12.0 (11.0; 12.0)
Min; Max	1.0; 26.0	0.0; 26.0	1.0; 48.0	0.0; 48.0
Time since last infusion before study inclusion (weeks)				
N	697	395	97	1189
Mean ± SD	3.6 ± 3.2	3.8 ± 5.8	4.0 ± 3.1	3.7 ± 4.2
Median (Q1; Q3)	4.1 (2.7; 4.6)	4.1 (1.1; 4.7)	4.1 (3.1; 4.6)	4.1 (2.1; 4.6)
Min; Max	0.1; 69.3	0.1; 109.6	0.1; 22.4	0.1; 109.6

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Source: Post-text Table 4.1.1a

Table 24: Post-matching: Natalizumab treatment prior to study inclusion (PSM)

Parameter	STAY (N=290)	SWITCH (N=290)
Number of all NTZ infusions before study inclusion		
N	290	290
Mean ± SD	39.6 ± 29.9	39.9 ± 30.1
Median (Q1; Q3)	27.0 (15.0; 56.0)	27.0 (15.0; 58.0)
Min; Max	11.0; 112.0	10.0; 122.0
Number of NTZ infusions during last 12 months before study inclusion		
N	290	290
Mean ± SD	11.7 ± 1.6	11.6 ± 2.1
Median (Q1; Q3)	12.0 (12.0; 12.0)	12.0 (11.0; 12.0)
Min; Max	1.0; 17.0	0.0; 26.0
Duration of prior NTZ treatment (months prior to V1)		
N	290	290
Mean ± SD	41.5 ± 30.9	42.0 ± 31.2
Median (Q1; Q3)	27.9 (14.9; 68.8)	28.5 (15.4; 67.4)
Min; Max	12.0; 112.4	12.0; 120.8
Time since last infusion before study inclusion (weeks)		
N	290	290
Mean ± SD	3.7 ± 1.9	3.9 ± 6.6
Median (Q1; Q3)	4.1 (3.7; 4.6)	4.1 (1.9; 4.7)
Min; Max	0.1; 9.0	0.1; 109.6

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; PSM = Propensity score matched
Source: Post-text Table 4.1.1b

The parameters on natalizumab treatment prior to study inclusion were analyzed by PML risk (for definitions see section 6.2.3.1) in both subcohorts (STAY and SWITCH), the results are fully tabulated in post-text Table 4.1.1c (STAY by PML risk) and Table 4.1.1d (SWITCH by PML risk), and summarized in Table 25.

In the STAY cohort, number of natalizumab infusions war higher in “intermediate risk” and “high risk” subgroups (median: 51.0 infusions and 55.5 infusions, respectively) compared with “no risk”, “low risk”, or “other” subgroups (median: 29.0 infusion, 27.0 infusions, and 30.0 infusions).

In the SWITCH cohort, number of natalizumab infusions was lower in the “no risk” subgroup (23.0 infusion) compared with “low/intermediate/high risk” or “other” subgroups (median value ranged between 32.0 infusions and 38.0 infusions).

In both cohorts (STAY and SWITCH), numerical differences regarding number of prior natalizumab infusions in the subgroups were also reflected by the differences regarding duration of natalizumab treatment prior to study inclusion.

Table 25: Natalizumab treatment prior to study inclusion by PML risk (TRP)

Parameter	STAY no risk (N=494)	STAY low risk (N=32)	STAY intermediate risk (N=122)	STAY high risk (N=50)	Other (N=493)
Number of all NTZ infusions before study inclusion					
N	465	29	113	46	462
Mean ± SD	40.5 ± 28.9	36.8 ± 27.5	51.0 ± 29.0	56.7 ± 33.5	41.6 ± 29.5
Median	29.0	27.0	51.0	55.5	30.0
Duration of NTZ prior to study inclusion (months prior to V1)					
N	494	32	122	50	493
Mean ± SD	43.4 ± 30.6	43.5 ± 31.6	56.6 ± 31.7	62.4 ± 32.2	45.3 ± 31.2
Median	31.2	32.0	66.0	75.0	33.4
	SWITCH no risk (N=143)	**SWITCH low risk (N=22)**	**SWITCH intermediate risk (N=120)**	**SWITCH high risk (N=111)**	**Other (N=795)**
Number of all NTZ infusions before study inclusion					
N	139	20	105	108	743
Mean ± SD	34.1 ± 27.6	50.8 ± 34.0	47.8 ± 30.3	44.7 ± 31.6	42.9 ± 29.1
Median	23.0	36.0	38.0	34.5	32.0
Duration of prior NTZ treatment (months prior to V1)					
N	143	22	120	111	795
Mean ± SD	36.7 ± 29.1	56.1 ± 35.1	52.6 ± 31.9	48.3 ± 32.9	46.6 ± 31.1
Median	24.7	46.9	45.4	40.1	36.8

NTZ = Natalizumab; SD = Standard deviation; PSM = Propensity score matched; TRP = Treated patients

Note: The PML risk (at study inclusion) was classified as: No risk, if anti-JCV antibody status was negative / Low risk, if ant-JCV antibody index between 0.4 and 0.9 / High risk, if anti-JCV antibody index ≥ 1.5 or positive anti-JCV antibody status in a patient previously treated with immune suppressive therapies / Intermediate risk, in all other cases (e.g. anti-JCV antibody status/index unknown or index between 0.9 and 1.5).

Note: Subgroups by PML risk were similar with regard to the number of NTZ infusions within the last 12 months before study inclusion (median 12.0 in any subgroup) or the time since last infusion before study inclusion (median 4.1 weeks in any subgroup), full details are presented in the post-text Tables.

Source: Post-text Table 4.1.1c and Table 4.1.1d

The physicians retrospectively documented **the reason for initializing natalizumab treatment (at start of therapy)**, the results are shown in Table 26. The most common reasons for starting treatment with natalizumab, overall and in any of the subcohorts, was "ineffectiveness of prior treatment" with 905 patients (76.0%) in total, and followed by "other clinical/medical reasons" with 165 patients (13.5%) in total. "Adverse events/side effects of prior treatment" was documented more frequently in the INDETERMINABLE cohort (11.3%) than in the STAY or SWITCH cohorts (6.4–6.6%).

Table 26: Reason for initializing natalizumab treatment (at start of therapy) (TRP)

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Any reason specified, n (%) [a]	**697 (99.9)**	**395 (99.7)**	**97 (100.0)**	**1189 (99.8)**
Ineffectiveness of prior treatment	548 (78.5)	288 (72.7)	69 (71.1)	905 (76.0)
Non-compliance to prior treatment	13 (1.9)	3 (0.8)	4 (4.1)	20 (1.7)
Requested by patient	64 (9.2)	30 (7.6)	10 (10.3)	104 (8.7)
Adverse events/side effects of prior treatment	45 (6.4)	26 (6.6)	11 (11.3)	82 (6.9)
Other clinical/medical reasons	81 (11.6)	68 (17.2)	16 (16.5)	165 (13.9)
Other non-clinical reasons	40 (5.7)	28 (7.1)	4 (4.1)	72 (6.0)
More than one reason specified	**85 (12.2)**	**44 (11.1)**	**16 (16.5)**	**145 (12.2)**

TRP = Treated patients
a: Multiple reasons possible
Source: Post-text Table 4.1.2

Table 27 summarizes information on **natalizumab interruptions prior study to inclusion** for the TRP. Altogether, in 157 TRP patients (13.2%) natalizumab had been interrupted at least once prior to study inclusion, in 56 patients (4.7%) it had been interrupted within the last 12 months prior to study inclusion (STAY 28 patients or 4.0% and SWITCH 26 patients or 6.6%); in the great majority of patients with an interruption of natalizumab treatment prior to inclusion it had been interrupted only once (overall 140 patients, 11.8%).

The median duration of the interruption was 9.6 months (Q1=5.3 months; Q3=14.7months) in the total TRP with only minor differences across subcohorts.

The most frequent reason for interrupting natalizumab therapy was "requested by patient" (overall 32.8%, 58 patients), followed by "other clinical/medical reasons" (23.7%, 42 patients), "positive anti-JCV antibody test" (22.6%, 40 patients), and "pregnancy/planning of pregnancy" (20.3%, 36 patients) (proportions based on the number of patients with interruption).

The reason "positive anti-JCV antibody test" was less common among STAY patients (17.1%, n=18) compared with SWITCH patients (33.3%, n=19), whilst "pregnancy/planning of pregnancy" was more common (24.8%, n=26) among STAY patients than in SWITCH patients (14.0%, n=8).

Table 27: Interruption of natalizumab treatment prior to study inclusion (TRP)

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Patients with NTZ interruptions prior to study inclusion, n (%)				
No	607 (87.0)	343 (86.8)	83 (85.6)	1033 (86.8)
Yes	91 (13.0)	52 (13.2)	14 (14.4)	157 (13.2)
missing values	0	1	0	1
Patients with NTZ interruptions during the last 12 months prior to study inclusion [a], n (%)				
No	670 (96.0)	370 (93.4)	95 (97.9)	1135 (95.3)
Yes	28 (4.0)	26 (6.6)	2 (2.1)	56 (4.7)
Number of interruptions per patient prior to study inclusion, n (%)				
0	607 (87.0)	343 (86.8)	83 (85.6)	1033 (86.8)
1	79 (11.3)	48 (12.2)	13 (13.4)	140 (11.8)
2	10 (1.4)	3 (0.8)	1 (1.0)	14 (1.2)
3	2 (0.3)	1 (0.3)	0 (0.0)	3 (0.3)
missing values	0	1	0	1
Duration of interruption (months) [a]				
N	100	52	14	166
Mean ± SD	12.8 ± 13.6	13.0 ± 12.6	12.9 ± 10.7	12.9 ± 13.0
Median (Q1; Q3)	9.6 (5.7; 14.6)	9.2 (5.0; 14.5)	8.0 (5.3; 21.0)	9.6 (5.3; 14.7)
Min; Max	0.0; 80.0	0.0; 61.2	4.1; 36.9	0.0; 80.0
Reason(s) for interruption, n (%)				
Ineffectiveness of treatment	4 (3.8)	1 (1.8)	0 (0.0)	5 (2.8)
Adverse events/side effects of treatment	3 (2.9)	0 (0.0)	0 (0.0)	3 (1.7)
Pregnancy/Planning of pregnancy	26 (24.8)	8 (14.0)	2 (13.3)	36 (20.3)
Positive anti-JCV antibody test	18 (17.1)	19 (33.3)	3 (20.0)	40 (22.6)
Requested by patient	33 (31.4)	18 (31.6)	7 (46.7)	58 (32.8)
Non-compliance to treatment	4 (3.8)	4 (7.0)	0 (0.0)	8 (4.5)
Other clinical/medical reasons	24 (22.9)	12 (21.1)	6 (40.0)	42 (23.7)

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Multiple durations per patient and multiple reasons per interruption possible.
a: Only interruptions with non-missing start or end dates could be assessed here.
Source: Post-text Table 4.1.3

8.1.2. Natalizumab treatment after study inclusion

8.1.2.1. Number of natalizumab infusions

Table 28 presents the number of natalizumab infusions per patient after study entry.

The number of natalizumab infusions after study start widely ranged across patients of both cohorts from 1 to 43 infusions, the mean ± SD number of infusions was 26.5 ± 11.6 infusions (median 31.0 infusions) in the total TRP.

The number of natalizumab infusions after study start also widely ranged across patients of both cohorts from 4 to 43 infusions in STAY, and from 1 to 41 in SWITCH patients. The mean ± SD number of infusions was 34.1 ± 5.3 infusions in the STAY and 15.9 ± 9.5 infusions in the SWITCH cohort.

In the STAY cohort, the great majority of patients (77.9%) received between 30 to <40 infusions, whilst in the SWITCH cohort, similar proportions of patients received <10 infusions (31.1%), between 10 and <20 infusions (33.8%), and between 20 to <30 infusions (25.8%).

Table 28: Number of natalizumab infusions after study entry (TRP)

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Number of NTZ infusions after study start				
N	698	396	97	1191
Mean ± SD	34.1 ± 5.3	15.9 ± 9.5	14.9 ± 8.1	26.5 ± 11.6
Median (Q1; Q3)	36.0 (32.0; 37.0)	15.0 (8.0; 23.0)	14.0 (8.0; 20.0)	31.0 (18.0; 36.0)
Min; Max	4.0; 43.0	1.0; 41.0	2.0; 34.0	1.0; 43.0
Number of NTZ infusions after study start, n (%)				
<10	5 (0.7)	123 (31.1)	28 (28.9)	156 (13.1)
10 - <20	7 (1.0)	134 (33.8)	43 (44.3)	184 (15.4)
20 - <30	94 (13.5)	102 (25.8)	23 (23.7)	219 (18.4)
30 - <40	544 (77.9)	35 (8.8)	3 (3.1)	582 (48.9)
≥40	48 (6.9)	2 (0.5)	0 (0.0)	50 (4.2)

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Source: Post-text Table 4.2.1

8.1.2.2. Natalizumab infusion intervals

Table 29 summarizes the length of the intervals between natalizumab infusions based on the total number of infusion intervals. The overall number of infusion intervals was 30331 weeks, with 23101 for the STAY and 5886 for the SWITCH cohort; the mean ± SD duration of the intervals between natalizumab infusions was 4.6 ± 1.9 weeks in the STAY cohort and 4.6 ± 1.3 weeks in the SWITCH cohort.

In both cohorts, the interval duration between infusions was mostly from 3.5 to <4.5 weeks (62.1% of intervals in STAY and 60.9% in SWITCH).

Overall, 11058 infusion intervals (36.5%) were ≥4.5 weeks. The proportion of intervals ≥4.5 weeks (pointing to an EID) was minimally greater among SWITCH patients (37.5% of the 5886 infusion intervals) compared with STAY patients (36.2% of the 23101 infusion intervals).

Table 29: Length of intervals between natalizumab infusions (TRP)

	STAY (N=23101)	SWITCH (N=5886)	INDETERMI-NABLE (N=1344)	Total (N=30331)
Duration of intervals between NTZ infusions (weeks)				
N	23101	5886	1344	30331
Mean ± SD	4.6 ± 1.9	4.6 ± 1.3	4.9 ± 3.2	4.6 ± 1.9
Median (Q1; Q3)	4.0 (4.0; 5.0)	4.0 (4.0; 5.0)	4.1 (4.0; 5.0)	4.0 (4.0; 5.0)
Min; Max	0.1; 124.3	1.4; 37.6	0.7; 66.3	0.1; 124.3
Duration of intervals between NTZ infusions, n (%)				
<2.5 weeks	59 (0.3)	12 (0.2)	3 (0.2)	74 (0.2)
2.5 - <3.5 weeks	333 (1.4)	82 (1.4)	15 (1.1)	430 (1.4)
3.5 - <4.5 weeks	14349 (62.1)	3583 (60.9)	837 (62.3)	18769 (61.9)
4.5 - <5.5 weeks	5535 (24.0)	1460 (24.8)	325 (24.2)	7320 (24.1)
5.5 weeks and longer	2825 (12.2)	749 (12.7)	164 (12.2)	3738 (12.3)

NTZ = Natalizumab; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
N refers to the number of infusion intervals not to the number of patients.
Source: Post-text Table 4.2.2

The proportions of patients with an EID which was greater than the SmPC recommended one in 4 weeks standard interval dosing (SID) were analyzed *post-hoc* based on the definitions provided by Zhovtis-Ryerson (see section 6.2.3.2). Table 30 presents the proportions of patients with EID by the different definitions.

- Applying the primary EID definition, the proportions of patients **with EID in the last 18 months of dosing history** were overall 15.8% (121 patients, with 16.4% (98 patients; STAY) and 14.3% (21 patients; SWITCH) in subcohorts.
- Applying the secondary EID definition, the proportions of patients **with an EID period occurring anytime in the dosing history** were overall (29.2%, 223 patients), with 30.0% (179 patients; STAY) and 26.5% (39 patients; SWITCH) in subcohorts.
- Applying the tertiary EID definition, the proportions of patients **with a primarily EID dosing history** were overall 9.0 %, 69 patients), with 9.4% (56 patients; STAY) and 8.2% (12 patients; SWITCH) in subcohorts.

Table 30: Extended interval dosing (EID) (TRP)

	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
EID (primary definition), n (%)				
EID	98 (16.4)	21 (14.3)	2 (9.5)	121 (15.8)
Other	499 (83.6)	126 (85.7)	19 (90.5)	644 (84.2)
missing values	101	249	76	426
EID (secondary definition), n (%)				
EID	179 (30.0)	39 (26.5)	5 (23.8)	223 (29.2)
Other	418 (70.0)	108 (73.5)	16 (76.2)	542 (70.8)
missing values	101	249	76	426
EID (tertiary definition), n (%)				
EID	56 (9.4)	12 (8.2)	1 (4.8)	69 (9.0)
Other	541 (90.6)	135 (91.8)	20 (95.2)	696 (91.0)
missing values	101	249	76	426

EID = Extended interval dosing; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TRP = Treated patients
Patients with less than 548 days of treatment (N=244) or gaps of >12 weeks between infusions (N=116) have been excluded, i.e. were displayed as 'missing values'.
EID definitions acc. to Z. Ryerson et al. presented at ACTRIMS Forum 2018; San Diego, CA; February 1-3, 2018 (see section 6.2.3.2).
Source: Post-text Table 4.2.3

8.1.2.3. Time on natalizumab treatment

The time on natalizumab (from treatment start as well as from study start) was analyzed by Kaplan-Meier estimates and curve. Patients for whom no natalizumab discontinuation was reported (e.g., patients who stayed on natalizumab or who were lost-to-follow up) were censored with the date of their last visit.

Table 31 presents the product-limit estimates of the survivor function (=patients being on natalizumab treatment) for the **time on natalizumab (from treatment start)** in TRP, Figure 2 displays the Kaplan-Meier curve for years on natalizumab in total TRP.

The Kaplan-Meier estimated median time on natalizumab from treatment start (including study period) was 10.3 years (95% CI: 10.0 years to 10.7 years), the 25% quartile was 6.5 years (95% CI: 5.7 years to 7.1 years), the 75% quartile was 13.1 years (95% CI: lower limit was 11.9 years, the upper limit was not calculable) (post-text Table 4.2.4a).

Table 31: Product-limit survival (% of patients on NTZ treatment) estimates (TRP)

Time Point [year]	Survival (% of patients on NTZ)	Failure (% of patients discontinued NTZ)	Survival Standard Error	Number Failed (discontinued)	Number Left [a]
0.0	100.00	0.00	0.000	0	1191
1.0	100.00	0.00	0.000	0	1191
2.0	98.07	1.93	0.399	23	1166
3.0	91.47	8.53	0.812	101	1071
4.0	85.85	14.15	1.018	166	970
5.0	81.08	18.92	1.182	212	681
6.0	76.84	23.16	1.332	245	542
7.0	72.37	27.63	1.491	274	437
8.0	68.64	31.36	1.622	295	359
9.0	60.54	39.46	1.871	335	277
10.0	53.56	46.44	2.090	362	171
11.0	44.25	55.75	2.463	386	74
12.0	32.73	67.27	4.477	393	12
13.0	25.71	74.29	5.756	395	2
14.0	12.86	87.14	9.536	396	1
15.0	12.86	87.14	9.536	396	1

NTZ = Natalizumab; TRP = Treated patients
Time calculated from start of NTZ to NTZ discontinuation (or last visit if patient was still exposed to NTZ) + 1 day
a: Remained on NTZ (and in study)
Post-text Table 4.2.4a

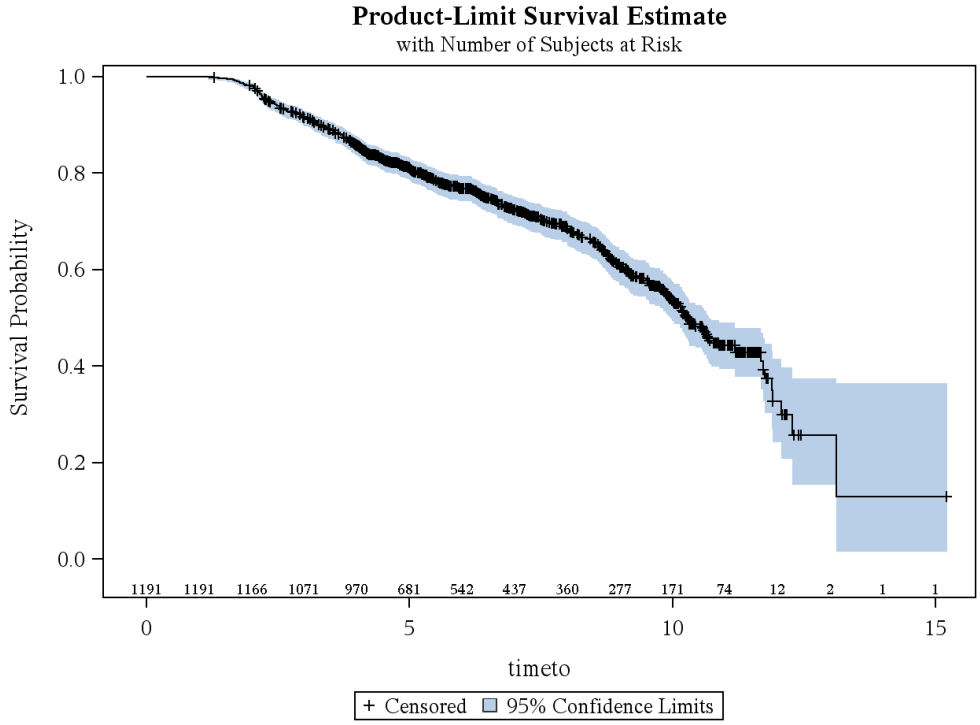
Figure 3 displays the Kaplan-Meier curve for **time on natalizumab by STAY vs. SWITCH** cohort. The median time on natalizumab since treatment start was about 4.5 years in the SWITCH cohort (graphically derived from the Kaplan-Meier curve by the writer).

Figure 4 displays the Kaplan-Meier curve for **time on natalizumab for subgroups by PML risk**. The median time on natalizumab decreased with increasing PML risk; it was shortest in the high PML risk group and longest in the no PML risk group: The median time on natalizumab was about 9.5 years for the high PML risk subgroup, about 9.7 years for intermediate PML risk subgroup, about 10.2 years for low PML risk subgroup, and about 12.0 years for no PML risk subgroup (all median times graphically derived from the Kaplan-Meier curve by the writer).

Figure 5 displays the Kaplan-Meier curve for **time on natalizumab for subgroups by EID (yes vs. no)**. The median time on natalizumab was comparable among patients with EID and those without EID, it was about 12.0 years in both subgroup (median times graphically derived from the Kaplan-Meier curve by the writer).

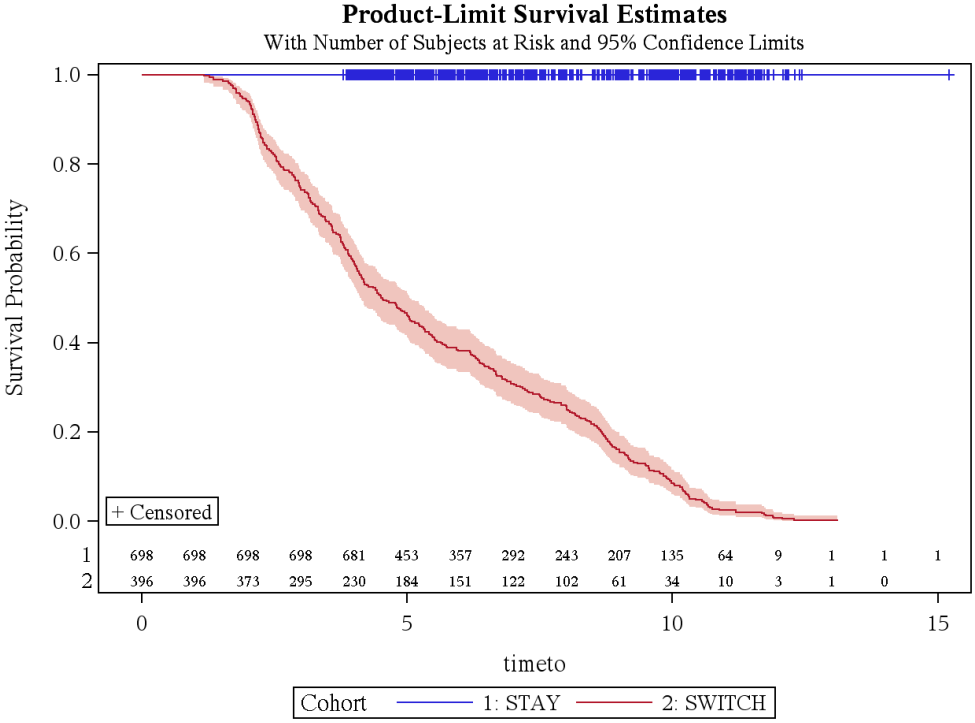
Post-text table 4.2.4b displays the product-limit survival estimates for staying on natalizumab (from treatment start) **for the PSM (N=580)** by year. The Kaplan-Meier estimated median time on natalizumab in the PSM was 8.2 years (95% CI: 7.1 years to 8.8 years), the 25% quartile was 4.1 years (95% CI: 3.8 years to 4.8 years), the 75% quartile was 11.7 years (95% CI: 10.2 years to 13.1 years). The Kaplan-Meier curves for the total PSM as well as for STAY vs. SWITCH cohorts in PSM are also presented in post-text table 4.2.4b.

Figure 2: Kaplan-Meier curve for time on natalizumab (years) (TRP)



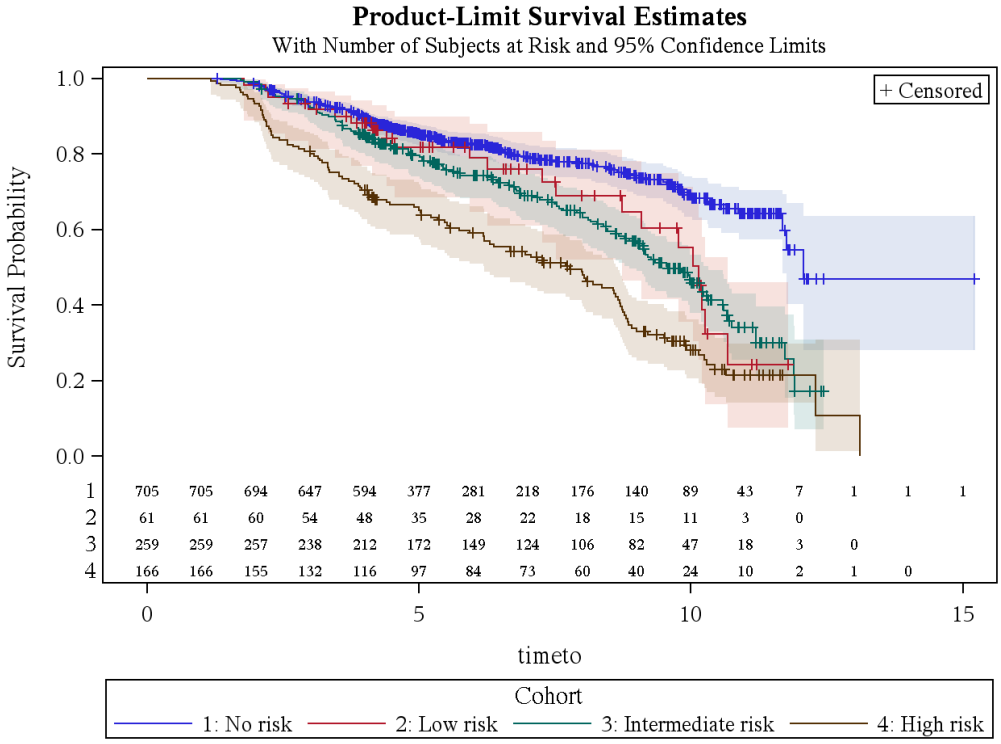
Time was calculated from start of NTZ to NTZ discontinuation (or last visit if patient is still exposed to NTZ) +1 day. Source: Post-text Table 4.2.4a

Figure 3: Kaplan-Meier curve for time on natalizumab (years): STAY vs. SWITCH (TRP)



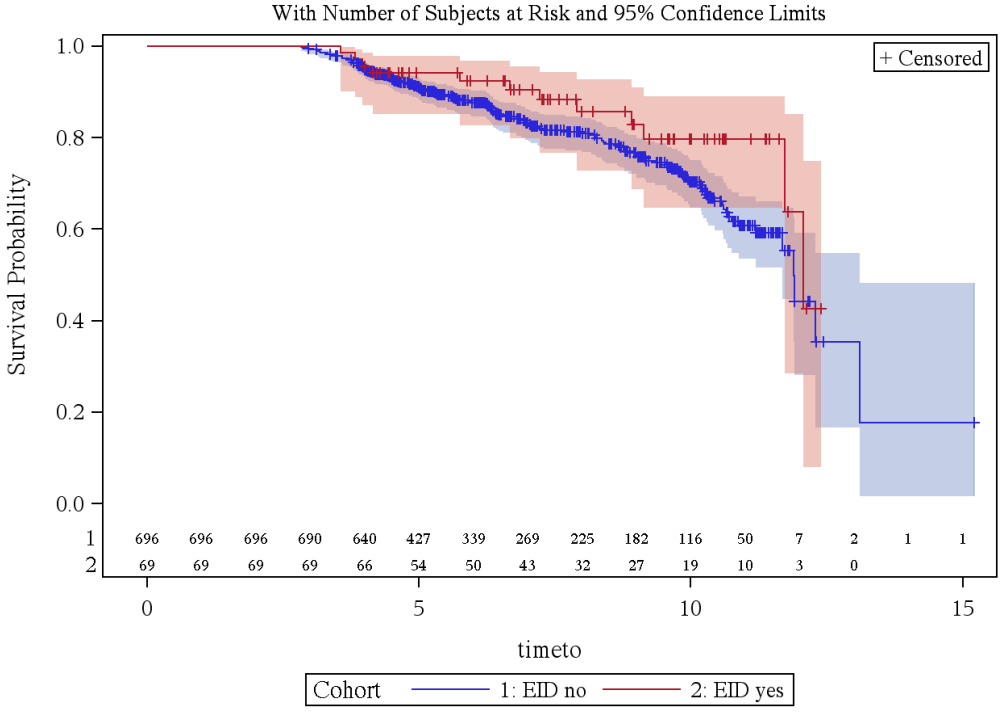
Time is calculated from start of NTZ to discontinuation of NTZ (or last visit if patient is still exposed to NTZ) +1 day. Source: Post-text Table 4.2.4a

Figure 4: Kaplan-Meier curve for time on natalizumab (years) by PML risk classes (TRP)



Time is calculated from start of NTZ to discontinuation of NTZ (or last visit if patient is still exposed to NTZ).
Source: Post-text Table 4.2.4a

Figure 5: Kaplan-Meier curve for time on natalizumab (years): EID vs. no EID (TRP)



Time is calculated from start of NTZ to discontinuation of NTZ (or last visit if patient is still exposed to NTZ).
Source: Post-text Table 4.2.4a

Table 32 presents the product-limit estimates of the survivor function (=patients being on natalizumab treatment) for the **time on natalizumab (since study entry)** in TRP, Figure 6 displays the Kaplan-Meier curve for years on natalizumab since study entry in total TRP.

The Kaplan-Meier estimated median **time on natalizumab since study entry** was 3.6 years (95% CI: 3.6 years to 3.8 years), the 25% quartile was 2.2 years (95% CI: 2.0 years to 2.4 years), the 75% quartile was 3.8 years (95% CI: lower and upper limits were not calculable) (post-text Table 4.2.5a).

Table 32: Product-limit survival (% of patients on natalizumab treatment) estimates for time on natalizumab since study entry (TRP)

Time Point [year]	Survival (% of patients on NTZ)	Failure (% of patients discontinued NTZ)	Survival Standard Error	Number Failed (discontinued)	Number Left [a]
0.0	100.00	0.00	0.000	0	1191
1.0	90.84	9.16	0.840	108	1061
2.0	77.86	22.14	1.223	256	869
3.0	66.11	33.89	1.424	381	411

NTZ = Natalizumab; TRP = Treated patients
Time calculated from study enrolment to discontinuation of NTZ (or last visit if patient was still exposed to NTZ) + 1 day.
a: Remained on NTZ (and in study)
Post-text Table 4.2.5a

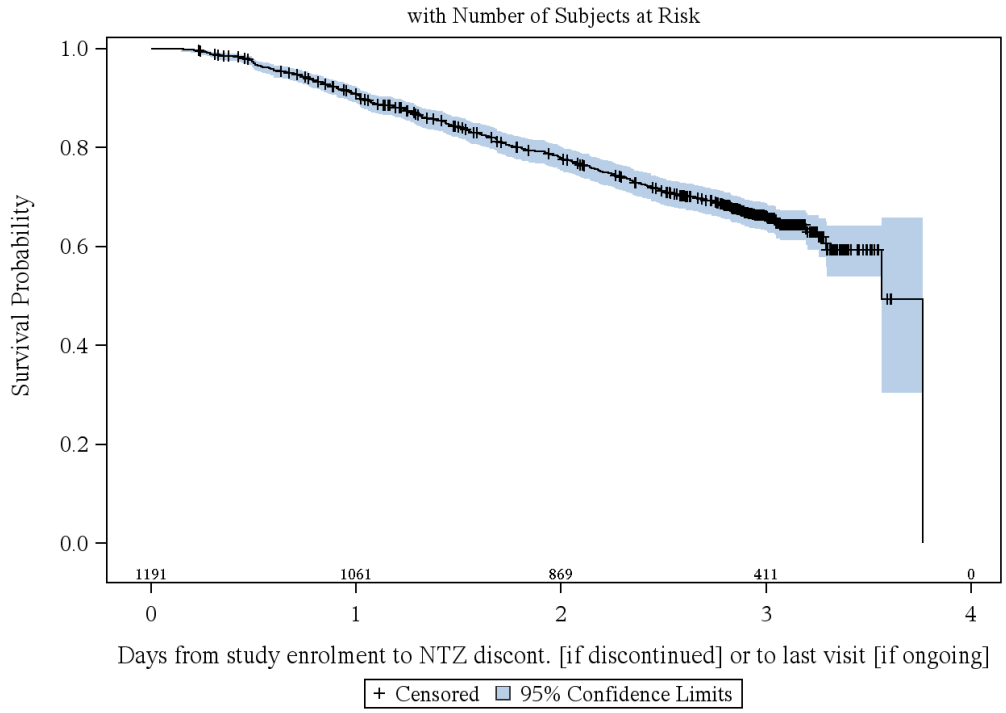
Figure 7 displays the Kaplan-Meier curve for time on natalizumab by **STAY vs. SWITCH** cohort. The median time on natalizumab since study entry was about 1.5 years in the SWITCH cohort (graphically derived from the figure by the writer).

Figure 8 displays the Kaplan-Meier curve for time on natalizumab for **subgroups by PML risk**. The median time on natalizumab decreased with increasing PML risk; it was shortest in the high PML risk group and longest in the no PML risk group: The median time on natalizumab was about 2.1 years for the high PML risk subgroup, about 3.2 years each for intermediate PML risk and for low PML risk subgroups, and not estimable for the no PML risk subgroup (all median times graphically derived from the Kaplan-Meier curve by the writer).

Figure 9 displays the Kaplan-Meier curve for time on natalizumab for **subgroups by EID (yes vs. no)**. The time on natalizumab tended to be slightly lower in patients without EID, however, due to the small number of patients with EID yes, which resulted in broad 95% CIs for the survival estimates, further interpretation of the results is not meaningful.

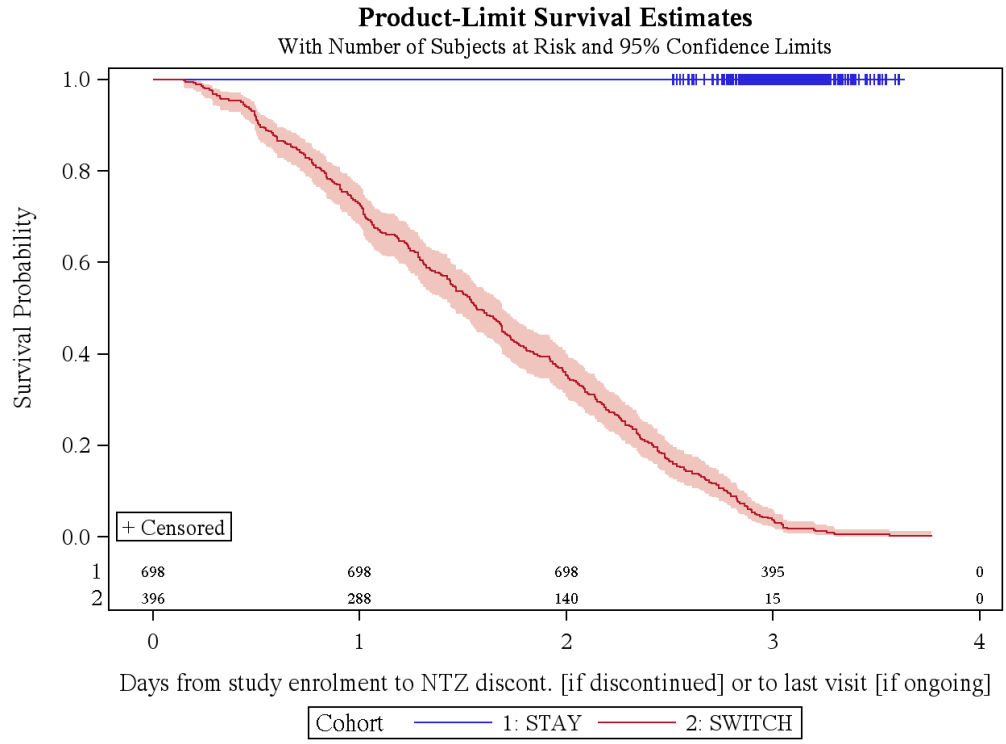
Post-text table 4.2.5b displays the product-limit survival estimates for **staying on natalizumab since study entry for the PSM (N=580)** by year. The Kaplan-Meier estimated median time on natalizumab in the PSM was 3.0 years (95% CI: 2.8 years to 3.3 years), the 25% quartile was 1.5 years (95% CI: 1.3 years to 1.6 years), the 75% quartile was 3.8 years (95% CI: 3.6 years to 3.8 years). The Kaplan-Meier curves for the total PSM as well as for STAY vs. SWITCH cohorts in PSM are also presented in post-text table 4.2.5b.

Figure 6: Kaplan-Meier curve for time on natalizumab since study entry (years) (TRP)



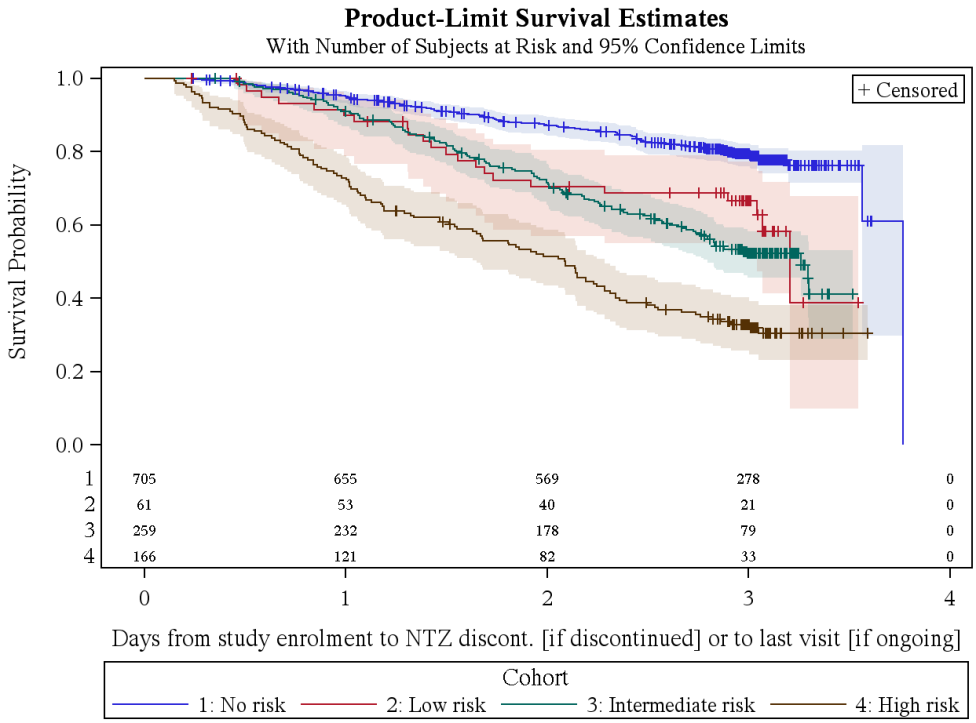
Time was calculated from study entry to NTZ discontinuation (or last visit if patient is still exposed to NTZ) +1 day.
Source: Post-text Table 4.2.5a

Figure 7: Kaplan-Meier curve for time on natalizumab since study entry (years): STAY vs. SWITCH (TRP)



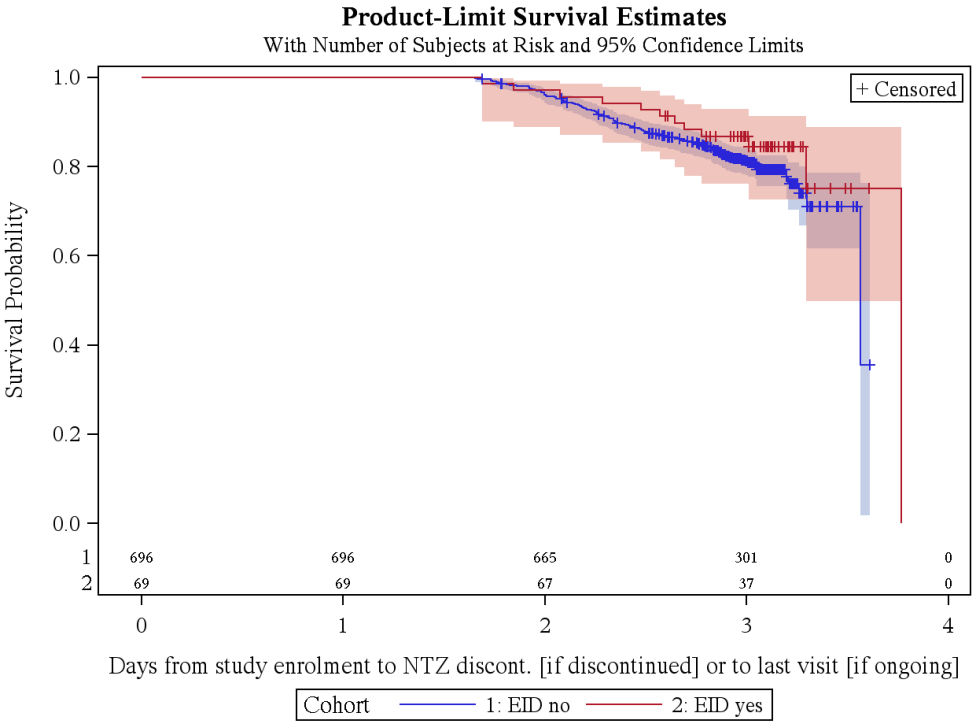
Time was calculated from study entry to NTZ discontinuation (or last visit if patient is still exposed to NTZ) +1 day.
Source: Post-text Table 4.2.5a

Figure 8: Kaplan-Meier curve for time on natalizumab since study entry (years) by PML risk classes (TRP)



Time was calculated from study entry to NTZ discontinuation (or last visit if patient is still exposed to NTZ).
Source: Post-text Table 4.2.5a

Figure 9: Kaplan-Meier curve for time on natalizumab since study entry (years): EID vs. no EID (TRP)



Time was calculated from study entry to NTZ discontinuation (or last visit if patient is still exposed to NTZ).
Source: Post-text Table 4.2.5a

Post-text Table 4.2.6 analyzes the duration of natalizumab treatment since treatment start **adjusted for non-safety discontinuations**. Overall, in the total TRP (N=1191), 235 patients discontinued natalizumab due to safety reasons (i.e., positive anti-JCV antibody test, PML risk, or AE), further 161 patients discontinued treatment due to non-safety reasons (competing events, i.e., reasons other than those mentioned before, which includes not specified reasons), 795 patients were censored (i.e., stayed on natalizumab treatment).

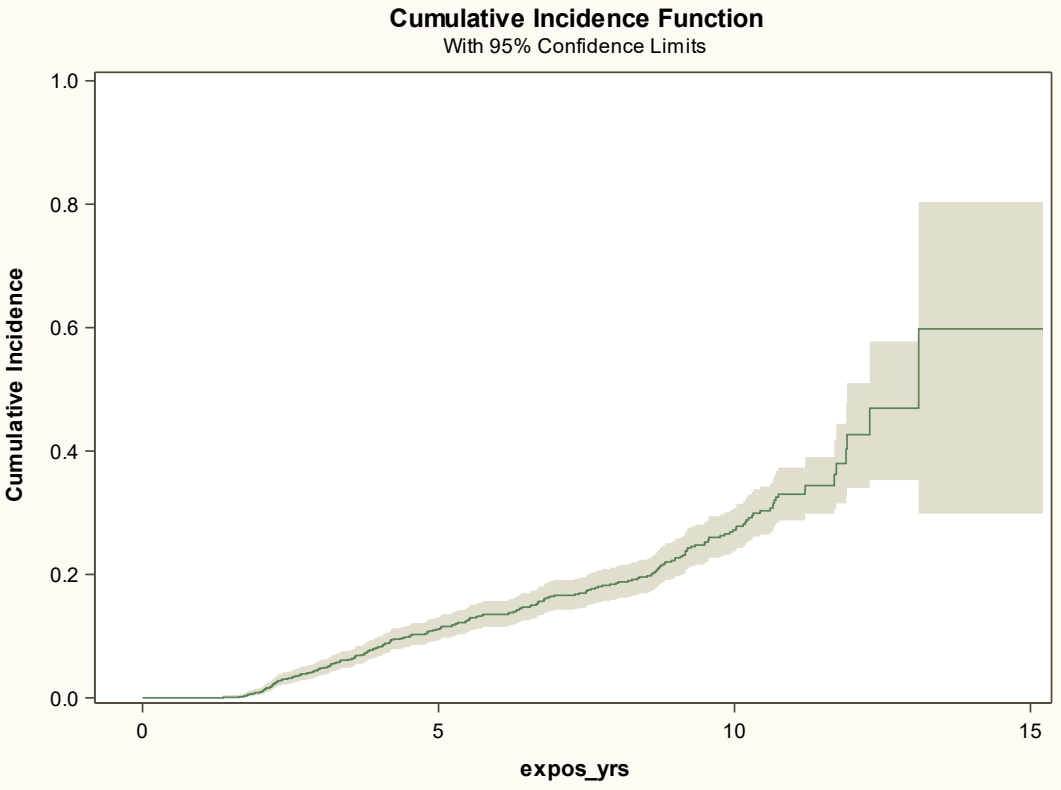
The cumulative incidence function for discontinuation due to safety reasons was calculated by a competing risk analysis (Table 33): After 2 years of natalizumab treatment, the cumulative incidence of discontinuation due to safety reasons was 0.9% (95% CI: 0.5% to 1.6%), after 3 years it increased to 4.7% (95% CI: 3.6% to 6.0%), and after 5 years to 11.1% (95% CI: 9.3% to 13.0%); After 10 years of natalizumab treatment, the cumulative incidence of discontinuation due to safety reasons in the TRP was 27.2% (95% CI: 23.7% to 30.7%).

Table 33: Cumulative incidence function for discontinuations due to safety reasons (TRP)

		95% Confidence Interval	
Exposure to NTZ [years]	**Cumulative Incidence [%]**	**Lower limit [%]**	**Upper limit [%]**
0	0.0	-	-
1	0.0	-	-
2	0.9	0.5	1.6
3	4.7	3.6	6.0
4	8.3	6.8	9.9
5	11.1	9.3	13.0
6	13.5	11.5	15.7
7	16.6	14.3	19.1
8	18.6	16.0	21.3
9	22.7	19.7	25.8
10	27.2	23.7	30.7
11	33.0	28.8	37.3
12	42.7	34.0	51.0
13	46.9	35.3	57.8
14	59.8	29.9	80.4
15	59.8	29.9	80.4

NTZ = Natalizumab; TRP = Treated patients
Time calculated from start of NTZ to discontinuation of NTZ (or last visit if patient was still exposed to NTZ) + 1 day.
Post-text Table 4.2.6

Figure 10: Cumulative incidence function plot for discontinuations due to safety reasons (TRP)



Time is calculated from start of NTZ to discontinuation of NTZ (or last visit if patient is still exposed to NTZ).
Source: Post-text Table 4.2.6

8.1.2.4. Prognostic factors for natalizumab discontinuation

A logistic regression to identify possible prognostic factors for natalizumab discontinuation was performed; the logistic regression model included the factors described in section 6.2.8.2.

No interaction terms were considered. A logistic regression model including all of these parameters was calculated (post-text Table 4.2.7) as well as a model with backward parameter selection (post-text Table 4.2.8).

Starting with the full model containing all parameters select (Table 34), the model determined the following parameters as possible prognostic factors contributing to natalizumab discontinuation (i.e., $p<0.05$ for continuous variables; 95% CI for combined odds ratio estimates did not include the value 1):

- Duration (days) of exposure to NTZ (including time before study start): Patients with a shorter treatment exposure were more likely to discontinue natalizumab.
- Duration (years) of disease (since diagnosis): Patients with a longer duration of disease were more likely to discontinue natalizumab.
- Last EDSS score before discontinuation/end of study: Patients with higher EDSS at last visit before discontinuation/end of study were more likely to discontinue natalizumab.

- EID not calculable vs. EID yes: Patients with EID not calculable were 5.91 times as likely to be discontinued from natalizumab than patients with EID yes. Please note that per definition an EID/SID can only be determined in patients with a longer treatment duration and thus this result might be biased.
- PML risk at baseline: Patients entering the study with a high / intermediate / low PML risk were 8.25 / 4.37 / 2.30 times as likely to be discontinued from natalizumab than patients classified with "no risk".

Table 34: Logistic regression for factors contributing to natalizumab discontinuation (TRP)

Analysis of Maximum Likelihood Estimates				
Parameter	**Combined Estimate**	**Combined Std Error**	**Combined Waldχ^2**	**Combined p-value**
Duration [days] of exposure to NTZ (including time before study start)	**-0.000592**	**0.000136**	**-4.35**	**<0.0001**
Duration [years] of disease (since diagnosis)	**0.028777**	**0.014221**	**2.02**	**0.0431**
Time [days] since last relapse before discontinuation respectively end of study	0.000072962	0.000146	0.50	0.6163
Last EDSS score before discontinuation respectively end of study	**0.115222**	**0.047784**	**2.41**	**0.0169**
Last treatment satisfaction (TSQM) value before discontinuation respectively end of study	-0.007255	0.004195	-1.73	0.0838

Combined Odds Ratio Estimates			
Effect	**Point estimate**	**Lower 95% Wald CL**	**Upper 95% Wald CL**
0 relapses vs. ≥ 2 relapses	0.72	0.41	1.29
1 relapse vs. ≥ 2 relapses	0.64	0.40	1.02
EID no vs. EID yes	1.46	0.72	2.99
EID not calculable vs. EID yes	**5.91**	**2.87**	**12.19**
Prior immunosuppressive treatment No vs. Yes	1.19	0.76	1.87
High risk vs. No risk	**8.25**	**5.37**	**12.69**
Intermediate risk vs. No risk	**4.37**	**3.07**	**6.24**
Low risk vs. No risk	**2.30**	**1.24**	**4.25**

CL = Confidence limit; EDSS = Expanded Disability Status Scale; EID = Extended interval dosing (tertiary definition); NTZ = Natalizumab; TRP = Treated patients; TSQM = Treatment Satisfaction Questionnaire on Medication

Missing continuous values were replaced by multiple imputation (seed=2020, k=5 imputations), while missing values in categorical variables were handled as separate category.

Post-text Table 4.2.7

Starting with the full model containing all parameters described in Table 34, backward stepwise selection (or backward elimination) was performed, and the least significant variables were removed one after the other (backward selection) from the model. The parameters were removed in the following order (see post-text Table 4.2.8): 1. Prior immunosuppressive treatment (no/yes); 2. Time since last MS relapse before discontinuation (days); 3. Number of MS relapses

during natalizumab treatment; 4. TSQM-9 global satisfaction scale. The model remaining after stepwise backward selection is described in Table 35, the results were similar to those of the full model (i.e., p<0.05 for continuous variables; 95% CI for combined odds ratio estimates did not include the value 1):

- Duration (days) of exposure to natalizumab (including time before study start): Patients with a shorter treatment exposure were more likely to discontinue natalizumab.
- Last EDSS score before discontinuation/end of study: Patients with higher EDSS at last visit before discontinuation/end of study were more likely to discontinue natalizumab.
- EID not calculable vs. EID yes: Patients with EID not calculable were 6.07 times as likely to be discontinued from natalizumab than patients with an EID yes.
- PML risk at baseline: Patients entering the study with a high / intermediate / low PML risk were 8.10 / 4.38 / 2.24 times as likely to be discontinued from natalizumab than patients classified as "no risk".

The p-value for the duration (years) of disease (since diagnosis) was only very close to the threshold value of <0.05, the combined estimate indicated that patients with a longer duration of disease were more likely to discontinue natalizumab.

Table 35: Logistic regression with backward parameter selection for factors contributing to natalizumab discontinuation (TRP)

Analysis of Maximum Likelihood Estimates				
Parameter	**Combined Estimate**	**Combined Std Error**	**Combined Waldχ^2**	**Combined p-value**
Duration [days] of exposure to NTZ (including time before study start)	-0.000572	0.000086461	-6.62	<0.0001
Duration [years] of disease (since diagnosis)	0.025956	0.013591	1.91	0.0563
Last EDSS score before discontinuation respectively end of study	0.129536	0.046311	2.80	0.0056

Combined Odds Ratio Estimates			
Effect	**Point estimate**	**Lower 95% Wald CL**	**Upper 95% Wald CL**
EID no vs. EID yes	1.48	0.72	3.03
EID not calculable vs. EID yes	6.07	2.94	12.52
High risk vs. No risk	8.10	5.28	12.42
Intermediate risk vs. No risk	4.38	3.08	6.24
Low risk vs. No risk	2.24	1.22	4.12

CL = Confidence limit; EDSS = Expanded Disability Status Scale; EID = Extended interval dosing (tertiary definition); NTZ = Natalizumab; TRP = Treated patients
Missing continuous values were replaced by multiple imputation (seed=2020, k=5 imputations), while missing values in categorical variables were handled as separate category.
Post-text Table 4.2.8

8.1.2.5. Reasons for temporary natalizumab discontinuation during study

The reasons for temporary natalizumab discontinuation during the study are presented in post-text Table 4.2.9 and Table 36.

Overall, 154 patients (12.9%) discontinued natalizumab temporarily during the study. The proportion of patients with **temporary natalizumab discontinuation due to any reason** was greater in the SWITCH cohort (22.0%) compared with the STAY (8.5%) or INDETERMINABLE (8.2%) cohorts.

The most frequent reasons for a temporary discontinuation in the total TRP were "(planned) pregnancy" with 3.4% (41 patients) with similar proportions across patients of the STAY and SWITCH cohorts (3.9% and 3.3%), and "other clinical/medical reasons" (total 3.4% or 41 patients with 1.6% in STAY vs. 6.8% in SWITCH).

The second most common reasons for a temporary discontinuation in the total TRP were "PML risk" (total 2.5% with 1.0% in STAY vs. 5.1% in SWITCH), and "requested by patient" (overall 2.5% with 1.6% in STAY vs. 4.5% in SWITCH).

Table 36: Reasons for temporary natalizumab discontinuation during study

Reason(s) for premature NTZ discontinuation	STAY (N=698)	SWITCH (N=396)	INDETERMINABLE (N=97)	Total (N=1191)
Any reason, n (%)	**59 (8.5)**	**87 (22.0)**	**8 (8.2)**	**154 (12.9)**
(Planned) pregnancy	27 (3.9)	13 (3.3)	1 (1.0)	41 (3.4)
Other clinical/medical reasons	11 (1.6)	27 (6.8)	3 (3.1)	41 (3.4)
Requested by patient	11 (1.6)	18 (4.5)	1 (1.0)	30 (2.5)
PML risk	7 (1.0)	20 (5.1)	3 (3.1)	30 (2.5)
Adverse events/side effects	7 (1.0)	7 (1.8)	1 (1.0)	15 (1.3)
Ineffectiveness	3 (0.4)	10 (2.5)	0 (0.0)	13 (1.1)
Positive JCV antibody test	1 (0.1)	7 (1.8)	0 (0.0)	8 (0.7)
Non-compliance	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.3)
Informed consent withdrawn	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

JCV = John-Cunningham virus; NTZ = Natalizumab; PML = Progressive multifocal leukoencephalopathy; TRP = Treated patients
Reasons sorted by descending frequency in the total group.
Source: Post-text Table 4.2.9

A listing by patient of all "other" reasons for interrupting natalizumab as reported verbatim (provided that a specific reason had been documented as additional information) is shown in post-text listing Table 4.2.9.2.

8.2. Effectiveness and other endpoints

All effectiveness and other endpoints were analyzed using the FAS (N=1189).

8.2.1. Relapses and annualized relapse rates

At baseline, the data on MS relapses after start of natalizumab but prior study entry as well as the number of MS relapses in the 12 months prior to start of natalizumab were collected retrospectively as the total number of relapses within the respective time interval. Data on each relapse

after study enrollment were collected prospectively at each documentation visit. Table 37 presents number of MS relapses prior to and after study enrollment.

During the last 12 months prior to initiating natalizumab, only 8.1% of the patients in the FAS were relapse-free with similar proportions in STAY (8.5%) and SWITCH (8.1%) cohorts. Patients with 1, 2, or >2 relapses within the last 12 months prior start of natalizumab were relatively equally distributed among the relapse frequency categories (1, 2, >2 relapses) and comparable across STAY and SWITCH cohorts (about 24.8%–27.1% in each relapse frequency category in both cohorts and overall).

After starting natalizumab, nearly two thirds of patients (total 64.9%, and 64.6%–67.4% across all cohorts) did not experience any MS relapses **between initiation of natalizumab and study enrollment**; overall 19.4% of patient in the total FAS had suffered from 1 relapse with similar proportions in STAY (19.1%) and SWITCH (18.7%) cohorts; 2 or more relapses occurred less frequently.

From after study enrollment to natalizumab discontinuation, 79.5% of patients in the STAY cohort and 76.0% in the SWITCH cohort were relapse-free, further 13.9% and 15.7% experienced 1 relapse, respectively; 2 or more relapses occurred less frequently.

After natalizumab discontinuation, 78.5% of patients (n=311) in the SWITCH cohort were relapse-free, 14.4% (57 patients) had 1 relapse, 4.0% (16 patients) had 2 relapses, and 3.0% (12 patients) had >2 relapses until their last visit.

Table 37: Number of MS relapses prior to and after study enrollment (FAS)

Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=95)	Total (N=1189)
Number of relapses in the 12 months prior to NTZ, n (%)				
0	59 (8.5)	32 (8.1)	5 (5.3)	96 (8.1)
1	182 (26.1)	98 (24.8)	30 (31.6)	310 (26.1)
2	177 (25.4)	106 (26.8)	20 (21.1)	303 (25.5)
>2	187 (26.8)	107 (27.1)	20 (21.1)	314 (26.4)
Unknown	93 (13.3)	52 (13.2)	20 (21.1)	165 (13.9)
missing values	0	1	0	1
Number of relapses after NTZ but prior to study enrollment [a], n (%)				
0	452 (64.8)	255 (64.6)	64 (67.4)	771 (64.9)
1	133 (19.1)	74 (18.7)	23 (24.2)	230 (19.4)
2	32 (4.6)	28 (7.1)	4 (4.2)	64 (5.4)
>2	44 (6.3)	24 (6.1)	3 (3.2)	71 (6.0)
unknown	37 (5.3)	14 (3.5)	1 (1.1)	52 (4.4)
missing values	0	1	0	1
Number of relapses after study enrollment until NTZ discontinuation/last visit [b], n (%)				
0	555 (79.5)	301 (76.0)	81 (85.3)	937 (78.8)
1	97 (13.9)	62 (15.7)	10 (10.5)	169 (14.2)
2	29 (4.2)	20 (5.1)	3 (3.2)	52 (4.4)
>2	17 (2.4)	13 (3.3)	1 (1.1)	31 (2.6)
unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
missing values	0	0	0	0
Number of relapses after NTZ discontinuation [c], n (%)				
0	698 (100.0)	311 (78.5)	95 (100.0)	1104 (92.9)
1	0 (0.0)	57 (14.4)	0 (0.0)	57 (4.8)
2	0 (0.0)	16 (4.0)	0 (0.0)	16 (1.3)
>2	0 (0.0)	12 (3.0)	0 (0.0)	12 (1.0)
unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
missing values	0	0	0	0

NTZ = Natalizumab; FAS = Full Analysis Set
Note: Data on number of MS relapses prior to study enrollment were collected retrospectively, data on relapses during study were collected prospectively.
a: During the interval "start of natalizumab - start of study (=date of visit 1)"
b: During the interval "start of study (=date of visit 1) - discontinuation of natalizumab (or last visit if patient is still exposed to NTZ)"
c: During the interval "discontinuation of natalizumab - last visit".
Source: Post-text Table 5.1.1

One of the main analyses was the analysis of the ARR in the total FAS. Considering the information on time intervals for the different study periods described in section 7.1.2, in Table 10 and using information on the number of relapses within a specific study period which is provided in Table 37, the data basis for the evaluation of ARR was created (Table 38).

Table 38: Data basis for ARR evaluation (FAS)

Time interval	Parameter	STAY (N=698)	SWITCH (N=396)	INDETERMINABLE (N=95)	Total (N=1189)
ARR after NTZ start but prior to study enrollment [a]	Number of non-missing relapse counts [d]	661	381	94	1136
	Total number of relapses	407	231	41	679
	Total subject-years followed	2738	1512	347	4597
	Total subject-years followed-restricted to subjects with non-missing relapse counts	2541	1425	339	4304
ARR after study inclusion until NTZ discontinuation or last visit (if patient is still exposed to NTZ) [b]	Number of non-missing relapse counts [d]	698	396	95	1189
	Total number of relapses	218	149	19	386
	Total subject-years followed	2114	641	153	2908
ARR after NTZ discontinuation [c]	Number of non-missing relapse counts [d]	698	396	95	1189
	Total number of relapses	0	139	0	139
	Total subject-years followed	-	362	-	362

ARR = Annualized Relapse Rate; NTZ = Natalizumab; FAS = Full Analysis Set
Note: Data on number of relapses prior to study enrollment were collected retrospectively, data on relapses during study were collected prospectively.
a: During the interval "start of natalizumab - start of study (=date of visit 1)"
b: During the interval "start of study (=date of visit 1) - discontinuation of natalizumab (or last visit)"
c: During the interval "discontinuation of natalizumab - last visit".
d: Relapse counts were "unknown": in 52 patients after natalizumab start but prior to study; in 0 cases after study inclusion until natalizumab discontinuation; in 0 cases after natalizumab discontinuation.
Source: Post-text Table 5.1.2

The **estimated ARR prior to and after natalizumab discontinuation** in the total FAS was adjusted for the covariates gender, baseline EDSS (<3 vs. ≥3), disease duration (<8 vs. ≥ 8 years), number of previous DMTs (0 vs. 1 vs. ≥2), and treatment duration (<3 vs. ≥ 3 years) (Table 39).

The estimated ARR **after start of natalizumab but prior to study enrollment** was 0.127 (95% CI: 0.099 to 0.165) relapses per year; it slightly decreased to 0.100 (95% CI 0.078 to 0.130) relapses per year for the time interval **from study inclusion to natalizumab discontinuation/ last visit** (if patient was still exposed to natalizumab at study end). **After discontinuation of natalizumab**, the estimated ARR markedly increased to 0.269 (95% CI: 0.193 to 0.374) relapses per year. The differences between estimated ARR after natalizumab discontinuation and the ARRs from start of natalizumab to study enrollment/from study enrollment until natalizumab discontinuation or last visit were statistically relevant because the 95% CIs did not overlap.

In the total PSM, the estimated ARRs for each time interval were generally slightly higher compared to those in the total FAS (Table 39). Again, non-overlapping 95% CIs were observed between the estimated ARR after natalizumab discontinuation and the ARRs from natalizumab to study enrollment or from study enrollment until natalizumab discontinuation/last visit.

Table 39: Annualized relapse rates for the total cohort (FAS and PSM)

Time interval	FAS		PSM	
	ARR estimate [a]	[95% CI]	ARR estimate [a]	[95% CI]
After NTZ start but prior to study enrollment	0.127	[0.099; 0.165]	0.150	[0.125; 0.180]
After study inclusion until NTZ discontinuation (or last visit if patient is still exposed to NTZ)	0.100	[0.078; 0.130]	0.126	[0.103; 0.153]
After NTZ discontinuation	0.269	[0.193; 0.374]	0.308	[0.235; 0.403]

ARR = Annualized Relapse Rate; NTZ = Natalizumab; FAS = Full Analysis Set
a: Negative binomial regression including covariates: gender, baseline EDSS (<3 vs. ≥3), disease duration (<8 vs. ≥8 years), number of previous DMTs (0 vs. 1 vs. ≥2), and treatment duration (<3 vs. ≥ 3 years). Missing data were handled as separate category.
Source: Post-text Table 5.1.3 and Table 5.1.4

Table 40 presents the ARR estimates by STAY vs. SWITCH cohorts for the FAS and the PSM.

In the FAS, the estimated ARR for the time interval after start of natalizumab but prior to study enrollment were similar in STAY and SWITCH patients (0.131 and 0.133, respectively). The ARR after study inclusion until last visit in the STAY cohort (0.078) was considerably lower than compared to the SWITCH cohort (0.175), the 95% CIs did not overlap. ARR further increased to 0.274 relapses per year for the interval after natalizumab discontinuation until end of study in the SWITCH cohort.

In the PSM, in both cohorts, the ARR estimates were mostly slightly higher for all time intervals compared with the FAS, but largely confirmed the qualitative findings from the FAS. However, the ARR estimate for the interval from start of natalizumab but prior to study enrollment, was numerically lower in the STAY cohort (0.129) than in the SWITCH cohort (0.170), but overlapping 95% CIs indicated that this difference might not be statistically relevant (Table 40).

Table 40: Annualized relapse rates by STAY vs. SWITCH cohorts (FAS and PSM)

Cohort	FAS		PSM	
Time interval	ARR estimate [a]	[95% CI]	ARR estimate [a]	[95% CI]
STAY				
After NTZ start but prior to study enrollment	0.131	[0.099; 0.175]	0.129	[0.099; 0.168]
After study inclusion until last visit	0.078	[0.058; 0.104]	0.081	[0.060; 0.110]
SWITCH				
After NTZ start but prior to study enrollment	0.133	[0.100; 0.177]	0.170	[0.137; 0.211]
After study inclusion until NTZ discontinuation	0.175	[0.131; 0.234]	0.198	[0.157; 0.251]
After NTZ discontinuation	0.274	[0.198; 0.380]	0.310	[0.237; 0.405]
INDETERMINABLE				
After NTZ start but prior to study enrollment	0.103	[0.066; 0.160]	-	-
After study inclusion until NTZ discontinuation (or last visit if patient is still exposed to NTZ)	0.087	[0.049; 0.152]	-	-

ARR = Annualized Relapse Rate; NTZ = Natalizumab; FAS = Full Analysis Set; PSM = Propensity score matching
a: Negative binomial regression including covariates: gender, baseline EDSS (<3 vs. ≥3), disease duration (<8 vs. ≥8 years), number of previous DMTs (0 vs. 1 vs. ≥2), and treatment duration (<3 vs. ≥ 3 years). Missing data were handled as separate category.
Source: Post-text Table 5.1.5 and Table 5.1.6

Table 41 presents the ARR estimates for EID yes vs. EID no (according to tertiary definition) cohorts for the FAS and the PSM.

In the FAS, the estimated ARR for the time interval after start of natalizumab but prior to study enrollment were minimally higher in patients with EID than in patients without (0.132 and 0.118, respectively). The estimated ARRs after study inclusion until last visit were lower and comparable in both populations (EID yes vs. EID no with 0.084 and 0.076, respectively). After discontinuation of natalizumab, the estimated ARRs increased in both populations; in addition, the ARR in the population with EID was markedly higher (1.441; 95% CI: 0.527 to 3.939) compared to the population without (0.233; 95% CI: 0.141; 0.386). However, the 95% CI for the estimated ARR in the EID yes cohort was quite wide indicating that this estimate was uncertain and not very precise.

Despite some numerical differences compared to the FAS, the ARR estimates in the PSM largely confirmed the qualitative findings from the FAS. The only exception was ARR estimate for the interval from start of natalizumab but prior to study enrollment, which was lower in the EID yes subgroup (0.112) than in the EID no subgroup (0.145), but overlapping 95% CIs indicated that this difference might not be statistically relevant (Table 41).

Table 41: Annualized relapse rates for EID yes vs. EID no subgroups (FAS and PSM)

Subgroup	FAS		PSM	
Time interval	ARR estimate [a]	[95% CI]	ARR estimate [a]	[95% CI]
EID yes				
After NTZ start but prior to study enrollment	0.132	[0.079; 0.220]	0.112	[0.054; 0.232]
After study inclusion until NTZ discontinuation/last visit (if patient is still exposed to NTZ)	0.084	[0.050; 0.142]	0.100	[0.046; 0.219]
After NTZ discontinuation	1.441	[0.527; 3.939]	1.048	[0.310; 3.548]
EID no				
After NTZ start but prior to study enrollment	0.118	[0.089; 0.156]	0.145	[0.115; 0.184]
After study inclusion until NTZ discontinuation/last visit (if patient is still exposed to NTZ)	0.076	[0.057; 0.101]	0.091	[0.069; 0.120]
After NTZ discontinuation	0.233	[0.141; 0.386]	0.237	[0.119; 0.472]
EID not calculable				
After NTZ start but prior to study enrollment	0.129	[0.098; 0.169]	0.164	[0.129; 0.209]
After study inclusion until NTZ discontinuation/last visit (if patient is still exposed to NTZ)	0.152	[0.114; 0.203]	0.218	[0.166; 0.285]
After NTZ discontinuation	0.250	[0.179; 0.350]	0.314	[0.234; 0.421]

ARR = Annualized Relapse Rate; EID = Extended interval dosing NTZ = Natalizumab; FAS = Full Analysis Set; PSM = Propensity score matching

a: Negative binomial regression including covariates: gender, baseline EDSS (<3 vs. ≥3), disease duration (<8 vs. ≥8 years), number of previous DMTs (0 vs. 1 vs. ≥2), and treatment duration (<3 vs. ≥ 3 years). Missing data were handled as separate category.

Source: Post-text Table 5.1.7 and Table 5.1.8

8.2.2. Expanded Disability Status Scale

The EDSS was analyzed as described in section 6.2.9.2. Table 42 shows the course of the total EDSS score at selected time points for the STAY and SWITCH populations, the full course is shown in post-text Table 5.3.1.

At start of natalizumab, the EDSS was (mean ± SD) 3.0 ± 1.5 in STAY and 3.2 ± 1.8 in SWITCH-ON patients (median: 3.0 in both cohorts) (retrospective documentation). At baseline, EDSS was numerically lower in STAY compared with SWITCH-ON cohort (2.7 ± 1.6, median 2.5 vs. 3.1 ± 1.8, median 3.0, respectively). No relevant mean or median changes from baseline were noted in either cohort throughout the study course. In the SWITCH-OFF subcohort, the last EDSS value before discontinuation of natalizumab was 3.1 ± 1.8 (median 3.0); again there were no relevant mean or median changes from baseline in EDSS until last visit. There were some marked individual changes, deteriorations and improvements, in all cohorts during study course.

Table 42: Expanded Disability Status Scale (FAS) – multipage table

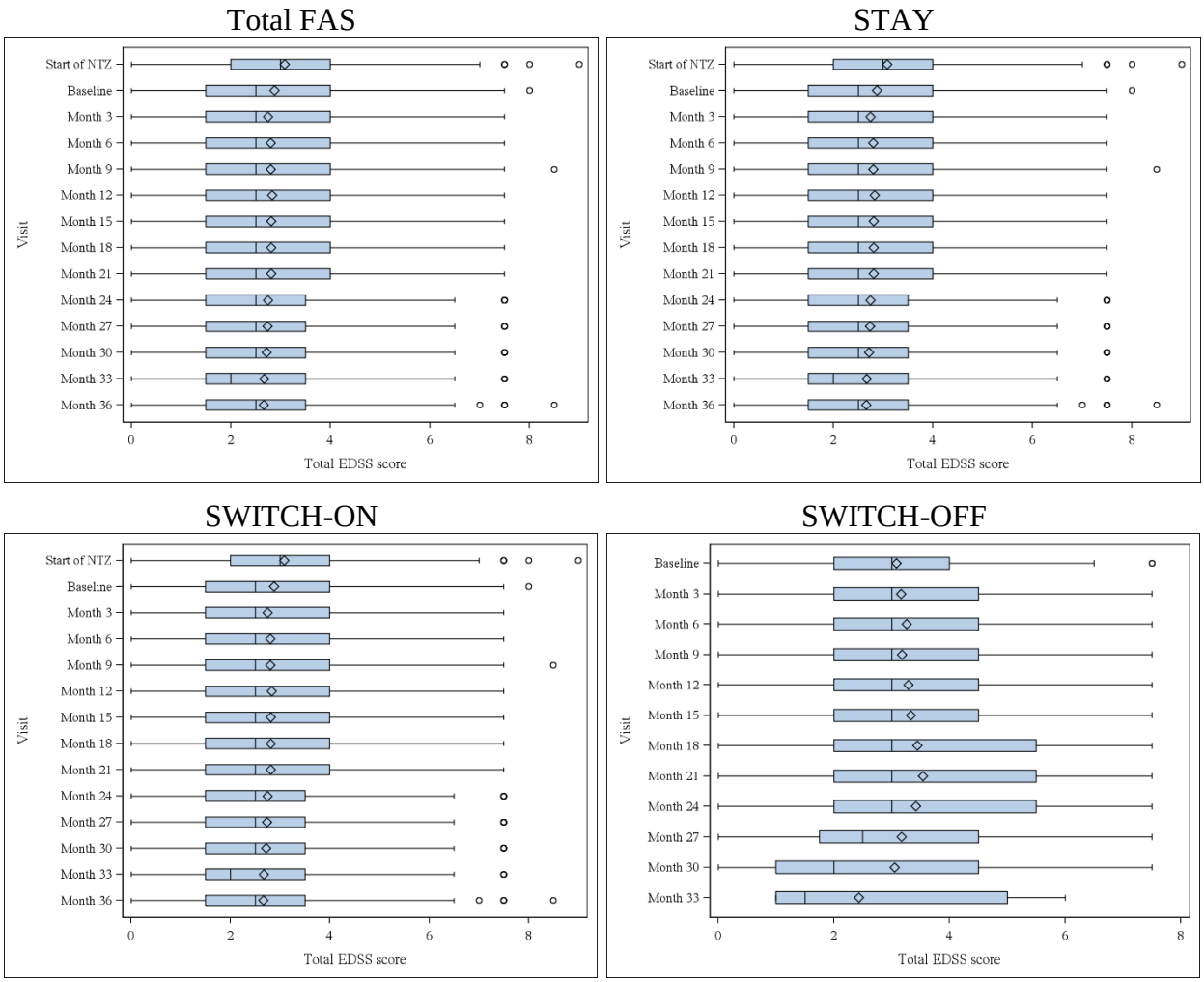
Time point	STAY	SWITCH-ON	SWITCH-OFF
Start of NTZ			
N (patients)	698	396	-
N (values / values imputed)	478 / 0	275 / 0	-
Mean ± SD	3.0 ± 1.5	3.2 ± 1.8	-
Median (Q1; Q3)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	-
Min; Max	0.0; 9.0	0.0; 8.0	-
Baseline			
N (patients)	698	396	325 [a]
N (values / values imputed)	613 / 0	351 / 0	153 / 0
Mean ± SD	2.7 ± 1.6	3.1 ± 1.8	3.1 ± 1.8
Median (Q1; Q3)	2.5 (1.5; 3.5)	3.0 (1.5; 4.0)	3.0 (2.0; 4.0)
Min; Max	0.0; 7.5	0.0; 8.0	0.0; 7.5
Month 12			
N (patients)	697	299	167
N (values / values imputed)	549 / 143	229 / 80	131 / 35
Mean ± SD	2.6 ± 1.7	3.1 ± 1.8	3.3 ± 1.9
Median (Q1; Q3)	2.5 (1.5; 3.5)	3.0 (1.5; 4.0)	3.0 (2.0; 4.5)
Min; Max	0.0; 7.5	0.0; 7.5	0.0; 7.5
Month 24			
N (patients)	693	139	66
N (values / values imputed)	592 / 202	111 / 49	58 / 18
Mean ± SD	2.6 ± 1.7	3.0 ± 1.9	3.4 ± 2.0
Median (Q1; Q3)	2.5 (1.5; 3.5)	2.5 (1.5; 4.5)	3.0 (2.0; 5.5)
Min; Max	0.0; 7.5	0.0; 7.5	0.0; 7.5
Month 36			
N (patients)	607	13	-
N (values / values imputed)	540 / 213	12 / 6	-
Mean ± SD	2.7 ± 1.7	2.7 ± 1.8	-
Median (Q1; Q3)	2.5 (1.5; 3.5)	2.0 (1.8; 4.0)	-
Min; Max	0.0; 8.5	0.0; 6.5	-
Last visit			
N (patients)	621	303 [b]	178 [c]
N (values / values imputed)	621 / 254	303 / 126	178 / 48
Mean ± SD	2.7 ± 1.7	3.2 ± 1.8	3.4 ± 1.9
Median (Q1; Q3)	2.5 (1.5; 3.5)	3.0 (2.0; 4.5)	3.0 (2.0; 4.5)
Min; Max	0.0; 8.5	0.0; 7.5	0.0; 7.5
Change from baseline to last visit			
N (patients)	621	303 [b]	178 [c]

N (values / values imputed)	573 / 228	284 / 114	114 / 21
Mean ± SD	0.0 ± 0.8	0.1 ± 0.9	0.1 ± 0.8
Median (Q1; Q3)	0.0 (0.0; 0.5)	0.0 (0.0; 0.5)	0.0 (0.0; 0.5)
Min; Max	-3.5; 3.5	-2.5; 5.5	-2.5; 3.0

EDSS = Expanded Disability Status Scale; FAS = Full Analysis Set; NTZ = Natalizumab; LOCF = Last observation carried forward; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
a: Last value before NTZ discontinuation
b: Last post-baseline value before NTZ discontinuation
c: Last value after NTZ discontinuation
EDSS was either documented as sum score or by all functional systems. When both versions were documented, the score resulting from individual functional systems was displayed. Missing EDSS values were replaced by LOCF.
Source: Post-text Table 5.3.1 and Table 5.3.2

Figure 11 graphically displays the course of EDSS in the FAS, overall and in the subcohorts.

Figure 11: Boxplots for EDSS



Source: Post-text Figure 5.3.4

The time from baseline to last EDSS assessment was longer across STAY patients (mean ± SD 2.7 ± 0.7 years, median 3.0 years, n=568) compared with SWITCH-ON (1.5 ± 0.8 years, median

1.4 years, n=282 and SWITCH-OFF patients (1.4 ± 0.7 years, median 1.3 years, n=112) (FAS; post-text Table 5.3.3).

Table 43 presents the proportion of patients who experienced a worsening in EDSS at any time point during the study (for definition of EDSS worsening see section 6.2.9.2) for the STAY and SWITCH cohort of the FAS and for subgroups by EID dosing in the FAS; the corresponding proportions for the PSM are also shown.

The proportions of patients with an EDSS worsening were lowest among STAY patients (6.6%) compared with SWITCH-ON (9.2%) or SWITCH-OFF (7.9%) patients.

A PSM set without the factor "EDSS at study start" was created for the analysis of EDSS worsening (see section 6.2.2). After propensity score matching, the proportions of patients with an EDSS worsening were again lowest among STAY patients (4.7%) compared with SWITCH-ON (9.3%) or SWITCH-OFF (7.5%) patients.

With regard to subgroups by EID in the (FAS), the proportions of patients with an EDSS worsening were lowest among patients with EID (5.0%) compared with patients without EID (8.2%) or patients where EID was not calculable (11.1%).

After propensity score matching, the proportions of patients with an EDSS worsening were again lowest among patients with EID (2.7%) compared with patients without EID (6.3%) or patients where EID was not calculable (12.9%).

Table 43: Worsening of EDSS for STAY and SWITCH cohorts and for subgroups by EID dosing (FAS and PSM)

Cohort	FAS			PSM		
Worsening of EDSS	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**	**STAY (N=326)**	**SWITCH-ON (N=326)**	**SWITCH-OFF (N=263)**
No	535 (93.4)	258 (90.8)	105 (92.1)	261 (95.3)	215 (90.7)	86 (92.5)
Yes	38 (6.6)	26 (9.2)	9 (7.9)	13 (4.7)	22 (9.3)	7 (7.5)
Missing	48	19	64	22	15	56
	EID no (N=698)	**EID yes (N=69)**	**EID not calc. (N=424)**	**EID no (N=352)**	**EID yes (N=42)**	**EID not calc. (N=258)**
No	516 (91.8)	57 (95.0)	280 (88.9)	268 (93.7)	36 (97.3)	176 (87.1)
Yes	46 (8.2)	3 (5.0)	35 (11.1)	18 (6.3)	1 (2.7)	26 (12.9)
Missing	111	7	94	56	3	51

EDSS = Expanded Disability Status Scale; FAS = Full Analysis Set; PSM = Propensity Score Matched
Note: EDSS worsening was defined as: Increase by >0.5 points and initial value >5.5; or increase by >1 point and initial value <5.5; or increase by ≥1.5 points and initial value=0
Source: Post-text Table 5.3.5a, Table 5.3.6a, Table 5.3.5b and Table 5.3.6b

Table 44 presents the proportion of patients who experienced a worsening in EDSS at any time point during the study (for definition of EDSS worsening see section 6.2.9.2) for subgroups by baseline PML risk in the FAS; the corresponding proportions for the PSM are also shown.

The proportions of patients with an EDSS worsening were lowest among patients with no PML risk (8.3%) and highest among patients with a high PML risk (11.1%).

In the PSM, the proportions of patients with a worsening in EDSS were lowest among patients with intermediate or no PML risk (7.1% and 7.8%) compared with low risk patients (10.3%) or high risk patients (11.9%).

Table 44: Worsening of EDSS by baseline PML risk (FAS and PSM)

Worsening of EDSS	No risk	Low risk	Intermediate risk	High risk
FAS	**N = 703, n (%)**	**N = 61, n (%)**	**N = 259, n (%)**	**N = 166, n (%)**
No	522 (91.7)	44 (89.8)	167 (90.8)	120 (88.9)
Yes	47 (8.3)	5 (10.2)	17 (9.2)	15 (11.1)
Missing	115	10	61	26
PSM	**N = 341, n (%)**	**N = 34, n (%)**	**N = 153, n (%)**	**N = 124, n (%)**
No	260 (92.2)	26 (89.7)	105 (92.9)	89 (88.1)
Yes	22 (7.8)	3 (10.3)	8 (7.1)	12 (11.9)
Missing	50	5	35	20

EDSS = Expanded Disability Status Scale; FAS = Full Analysis Set; PSM = Propensity Score Matched
Note: EDSS worsening was defined as: Increase by >0.5 points and initial value >5.5; or increase by >1 point and initial value <5.5; or increase by ≥1.5 points and initial value=0
Source: Post-text Table 5.3.5c and Table 5.3.6c

8.2.3. Symptoms of multiple sclerosis

Table 45 presents the MS symptoms present at baseline for the FAS. Overall, 890 patients (74.9%) in the total FAS entered the study with **a symptom present** at baseline. The proportion of patients with "any symptom present" at baseline was greatest in the INDETERMINABLE cohort (81.1%) and lowest in the STAY cohort (73.5%), in the SWITCH cohort it was 75.8%.

About half of the patients in the total FAS (651 patients, 54.8%) had **more than one symptom present at baseline**, the proportion was lower in STAY patients (52.0%) compared with SWITCH (58.3%) and INDETERMINABLE (60.0%) patients.

The relative frequency of MS symptoms present at study start differed between STAY and SWICHT cohort (between cohort difference ≥ 3.0%) with regard to

- Fatigue (23.5% STAY and 27.0% SWITCH patients), and
- Coordinative dysfunction (16.0% STAY and 22.0% SWITCH patients).

Table 45: MS symptoms present at study start (FAS)

Symptoms	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETERMI-NABLE (N=95) n (%)	Total (N=1189) n (%)
Any symptom present at study start	**513 (73.5)**	**300 (75.8)**	**77 (81.1)**	**890 (74.9)**
More than one symptom	**363 (52.0)**	**231 (58.3)**	**57 (60.0)**	**651 (54.8)**
Dys-/hyperesthesia	220 (31.5)	114 (28.8)	39 (41.1)	373 (31.4)
Other	168 (24.1)	106 (26.8)	22 (23.2)	296 (24.9)
Fatigue	164 (23.5)	107 (27.0)	19 (20.0)	290 (24.4)
Bladder/intestinal disorders	158 (22.6)	90 (22.7)	23 (24.2)	271 (22.8)
Coordinative dysfunction	112 (16.0)	87 (22.0)	17 (17.9)	216 (18.2)
Paralysis	106 (15.2)	61 (15.4)	18 (18.9)	185 (15.6)
Visual impairment	92 (13.2)	55 (13.9)	15 (15.8)	162 (13.6)
Concentration dysfunction	89 (12.8)	48 (12.1)	10 (10.5)	147 (12.4)
Muscular weakness	74 (10.6)	42 (10.6)	11 (11.6)	127 (10.7)
Depression	71 (10.2)	36 (9.1)	12 (12.6)	119 (10.0)
Pain	47 (6.7)	25 (6.3)	5 (5.3)	77 (6.5)
Cognitive dysfunction	43 (6.2)	21 (5.3)	4 (4.2)	68 (5.7)
Nausea	34 (4.9)	25 (6.3)	6 (6.3)	65 (5.5)
Swallow/speech disorder	12 (1.7)	11 (2.8)	3 (3.2)	26 (2.2)
Sexual impairment	11 (1.6)	7 (1.8)	-	18 (1.5)

FAS = Full Analysis Set
Source: Post-text Table 5.2.1

Table 46 presents the most frequent MS symptoms (in ≥2.5% of patients in the total FAS) that improved or worsened after study start, a tabulation of all MS symptoms improving after study start is shown in post-text Table 5.2.2 (improved) and Table 5.2.3 (worsened). Overall, in 306 patients (25.7%) of the total FAS **at least one MS symptom improved after study start**. The proportion of patients with at least one MS symptom improved after study start was slightly greater in the SWITCH cohort (28.8%) than in the STAY cohort (26.1%), in the INDETERMINABLE cohort it was only 10.5%.

The most common MS symptoms (documented in ≥5.0% of all FAS patients) which improved after study start were “dys-/hyperesthesia” (6.3%), “other” (5.5%), and “fatigue” (5.2%), with only minor differences between STAY and SWITCH patients.

Overall, in 359 patients (30.2%) of the total FAS **at least one MS symptom worsened after study start**. The proportion of patients with at least one MS symptom worsened after study start was greater in the SWITCH cohort (36.1%) than in the STAY cohort (27.9%), in the INDETERMINABLE cohort it was only 22.1%.

The most common MS symptoms (documented in ≥5.0% of all FAS patients) which worsened after study start were also “dys-/hyperesthesia” (8.3%), “other” (7.9%), and “fatigue” (7.5%), with constantly lower percentages in STAY compared with SWITCH patients.

Table 46: MS symptoms improved/worsened in ≥2.5% of patients in total after study start (FAS)

Symptoms	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETERMI-NABLE (N=95) n (%)	Total (N=1189) n (%)
At least one symptom improved after study start	**182 (26.1)**	**114 (28.8)**	**10 (10.5)**	**306 (25.7)**
Dys-/hyperesthesia	46 (6.6)	25 (6.3)	4 (4.2)	75 (6.3)
Other	37 (5.3)	27 (6.8)	1 (1.1)	65 (5.5)
Fatigue	37 (5.3)	24 (6.1)	1 (1.1)	62 (5.2)
Bladder/intestinal disorders	28 (4.0)	14 (3.5)	3 (3.2)	45 (3.8)
Depression	31 (4.4)	9 (2.3)	2 (2.1)	42 (3.5)
Visual impairment	24 (3.4)	14 (3.5)	1 (1.1)	39 (3.3)
Coordinative dysfunction	19 (2.7)	19 (4.8)	-	38 (3.2)
Paralysis	20 (2.9)	15 (3.8)	-	35 (2.9)
At least one symptom worsened after study start	**195 (27.9)**	**143 (36.1)**	**21 (22.1)**	**359 (30.2)**
Dys-/hyperesthesia	52 (7.4)	43 (10.9)	4 (4.2)	99 (8.3)
Other	55 (7.9)	35 (8.8)	4 (4.2)	94 (7.9)
Fatigue	46 (6.6)	41 (10.4)	2 (2.1)	89 (7.5)
Bladder/intestinal disorders	35 (5.0)	21 (5.3)	2 (2.1)	58 (4.9)
Coordinative dysfunction	24 (3.4)	27 (6.8)	1 (1.1)	52 (4.4)
Paralysis	23 (3.3)	24 (6.1)	2 (2.1)	49 (4.1)
Muscular weakness	17 (2.4)	20 (5.1)	3 (3.2)	40 (3.4)
Depression	23 (3.3)	9 (2.3)	3 (3.2)	35 (2.9)

FAS= Full Analysis Set
A symptom might have improved/worsened several times but was counted only once.
Source: Post-text Table 5.2.2 and Table 5.2.3

Table 47 presents the most frequent MS symptoms (in ≥5.0% of patients in the total FAS) that occurred newly after study start in the FAS, a tabulation of all new MS symptoms after study start is shown in post-text Table 5.2.4. Overall, in 585 patients (49.2%) of the total FAS **at least one MS symptom newly occurred after study start**. The proportion of patients with at least one new MS symptom after study start was slightly greater in the SWITCH cohort (52.5%) than in the STAY cohort (49.4%), in the INDETERMINABLE cohort it was only 33.7%.

The most common new MS symptoms (occurring in ≥6.0% of FAS patients) which occurred after study start were “other” (20.2%), “fatigue” (15.4%), “dys-/hyperesthesia” (12.6%), “bladder/intestinal disorders” (10.2%), and “depression” (6.2%), with only minor differences between STAY and SWITCH patients.

Table 47: MS symptoms occurring newly in ≥2.5% of patients in total after study start (FAS)

Symptoms	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETERMI-NABLE (N=95) n (%)	Total (N=1189) n (%)
At least one new symptom after study start	**345 (49.4)**	**208 (52.5)**	**32 (33.7)**	**585 (49.2)**
Other	149 (21.3)	78 (19.7)	13 (13.7)	240 (20.2)
Fatigue	109 (15.6)	65 (16.4)	9 (9.5)	183 (15.4)
Dys-/hyperesthesia	92 (13.2)	52 (13.1)	6 (6.3)	150 (12.6)
Bladder/intestinal disorders	72 (10.3)	45 (11.4)	4 (4.2)	121 (10.2)
Depression	47 (6.7)	25 (6.3)	2 (2.1)	74 (6.2)
Visual impairment	33 (4.7)	29 (7.3)	-	62 (5.2)
Pain	32 (4.6)	26 (6.6)	2 (2.1)	60 (5.0)
Concentration dysfunction	29 (4.2)	17 (4.3)	-	46 (3.9)
Nausea	22 (3.2)	22 (5.6)	2 (2.1)	46 (3.9)
Muscular weakness	25 (3.6)	19 (4.8)	1 (1.1)	45 (3.8)
Coordinative dysfunction	19 (2.7)	16 (4.0)	3 (3.2)	38 (3.2)
Paralysis	15 (2.1)	22 (5.6)	1 (1.1)	38 (3.2)

FAS= Full Analysis Set
A symptom might have newly occurred several times but was counted only once.
Source: Post-text Table 5.2.4

8.2.4. John-Cunningham-Virus tests

The frequencies of JCV tests at each visit are tabulated in post-text Table 5.4.1 (FAS), the frequencies for selected time points are presented in Table 48.

At baseline, information on JCV test (anti-JCV antibody index or status) was available in almost all patients (≥96.0% in STAY and SWITCH-ON cohort). In 49.0% of STAY patients and 60.9% of SWITCH-ON patients the anti-JCV antibody index was available. At the follow-up visit, no information on JCV test were available for about half of the patients in STAY and SWITCH-ON cohorts, and for >80% in SWITCH-OFF cohort at each 3-month visit after baseline. At their last documented study visit, in 57.3% of STAY, in 57.6% of SWITCH, and in 76.9% of SWITCH-OFF no information on JCV test were available.

The mean duration of the time interval between JCV tests was similar across STAY, SWITCH-ON, and SWITCH-OFF of cohorts (mean 5.2 to 5.7 months), whilst the median value was greater in the STAY cohort (median 5.2 months) than in SWITCH-ON (median 3.7 months) or SWITCH-OFF (median 3.2 months) cohorts.

Table 48: Frequency of JCV test (FAS)

Time point JCV test	STAY (N=698) n (%)	SWITCH-ON (N=396) n (%)	SWITCH-OFF (N=325) n (%)
Baseline			
Anti-JCV Ab index available	342 (49.0)	241 (60.9)	103 (31.7)
Anti-JCV Ab status available only	330 (47.3)	139 (35.1)	15 (4.6)
No information on JCV available	26 (3.7)	16 (4.0)	207 (63.7)
Month 12			
Anti-JCV Ab index available	200 (28.7)	105 (35.1)	15 (9.0)
Anti-JCV AB status available only	162 (23.2)	34 (11.4)	4 (2.4)
No information on JCV available	335 (48.1)	160 (53.5)	148 (88.6)
Month 24			
Anti-JCV Ab index available	82 (11.8)	43 (30.9)	4 (6.1)
Anti-JCV Ab status available only	217 (31.3)	17 (12.2)	0 (0.0)
No information on JCV available	394 (56.9)	79 (56.8)	62 (93.9)
Month 36			
Anti-JCV Ab index available	80 (13.2)	3 (23.1)	0 (0.0)
Anti-JCV Ab status available only	175 (28.8)	0 (0.0)	0 (0.0)
No information on JCV available	352 (58.0)	10 (76.9)	0 (0.0)
Last value after baseline			
Anti-JCV Ab index available	86 (16.9)	124 (39.5)	12 (23.1)
Anti-JCV Ab status available only	132 (25.9)	9 (2.9)	0 (0.0)
No information on JCV available	292 (57.3)	181 (57.6)	40 (76.9)
Time between JCV tests, months			
N [a]	3881	1092	117
Mean ± SD	5.7 ± 3.8	5.2 ± 3.4	5.5 ± 4.6
Median (Q1; Q3)	5.2 (3.0; 6.6)	3.7 (3.0; 6.2)	3.2 (3.0; 6.5)
Min; Max	0.9; 37.7	0.9; 29.2	1.7; 25.6

FAS= Full Analysis Set; JCV = John-Cunningham Virus; Ab = Antibody; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
Source: Post-text Table 5.4.1 and Table 5.4.2

The categorized anti-JCV antibody index at baseline and summary statistics of the anti-JCV antibody index at selected time points are presented Table 50, the full course of the anti-JCV antibody index at each visit is tabulated in post-text Table 5.4.4 (FAS).

At baseline, 70.8% of STAY patients had an anti-JCV antibody index (<0.4) indicating “no PML risk” compared to 35.7% of SWITCH-ON patients. Conversely, at baseline, 44.4% of SWITCH-ON patients had an anti-JCV antibody index (>1.5) indicating “high PML risk” compared with 13.2% of STAY patients.

At baseline, the anti-JCV antibody index was mean ± SD 0.6 ± 0.9 in STAY and 1.5 ± 1.3 in SWITCH-ON cohorts. The baseline value of the SWITCH-OFF cohort, i.e., when natalizumab

discontinuation was first documented, was mean ± SD 2.4 ± 1.1. Mean and median values of the anti-JCV antibody index did not relevantly change over time in STAY patients, whilst they mildly increased in SWITCH-ON, and mildly decreased in SWITCH-OFF cohorts (LOCF).

The last reported value was (mean ± SD) 0.8 ± 1.1 in the STAY cohort. Summary statistics for the last value reported in the SWITCH-ON cohort (2.0 ± 1.2) were relatively similar to the baseline value in the SWITCH-OFF cohort, and nearly identical to last value for SWICHT-OFF cohort (2.1 ± 1.2) (LOCF).

Table 49 tabulates the cross frequencies of baseline anti-JCV antibody status versus the last anti-JCV antibody status as a shift table. The following findings were derived from this table:

- At baseline, overall 441 FAS patients (37.1%) had a "positive" anti-JCV antibody status, 703 (59.1%) were "negative", in 45 patients (3.8%) information on anti-JCV antibody status were "missing".
- At last visit, overall 472 FAS patients (39.7%) had a "positive" anti-JCV antibody status, 641 (53.9%) were "negative", in 76 patients (6.4%) information on anti-JCV antibody status were "missing".
- Of the 703 patients with a "negative" JCV antibody status at baseline, 102 patients (8.6% of all FAS patients) were tested with anti-JCV antibody "positive" at their last visit.
- Vice versa, of the 441 patients with a "positive" JCV status at baseline, 41 patients (3.4% of all FAS patients) were tested as anti-JCV antibody "negative" at last visit.
- Of the 45 patients with "missing" baseline information, 19 patients (1.6% of all FAS patients) were anti-JCV antibody "positive" at their last visit.

Table 49: Shift table for first versus last JCV antibody status (FAS)

	Last anti-JCV antibody status							
	Positive		Negative		Missing		Total	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
JCV status at baseline								
Positive	351	29.5	41	3.4	49	4.1	441	37.1
Negative	102	8.6	579	48.7	22	1.9	703	59.1
Missing values	19	1.6	21	1.8	5	0.4	45	3.8
Total	472	39.7	641	53.9	76	6.4	1189	100.0

FAS= Full Analysis Set; JCV = John-Cunningham Virus
Source: Post-text Table 5.4.5

Table 50: Anti-JCV antibody index over time (FAS)

Time point Anti-JCV antibody index	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline anti-JCV antibody index, n (%)			Not calculated.
0 to <0.4	242 (70.8)	86 (35.7)	-
0.4 to <0.9	35 (10.2)	22 (9.1)	-
0.9 to 1.5	20 (5.8)	26 (10.8)	-
>1.5	45 (13.2)	107 (44.4)	-
missing values	356	155	-
Baseline			
N	342	241	103
Mean ± SD	0.6 ± 0.9	1.5 ± 1.3	2.4 ± 1.1
Median (Q1; Q3)	0.2 (0.1; 0.5)	1.2 (0.2; 2.8)	2.6 (1.7; 3.3)
Min; Max	0.0; 4.2	0.0; 4.4	0.0; 4.4
Month 12			
N	439	199	39
Mean ± SD	0.6 ± 0.9	1.6 ± 1.3	2.1 ± 1.2
Median (Q1; Q3)	0.2 (0.2; 0.5)	1.4 (0.4; 2.9)	1.9 (1.0; 3.2)
Min; Max	0.0; 4.6	0.0; 4.2	0.1; 4.0
Month 24			
N	493	119	24
Mean ± SD	0.7 ± 1.0	1.8 ± 1.4	2.0 ± 1.1
Median (Q1; Q3)	0.2 (0.2; 0.6)	1.7 (0.4; 3.1)	2.0 (0.9; 3.0)
Min; Max	0.0; 4.1	0.1; 6.7	0.1; 4.0
Month 36			
N	450	13	-
Mean ± SD	0.8 ± 1.1	1.5 ± 1.1	-
Median (Q1; Q3)	0.3 (0.2; 0.8)	1.2 (0.8; 2.4)	-
Min; Max	0.0; 4.2	0.1; 3.2	-
Last value after baseline			
N	510	314	52
Mean ± SD	0.8 ± 1.1	2.0 ± 1.2	2.1 ± 1.2
Median (Q1; Q3)	0.2 (0.2; 0.7)	2.1 (0.9; 3.1)	2.3 (0.9; 3.1)
Min; Max	0.0; 4.2	0.0; 4.6	0.1; 4.0

FAS= Full Analysis Set; JCV = John-Cunningham Virus; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
Missing anti-JCV index values were replaced by last available value (LOCF).
Source: Post-text Table 5.4.3 and Table 5.4.4

8.2.5. Data density of magnetic resonance imaging scans

The data densities of MRI check-ups until and after natalizumab discontinuation are tabulated in Table 51 and Table 52, respectively.

Until natalizumab discontinuation

The number of MRIs per patient **until** natalizumab discontinuation was median 5.0 (Q1 = 4.0; Q3 = 7.0) MRIs per patient in the STAY and 3.0 (Q1 = 2.0; Q3 = 5.0) MRIs per patient in the SWITCH cohort. The majority of patients in the STAY cohort had received 5–8 MRI scans (52.7%, 368 patients) whilst in the SWITCH cohort the majority of patients had received 2–4 MRI scans (60.9%, 241 patients).

The mean (± SD) and median duration of the time interval between MRI check-ups was mildly greater among STAY (8.0 ± 6.4 months, median 6.3 months) compared with SWITCH patients (7.0 ± 5.4 months, median 5.8 months).

After natalizumab discontinuation

The number of MRIs per patient **after** natalizumab discontinuation was median 1.0 (Q1 = 0.0; Q3 = 2.0) MRIs per patient in the SWITCH cohort. Patients of the SWITCH cohort mostly had received either no MRI scans (32.8%, 130 patients) or 1 MRI scan (44.2%, 175 patients).

The mean (± SD) and median duration of the time interval between MRI scans was (7.3 ± 4.2 months, median 6.2 months) in SWITCH patients.

Table 51: Data density of MRI scans until natalizumab discontinuation (FAS)

Parameter MRI scan	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETER-MINABLE (N=95) n (%)	TOTAL (N=1189) n (%)
Number of MRI per patient until NTZ discont.				
N [a]	698	396	95	1189
Mean ± SD	5.4 ± 2.4	3.8 ± 2.0	2.8 ± 1.2	4.7 ± 2.4
Median (Q1; Q3)	5.0 (4.0; 7.0)	3.0 (2.0; 5.0)	3.0 (2.0; 3.0)	4.0 (3.0; 6.0)
Min; Max	0.0; 13.0	1.0; 11.0	1.0; 7.0	0.0; 13.0
Number of MRI per patient until NTZ discont., n (%)				
0	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)
1	20 (2.9)	37 (9.3)	11 (11.6)	68 (5.7)
2-4	237 (34.0)	241 (60.9)	76 (80.0)	554 (46.6)
5-8	368 (52.7)	106 (26.8)	8 (8.4)	482 (40.5)
9-12	65 (9.3)	12 (3.0)	0 (0.0)	77 (6.5)
>12	6 (0.9)	0 (0.0)	0 (0.0)	6 (0.5)
Years between 1st and last MRI until NTZ discont.				
N	685	390	94	1169
Mean ± SD	2.9 ± 0.9	1.6 ± 1.0	1.4 ± 1.0	2.4 ± 1.2
Median (Q1; Q3)	3.0 (2.7; 3.3)	1.5 (0.9; 2.2)	1.3 (0.8; 2.0)	2.7 (1.6; 3.1)
Min; Max	0.0; 12.8	0.0; 5.4	0.0; 5.8	0.0; 12.8
Months between (subsequent) MRIs until NTZ discont.				
N [a]	3071	1096	168	4335
Mean ± SD	8.0 ± 6.4	7.0 ± 5.4	9.7 ± 7.6	7.8 ± 6.2
Median (Q1; Q3)	6.3 (4.6; 9.5)	5.8 (3.7; 8.0)	7.9 (5.5; 12.1)	6.2 (4.3; 9.2)
Min; Max	0.0; 139.2	0.7; 65.2	1.1; 69.8	0.0; 139.2

Discont. = Discontinuation; FAS= Full Analysis Set; MRI = Magnetic resonance imaging; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

a: N is the number of intervals between check-ups, not the number of patients

Note: Data at time point of natalizumab discontinuation are included. MRI of different types are displayed here. This includes MRI of different scanner type and different MRI sequences. Type and sequences may change during different visits in one patient.

Source: Post-text Table 5.5.1

Table 52: Data density of MRI scans after natalizumab discontinuation (FAS)

Parameter MRI scan	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETER-MINABLE (N=95) n (%)	TOTAL (N=1189) n (%)
Number of MRI per patient after NTZ discont.				
N [a]	698	396	95	1189
Mean ± SD	0.0 ± 0.0	1.5 ± 1.5	0.0 ± 0.0	0.5 ± 1.1
Median (Q1; Q3)	0.0 (0.0; 0.0)	1.0 (0.0; 2.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 0.0	0.0; 10.0	0.0; 0.0	0.0; 10.0
Number of MRI per patient after NTZ discont., n (%)				
0	698 (100.0)	130 (32.8)	95 (100.0)	923 (77.6)
1	0 (0.0)	175 (44.2)	0 (0.0)	175 (14.7)
2-4	0 (0.0)	78 (19.7)	0 (0.0)	78 (6.6)
5-8	0 (0.0)	12 (3.0)	0 (0.0)	12 (1.0)
9-12	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
>12	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Years between 1st and last MRI after NTZ discont.				
N	0	263	0	263
Mean ± SD	n.a.	0.7 ± 0.8	n.a.	0.7 ± 0.8
Median (Q1; Q3)	n.a.	0.6 (0.0; 1.2)	n.a.	0.6 (0.0; 1.2)
Min; Max	n.a.	0.0; 3.4	n.a.	0.0; 3.4
Months between (subsequent) MRIs after NTZ discont.				
N [a]	0	325	0	325
Mean ± SD	n.a.	7.3 ± 4.2	n.a.	7.3 ± 4.2
Median (Q1; Q3)	n.a.	6.2 (3.7; 10.8)	n.a.	6.2 (3.7; 10.8)
Min; Max	n.a.	0.9; 24.7	n.a.	0.9; 24.7

Discont. = Discontinuation; FAS= Full Analysis Set; MRI = Magnetic resonance imaging; n. a. = Not applicable; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

a: N is the number of intervals between check-ups, not the number of patients.

Note: Data at time point of natalizumab discontinuation are included. MRI of different types are displayed here. This includes MRI of different scanner type and different MRI sequences. Type and sequences may change during different visits in one patient.

Source: Post-text Table 5.5.2

8.3. Patient reported outcomes and tests

8.3.1. Treatment Satisfaction Questionnaire for Medication (TSQM)

The satisfaction with treatment was evaluated by using the TSQM-9.

8.3.1.1. TSQM effectiveness subscores

Table 53 presents summary statistics for the **TSQM effectiveness subscores** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.1.1 (TSQM – Effectiveness score) including corresponding changes from baseline over time (post-text Table 6.1.4). In addition post-Text Figure 6.1.7 displays the course of TSQM effectiveness scale as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the TSQM effectiveness subscores were (mean ± SD) 79.4 ± 27.3 in STAY and 77.0 ± 28.2 in SWITCH-ON patients (median: 88.9 in either cohort), thereby indicating a relatively high satisfaction with regard to effectiveness. During the observation phase on natalizumab therapy up to last visit the mean and median TSQM scores did not change remarkably.

Up to last documented value, the TSQM effectiveness subscore mean values only minimally changed from baseline by mean ± SD 1.9 ± 35.1 and -3.3 ± 35.8 with a broad variation across changes (the median change was 0.0 in either cohort).

In the SWITCH-OFF subcohort, the TSQM effectiveness score at discontinuation of natalizumab (baseline value from re-baselining) was mean ± SD 70.4 ± 32.1 (median 77.8) and somewhat lower compared with STAY and SWITCH-ON patients. Up to last visit, mean values of effectiveness subscore minimally changed under subsequent therapy (by -1.3 ± 38.4), the median change from baseline was by 0.0. The small number of available values for this cohort should also be noted.

In any of the 3 cohorts, there were always distinctive individual changes in TSQM effectiveness, deteriorations (by -100) as well as improvements (by 100), at any visit during study course up to last visit.

Table 53: TSQM - Effectiveness (FAS)

Time point TSQM - Effectiveness	STAY (N=698)	SWITCH-ON (N=396)	SWITCH-OFF (N=325)
Baseline			
N	637	356	64
Mean ± SD	79.4 ± 27.3	77.0 ± 28.2	70.4 ± 32.1
Median (Q1; Q3)	88.9 (72.2; 100.0)	88.9 (66.7; 100.0)	77.8 (58.3; 100.0)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Month 12			
N	542	197	41
Mean ± SD	78.4 ± 28.6	73.2 ± 32.4	64.2 ± 30.0
Median (Q1; Q3)	88.9 (72.2; 100.0)	83.3 (61.1; 100.0)	66.7 (50.0; 83.3)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Month 24			
N	512	81	16
Mean ± SD	79.8 ± 27.9	77.1 ± 31.7	67.7 ± 28.8
Median (Q1; Q3)	88.9 (72.2; 100.0)	94.4 (75.0; 100.0)	72.2 (50.0; 94.4)
Min; Max	0.0; 100.0	0.0; 100.0	16.7; 100.0
Month 36			
N	374	3	-
Mean ± SD	83.4 ± 24.2	85.2 ± 14.0	-
Median (Q1; Q3)	94.4 (77.8; 100.0)	83.3 (72.2; 100.0)	-
Min; Max	0.0; 100.0	72.2; 100.0	-
Last value after baseline			
N	656	312	116
Mean ± SD	81.6 ± 25.6	74.3 ± 29.5	65.3 ± 27.9
Median (Q1; Q3)	88.9 (77.8; 100.0)	83.3 (63.9; 100.0)	66.7 (50.0; 83.3)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Change from baseline to last value after baseline			
N	621	293	44
Mean ± SD	1.9 ± 35.1	-3.3 ± 35.8	-1.3 ± 38.4
Median (Q1; Q3)	0.0 (-5.6; 11.1)	0.0 (-11.1; 5.6)	0.0 (-19.4; 8.3)
Min; Max	-100.0; 100.0	-100.0; 100.0	-100.0; 100.0

FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TSQM = Treatment Satisfaction Questionnaire for Medication
The subscale ranged from 0 to 100. Higher scores indicate greater satisfaction on that domain.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.1.1 and Table 6.1.4

8.3.1.2. TSQM convenience subscores

Table 54 presents summary statistics for the **TSQM convenience subscores** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.1.2 (TSQM – Convenience score) including corresponding changes from baseline over time (post-text Table 6.1.5).

In addition, post-Text Figure 6.1.8 displays the course of TSQM convenience scale as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the **TSQM convenience subscores** were (mean ± SD) 78.0 ± 17.2 (median 80.6) in STAY and 79.3 ± 17.1 (median 83.3) in SWITCH-ON patients, thereby indicating a relatively high satisfaction with regard to convenience of therapy. During the observation phase on natalizumab therapy up to last visit the mean and median TSQM scores did not change remarkably in the STAY cohort and numerically decreased in the SWITCH-ON cohort.

Up to last documented value, the TSQM convenience subscores values only minimally changed from baseline by mean ± SD 0.1 ± 16.5 and -2.5 ± 18.0 with a broad variation across changes (the median change was 0.0 in either cohort).

In the SWITCH-OFF subcohort, the TSQM convenience score at discontinuation of natalizumab (baseline value resulting from re-baselining) was with mean ± SD 79.5 ± 17.8 (median 83.3) similar to STAY and SWITCH-ON patients.

Up to last visit, the mean values of convenience subscore minimally changed under subsequent therapy by -1.6 ± 19.1, the median change from baseline to last visit was median 0.0. The small number of available values for this cohort should also be noted.

In any of the 3 cohorts, there were always distinctive individual changes in TSQM convenience, deteriorations as well as improvements, at any visit during study course up to last visit.

Table 54: TSQM - Convenience (FAS)

Time point TSQM - Convenience	STAY (N=698)	SWITCH-ON (N=396)	SWITCH-OFF (N=325)
Baseline			
N	636	358	64
Mean ± SD	78.0 ± 17.2	79.3 ± 17.1	79.5 ± 17.8
Median (Q1; Q3)	80.6 (66.7; 94.4)	83.3 (66.7; 94.4)	83.3 (69.4; 94.4)
Min; Max	0.0; 100.0	0.0; 100.0	22.2; 100.0
Month 12			
N	541	198	41
Mean ± SD	76.7 ± 18.2	79.3 ± 17.1	79.3 ± 21.2
Median (Q1; Q3)	77.8 (66.7; 94.4)	83.3 (66.7; 94.4)	83.3 (66.7; 100.0)
Min; Max	11.1; 100.0	16.7; 100.0	11.1; 100.0
Month 24			
N	511	82	17
Mean ± SD	77.8 ± 18.0	77.2 ± 18.7	81.7 ± 19.8
Median (Q1; Q3)	83.3 (66.7; 94.4)	77.8 (66.7; 88.9)	88.9 (66.7; 100.0)
Min; Max	5.6; 100.0	5.6; 100.0	44.4; 100.0
Month 36			
N	375	3	-
Mean ± SD	77.8 ± 17.8	61.1 ± 25.5	-
Median (Q1; Q3)	83.3 (66.7; 94.4)	66.7 (33.3; 83.3)	-
Min; Max	22.2; 100.0	33.3; 83.3	-
Last value after baseline			
N	656	310	116
Mean ± SD	78.0 ± 17.6	77.1 ± 18.5	77.7 ± 19.6
Median (Q1; Q3)	83.3 (66.7; 94.4)	77.8 (66.7; 94.4)	77.8 (66.7; 100.0)
Min; Max	22.2; 100.0	5.6; 100.0	0.0; 100.0
Change from baseline to last value after baseline			
N	619	292	44
Mean ± SD	0.1 ± 16.5	-2.5 ± 18.0	-1.6 ± 19.1
Median (Q1; Q3)	0.0 (-11.1; 11.1)	0.0 (-11.1; 5.6)	0.0 (-11.1; 2.8)
Min; Max	-77.8; 50.0	-77.8; 66.7	-66.7; 44.4

FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TSQM = Treatment Satisfaction Questionnaire for Medication
The subscale ranged from 0 to 100. Higher scores indicate greater satisfaction on that domain.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.1.2 and Table 6.1.5

8.3.1.3. TSQM global satisfaction subscores

Table 55 presents summary statistics for the **TSQM global satisfaction subscores** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.1.3 (TSQM – Global satisfaction score) including corresponding changes from baseline over time in post-text Table 6.1.6.

In addition, post-Text Figure 6.1.9 displays the course of TSQM global satisfaction scale as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the TSQM global satisfaction subscores were (mean ± SD) 84.4 ± 15.7 in STAY and 82.1± 17.5 in SWITCH-ON patients (median: 85.7 in either cohort), thereby indicating a relatively high satisfaction with regard to global satisfaction with therapy. During the observation period on natalizumab therapy up to last visit the mean and median TSQM scores did not change remarkably in the STAY and SWITCH-ON cohorts.

Up to last documented value, the TSQM global satisfaction subscores mean values only minimally changed from baseline by mean ± SD 0.2 ± 16.1 and -4.4 ± 19.0 with a broad variation across changes (the median change was 0.0 in either cohort).

In the SWITCH-OFF subcohort, the first TSQM global satisfaction score at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 72.3 ± 23.2 (median 71.4) and somewhat lower compared with STAY and SWITCH-ON patients.

Up to last visit, mean and median values of global satisfaction subscore did not considerably change under subsequent therapy, the change from baseline to last visit was by 1.9 ± 26.3 (median 0.0). The small number of available values for this cohort should also be noted.

In any of the 3 cohorts, there were always distinctive individual changes in TSQM global satisfaction, deteriorations as well as improvements, during study course up to last visit.

Table 55: TSQM – Global satisfaction (FAS)

Time point TSQM - Global satisfaction	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	637	359	64
Mean ± SD	84.4 ± 15.7	82.1 ± 17.5	72.3 ± 23.2
Median (Q1; Q3)	85.7 (78.6; 100.0)	85.7 (71.4; 92.9)	71.4 (53.6; 92.9)
Min; Max	14.3; 100.0	0.0; 100.0	0.0; 100.0
Month 12			
N	541	198	40
Mean ± SD	84.5 ± 16.2	82.0 ± 17.9	74.3 ± 22.9
Median (Q1; Q3)	85.7 (78.6; 100.0)	85.7 (71.4; 100.0)	75.0 (57.1; 100.0)
Min; Max	28.6; 100.0	21.4; 100.0	21.4; 100.0
Month 24			
N	511	82	17
Mean ± SD	83.8 ± 17.3	81.1 ± 19.7	68.1 ± 30.1
Median (Q1; Q3)	85.7 (78.6; 100.0)	85.7 (71.4; 100.0)	78.6 (50.0; 92.9)
Min; Max	0.0; 100.0	28.6; 100.0	7.1; 100.0
Month 36			
N	376	3	-
Mean ± SD	84.6 ± 16.3	76.2 ± 21.8	-
Median (Q1; Q3)	85.7 (78.6; 100.0)	71.4 (57.1; 100.0)	-
Min; Max	0.0; 100.0	57.1; 100.0	-
Last value after baseline			
N	656	310	116
Mean ± SD	84.7 ± 16.4	78.6 ± 20.0	69.4 ± 24.8
Median (Q1; Q3)	85.7 (78.6; 100.0)	82.9 (64.3; 92.9)	78.6 (50.0; 85.7)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Change from baseline to last value after baseline			
N	620	293	44
Mean ± SD	0.2 ± 16.1	-4.4 ± 19.0	1.9 ± 26.3
Median (Q1; Q3)	0.0 (-7.1; 7.1)	0.0 (-14.3; 7.1)	0.0 (-7.1; 7.1)
Min; Max	-85.7; 85.7	-92.9; 50.0	-50.0; 85.7

FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; TSQM = Treatment Satisfaction Questionnaire for Medication
The subscale ranged from 0 to 100. Higher scores indicate greater satisfaction on that domain.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.1.3 and Table 6.1.6

8.3.2. Fatigue Scale for Motor and Cognitive functions

8.3.2.1. FSMC total sum score

The patient-reported fatigue during observational period was evaluated by using the FSMC. The FSMC provides differential quantification and graduation of cognitive and motor fatigue.

Table 56 presents summary statistics for the **FSMC total sum scores** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.2.1 (FSMC – Total sum score) including corresponding changes from baseline over time in post-text Table 6.2.4.

In addition, post-Text Figure 6.2.7 displays the course of FSMC total sum score as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the FSMC total scores were (mean ± SD) 57.6 ± 20.3 (median 58.0) in STAY and 59.2 ± 19.5 in SWITCH-ON patients (median: 60.0), indicating on average moderate fatigue in both subcohorts. During the observational period on natalizumab therapy up to last visit the mean and median scores of FSMC total score did not change remarkably in the STAY and SWITCH-ON cohorts.

Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the FSMC total sum score at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 58.6 ± 19.7 (median 60.5) and comparable to mean/median values in STAY and SWITCH-ON patients. Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in FSMC total scores, deteriorations as well as improvements, at each visit during the observational period up to last visit.

Table 56: FSMC – Total sum score (FAS)

Time point FSMC – Total sum score	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	588	313	60
Mean ± SD	57.6 ± 20.3	59.2 ± 19.5	58.6 ± 19.7
Median (Q1; Q3)	58.0 (42.5; 74.0)	60.0 (46.0; 74.0)	60.5 (43.0; 75.0)
Min; Max	20.0; 98.0	20.0; 100.0	20.0; 94.0
Month 12			
N	493	176	34
Mean ± SD	57.1 ± 21.0	58.7 ± 19.5	59.4 ± 20.7
Median (Q1; Q3)	59.0 (39.0; 75.0)	62.0 (45.0; 72.5)	59.0 (45.0; 72.0)
Min; Max	20.0; 100.0	20.0; 98.0	20.0; 99.0
Month 24			
N	462	75	16
Mean ± SD	57.9 ± 21.0	61.2 ± 22.0	56.6 ± 16.9
Median (Q1; Q3)	60.0 (41.0; 75.0)	64.0 (41.0; 79.0)	54.0 (47.5; 68.5)
Min; Max	20.0; 100.0	20.0; 96.0	27.0; 91.0
Month 36			
N	355	3	-
Mean ± SD	56.4 ± 21.1	62.0 ± 7.2	-
Median (Q1; Q3)	58.0 (39.0; 73.0)	60.0 (56.0; 70.0)	-
Min; Max	20.0; 99.0	56.0; 70.0	-
Last value after baseline			
N	644	288	111
Mean ± SD	58.2 ± 21.2	59.2 ± 20.3	62.5 ± 20.0
Median (Q1; Q3)	61.0 (41.0; 75.0)	61.0 (44.0; 74.5)	64.0 (50.0; 78.0)
Min; Max	20.0; 100.0	20.0; 98.0	20.0; 100.0
Change from baseline to last value after baseline			
N	567	243	39
Mean ± SD	0.1 ± 11.9	0.4 ± 10.8	-0.1 ± 9.2
Median (Q1; Q3)	0.0 (-7.0; 7.0)	0.0 (-5.0; 6.0)	0.0 (-7.0; 5.0)
Min; Max	-43.0; 43.0	-27.0; 37.0	-19.0; 19.0

FSMC = Fatigue Scale for Motor and Cognitive functions; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

The total sum score ranges from 20 to 100. Higher scores indicated more pronounced fatigue.

For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.

Source: Post-text Table 6.2.1 and Table 6.2.4

8.3.2.2. FSMC cognitive subscore

Table 57 presents summary statistics for the **FSMC cognitive subscore** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.2.2 (FSMC cognitive subscore) including corresponding changes from baseline over time in post-text Table 6.2.5 (changes from baseline in FSMC cognitive subscore).

In addition, post-Text Figure 6.2.8 displays the course of FSMC cognitive subscore as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the FSMC cognitive subscores were (mean ± SD) 27.6 ± 10.8 (median 28.0) in STAY and 28.2 ± 10.2 in SWITCH-ON patients (median: 29.0), indicating on average moderate cognitive fatigue in both subcohorts.

During the observational period on natalizumab therapy up to last visit the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts. Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the FSMC cognitive subscore at discontinuation of natalizumab (baseline value from re-baselining) was mean ± SD 27.9 ± 9.9 (median 29.0) and similar to mean/median values in STAY and SWITCH-ON patients.

Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in FSMC cognitive subscores, deteriorations as well as improvements, at any visit during the observational period up to last visit.

Table 57: FSMC – Cognitive subscore (FAS)

Time point FSMC – Cognitive subscore	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	591	316	60
Mean ± SD	27.6 ± 10.8	28.2 ± 10.2	27.9 ± 9.9
Median (Q1; Q3)	28.0 (18.0; 36.0)	29.0 (21.0; 37.0)	29.0 (19.5; 35.0)
Min; Max	10.0; 49.0	10.0; 50.0	10.0; 48.0
Month 12			
N	498	179	34
Mean ± SD	27.4 ± 11.1	28.2 ± 10.1	28.3 ± 10.9
Median (Q1; Q3)	28.0 (18.0; 36.0)	29.0 (20.0; 36.0)	28.5 (18.0; 35.0)
Min; Max	10.0; 50.0	10.0; 50.0	10.0; 49.0
Month 24			
N	468	75	16
Mean ± SD	28.0 ± 11.0	29.7 ± 11.1	26.1 ± 10.4
Median (Q1; Q3)	29.0 (19.0; 36.0)	32.0 (20.0; 38.0)	24.0 (18.5; 34.5)
Min; Max	10.0; 50.0	10.0; 49.0	10.0; 47.0
Month 36			
N	358	3	-
Mean ± SD	27.2 ± 11.2	30.0 ± 3.6	-
Median (Q1; Q3)	27.5 (17.0; 36.0)	31.0 (26.0; 33.0)	-
Min; Max	10.0; 50.0	26.0; 33.0	-
Last value after baseline			
N	646	289	111
Mean ± SD	28.2 ± 11.2	28.4 ± 10.5	29.8 ± 10.5
Median (Q1; Q3)	29.0 (19.0; 37.0)	29.0 (20.0; 36.0)	32.0 (22.0; 37.0)
Min; Max	10.0; 50.0	10.0; 50.0	10.0; 50.0
Change from baseline at last value after baseline			
N	572	247	39
Mean ± SD	0.3 ± 6.6	0.5 ± 6.0	0.3 ± 6.6
Median (Q1; Q3)	0.0 (-3.0; 4.0)	0.0 (-3.0; 4.0)	0.0 (-4.0; 5.0)
Min; Max	-22.0; 29.0	-18.0; 20.0	-13.0; 20.0

FSMC = Fatigue Scale for Motor and Cognitive functions; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

The cognitive subscore ranges from 10 to 50. Higher scores indicated more pronounced fatigue.

For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.

Source: Post-text Table 6.2.2 and Table 6.2.5

8.3.2.3. FSMC physical subscore

Table 58 presents summary statistics for the **FSMC physical subscore** at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.2.3 (FSMC physical subscore) including corresponding changes from baseline over time in post-text Table 6.2.6 (changes from baseline in FSMC physical subscore).

In addition, post-Text Figure 6.2.9 displays the course of FSMC physical subscore as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the FSMC physical subscores were (mean ± SD) 30.3 ± 10.5 (median 32.0) in STAY and 31.6 ± 10.3 in SWITCH-ON patients (median: 33.0), indicating on average moderate to severe motor fatigue in both subcohorts. During the observational period on natalizumab therapy up to last visit the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts.

Up to last documented value, the mean changes from baseline in FSMC physical subscores were by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the FSMC cognitive subscore at discontinuation of natalizumab (baseline value from re-baselining) was mean ± SD 31.1 ± 10.6 (median 33.0) and similar to mean/median values in STAY and SWITCH-ON patients. Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in FSMC physical subscores, deteriorations as well as improvements, at any visit during the observational period up to last visit.

Table 58: FSMC – Physical subscore (FAS)

Time point FSMC – Cognitive subscore	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	612	343	65
Mean ± SD	30.3 ± 10.5	31.6 ± 10.3	31.1 ± 10.6
Median (Q1; Q3)	32.0 (23.0; 39.0)	33.0 (25.0; 40.0)	33.0 (23.0; 40.0)
Min; Max	10.0; 50.0	10.0; 50.0	10.0; 49.0
Month 12			
N	523	187	39
Mean ± SD	30.0 ± 10.6	30.7 ± 10.2	31.9 ± 10.4
Median (Q1; Q3)	31.0 (22.0; 39.0)	31.0 (25.0; 39.0)	32.0 (27.0; 39.0)
Min; Max	10.0; 50.0	10.0; 49.0	10.0; 50.0
Month 24			
N	488	76	17
Mean ± SD	30.2 ± 10.8	31.7 ± 11.5	30.4 ± 8.2
Median (Q1; Q3)	32.0 (21.0; 39.0)	33.5 (21.5; 41.0)	32.0 (24.0; 37.0)
Min; Max	10.0; 50.0	10.0; 49.0	17.0; 44.0
Month 36			
N	373	3	-
Mean ± SD	29.3 ± 10.8	32.0 ± 4.4	-
Median (Q1; Q3)	30.0 (21.0; 38.0)	30.0 (29.0; 37.0)	-
Min; Max	10.0; 49.0	29.0; 37.0	-
Last value after baseline			
N	653	301	115
Mean ± SD	30.1 ± 10.8	31.1 ± 10.7	32.8 ± 10.3
Median (Q1; Q3)	31.0 (22.0; 39.0)	33.0 (24.0; 39.0)	34.0 (26.0; 41.0)
Min; Max	10.0; 50.0	10.0; 49.0	10.0; 50.0
Change from baseline at last value after baseline			
N	594	271	44
Mean ± SD	-0.3 ± 6.3	-0.1 ± 5.9	-0.4 ± 4.7
Median (Q1; Q3)	0.0 (-4.0; 4.0)	0.0 (-4.0; 3.0)	-1.0 (-3.0; 1.5)
Min; Max	-26.0; 25.0	-18.0; 21.0	-10.0; 11.0

FSMC = Fatigue Scale for Motor and Cognitive functions; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

The physical subscore ranges from 10 to 50. Higher scores indicated more pronounced fatigue.

For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.

Source: Post-text Table 6.2.3 and Table 6.2.6

8.3.3. Hospital Anxiety and Depression Scale

The levels of anxiety and depression that patients were experiencing were evaluated by using HADS.

8.3.3.1. HADS anxiety subscore

Table 59 presents summary statistics for the HADS anxiety subscore at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.3.1 (HADS anxiety subscore) including corresponding changes from baseline over time in post-text Table 6.3.3 (changes from baseline in HADS anxiety subscore).

In addition, post-Text Figure 6.3.5 displays the course of HADS anxiety subscore as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, HADS anxiety subscores were (mean ± SD) 6.1 ± 3.9 (median 6.0) in STAY and 6.3 ± 3.9 in SWITCH-ON patients (median: 6.0), indicating that on average patient status regarding anxiety was “normal” in both subcohorts.

During the observational period on natalizumab therapy up to last visit the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts. Up to last documented value, the mean changes from baseline in HADS anxiety subscores were minimal, the mean changes from baseline were by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the HADS anxiety subscore at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 5.6 ± 3.9 (median 5.0) and similar to mean/median values in STAY and SWITCH-ON patients. Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in HADS anxiety subscores, deteriorations as well as improvements, at any visit during the observational period up to last visit.

Table 59: HADS – Anxiety subscore (FAS)

Time point HADS – Anxiety subscore	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	631	354	66
Mean ± SD	6.1 ± 3.9	6.3 ± 3.9	5.6 ± 3.9
Median (Q1; Q3)	6.0 (3.0; 9.0)	6.0 (3.0; 9.0)	5.0 (3.0; 8.0)
Min; Max	0.0; 18.0	0.0; 19.0	0.0; 16.0
Month 12			
N	542	199	42
Mean ± SD	5.8 ± 4.1	5.9 ± 3.6	5.4 ± 3.5
Median (Q1; Q3)	5.0 (2.0; 8.0)	6.0 (3.0; 8.0)	5.5 (3.0; 8.0)
Min; Max	0.0; 19.0	0.0; 18.0	0.0; 15.0
Month 24			
N	505	82	17
Mean ± SD	5.6 ± 4.3	6.0 ± 3.9	4.6 ± 2.3
Median (Q1; Q3)	5.0 (2.0; 8.0)	5.0 (3.0; 9.0)	5.0 (3.0; 6.0)
Min; Max	0.0; 21.0	0.0; 16.0	1.0; 8.0
Month 36			
N	380	2	-
Mean ± SD	5.8 ± 4.1	1.0 ± 1.4	-
Median (Q1; Q3)	5.0 (2.0; 9.0)	1.0 (0.0; 2.0)	-
Min; Max	0.0; 20.0	0.0; 2.0	-
Last value after baseline			
N	657	310	118
Mean ± SD	5.8 ± 4.1	6.0 ± 3.8	6.0 ± 3.6
Median (Q1; Q3)	5.0 (2.0; 9.0)	6.0 (3.0; 9.0)	6.0 (3.0; 8.0)
Min; Max	0.0; 20.0	0.0; 18.0	0.0; 15.0
Change from baseline at last value after baseline			
N	617	292	47
Mean ± SD	-0.3 ± 3.1	-0.2 ± 3.1	-0.7 ± 2.7
Median (Q1; Q3)	0.0 (-2.0; 2.0)	0.0 (-2.0; 2.0)	0.0 (-2.0; 0.0)
Min; Max	-11.0; 11.0	-10.0; 10.0	-9.0; 7.0

HADS = Hospital Anxiety and Depression Scale; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
The HADS Anxiety subscore ranges from 0 to 21. Higher scores indicated more pronounced anxiety.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.3.1 and Table 6.3.3

8.3.3.2. HADS depression subscore

Table 60 presents summary statistics for the HADS depression subscore at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.3.2 (HADS depression subscore) as well as corresponding changes from baseline over time in post-text Table 6.3.4 (changes from baseline in HADS depression subscore).

In addition, post-Text Figure 6.3.6 displays the course of HADS depression subscore as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, HADS depression subscores were (mean ± SD) 4.6 ± 3.9 (median 3.0) in STAY and 4.9 ± 3.9 in SWITCH-ON patients (median: 4.0), indicating that on average depression was absent in both subcohorts.

During the observational period on natalizumab therapy up to last visit the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts.

Up to last documented value, the mean changes from baseline in HADS depression subscores were minimal: The mean changes from baseline were by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the HADS depression subscore at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 4.5 ± 4.0 (median 4.0) and similar to mean/median values in STAY and SWITCH-ON patients.

Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in HADS depression subscores, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 60: HADS – Depression subscore (FAS)

Time point HADS – Depression subscore	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	629	353	66
Mean ± SD	4.6 ± 3.9	4.9 ± 3.9	4.5 ± 4.0
Median (Q1; Q3)	3.0 (1.0; 7.0)	4.0 (2.0; 7.0)	4.0 (2.0; 6.0)
Min; Max	0.0; 18.0	0.0; 17.0	0.0; 18.0
Month 12			
N	544	199	42
Mean ± SD	4.4 ± 3.8	4.5 ± 3.7	4.5 ± 3.6
Median (Q1; Q3)	3.0 (1.0; 7.0)	4.0 (1.0; 7.0)	4.0 (1.0; 7.0)
Min; Max	0.0; 16.0	0.0; 19.0	0.0; 15.0
Month 24			
N	505	82	17
Mean ± SD	4.5 ± 4.1	5.1 ± 4.5	3.3 ± 3.2
Median (Q1; Q3)	3.0 (1.0; 7.0)	4.0 (1.0; 8.0)	2.0 (1.0; 5.0)
Min; Max	0.0; 19.0	0.0; 18.0	0.0; 11.0
Month 36			
N	381	2	-
Mean ± SD	4.3 ± 3.9	5.5 ± 2.1	-
Median (Q1; Q3)	3.0 (1.0; 7.0)	5.5 (4.0; 7.0)	-
Min; Max	0.0; 16.0	4.0; 7.0	-
Last value after baseline			
N	657	310	118
Mean ± SD	4.4 ± 4.1	4.8 ± 4.1	5.3 ± 4.0
Median (Q1; Q3)	3.0 (1.0; 7.0)	4.0 (1.0; 7.0)	5.0 (2.0; 8.0)
Min; Max	0.0; 19.0	0.0; 20.0	0.0; 17.0
Change from baseline at last value after baseline			
N	615	291	47
Mean ± SD	-0.2 ± 3.0	-0.0 ± 3.0	-0.2 ± 2.4
Median (Q1; Q3)	0.0 (-2.0; 1.0)	0.0 (-1.0; 1.3)	0.0 (-1.0; 1.0)
Min; Max	-13.0; 12.0	-11.0; 10.0	-6.0; 5.0

HADS = Hospital Anxiety and Depression Scale; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation

The HADS depression subscore ranges from 0 to 21. Higher scores indicated more pronounced depression.

For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.

Source: Post-text Table 6.3.2 and Table 6.3.4

8.3.4. Multiple Sclerosis Impact Scale (29 items)

The patient-reported impact of MS therapy was evaluated by using the MSIS-29 v2.

8.3.4.1. MSIS-29 physical impact score

Table 61 presents summary statistics for the MSIS-29 physical impact score at selected time points including the change from baseline to the last documented value in the respective time period; the full course over time can be found in post-text Table 6.4.1 (MSIS-29 physical impact score) as well as corresponding changes from baseline over time in post-text Table post-text Table 6.4.3 (changes from baseline in MSIS-29 physical impact score).

In addition, post-Text Figure 6.4.5 displays the course of MSIS-29 physical impact score as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, MSIS-29 physical impact scores were (mean ± SD) 35.5 ± 13.0 (median 33.0) in STAY and 38.2 ± 14.7 in SWITCH-ON patients (median: 35.0). During the observational period on natalizumab therapy up to last visit the mean and median scores did not remarkably change in either cohort (the median change was 0.0 in either cohort).

During the observational period on natalizumab therapy up to last visit the mean score and did not change remarkably in the STAY cohort and minimally changed in the SWITCH-ON cohort (by 1.8 ± 9.1, median 0.0).

In the SWITCH-OFF subcohort, the MSIS-29 physical impact score at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 39.5 ± 15.9 (median 35.5) and similar to mean/median values in STAY and SWITCH-ON patients. Up to last visit, mean and median values of MSIS-29 physical impact score only minimally increased (worsened) under subsequent therapy, the change from baseline to last visit was by 1.0 ± 8.4 (median 1.2). However, the small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in MSIS-29 physical impact score, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 61: MSIS-29 – Physical impact score (FAS)

Time point Physical impact score	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	628	359	66
Mean ± SD	35.5 ± 13.0	38.2 ± 14.7	39.5 ± 15.9
Median (Q1; Q3)	33.0 (24.0; 44.0)	35.0 (26.0; 49.0)	35.5 (26.0; 49.0)
Min; Max	20.0; 78.0	20.0; 80.0	20.0; 78.0
Month 12			
N	543	200	42
Mean ± SD	35.5 ± 13.4	37.6 ± 14.5	39.0 ± 14.6
Median (Q1; Q3)	32.0 (24.0; 45.0)	35.0 (25.5; 47.0)	37.0 (27.0; 47.0)
Min; Max	20.0; 76.0	20.0; 79.0	20.0; 71.6
Month 24			
N	510	81	18
Mean ± SD	35.8 ± 13.5	38.8 ± 16.1	36.9 ± 12.5
Median (Q1; Q3)	32.5 (24.0; 46.0)	37.0 (23.0; 51.0)	34.5 (28.0; 47.0)
Min; Max	20.0; 80.0	20.0; 78.0	20.0; 63.0
Month 36			
N	379	2	-
Mean ± SD	35.2 ± 13.7	29.0 ± 2.8	-
Median (Q1; Q3)	32.0 (24.0; 44.0)	29.0 (27.0; 31.0)	-
Min; Max	20.0; 79.0	27.0; 31.0	-
Last value after baseline			
N	657	314	117
Mean ± SD	35.9 ± 13.6	39.5 ± 15.6	40.6 ± 15.0
Median (Q1; Q3)	33.0 (24.0; 45.0)	37.0 (25.3; 50.0)	40.0 (28.0; 52.0)
Min; Max	20.0; 79.0	20.0; 79.0	20.0; 79.0
Change from baseline at last value after baseline			
N	612	296	46
Mean ± SD	0.4 ± 8.5	1.8 ± 9.1	1.0 ± 8.4
Median (Q1; Q3)	0.0 (-4.0; 5.0)	0.0 (-3.0; 6.0)	1.2 (-2.0; 4.0)
Min; Max	-34.0; 34.0	-28.0; 38.0	-33.0; 18.6

MSIS-29 = Multiple Sclerosis Impact Scale (29 items); FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
The MSIS-29 physical impact score ranges from 20 to 80. Higher scores indicated worse disability.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.4.1 and Table 6.4.3

8.3.4.2. MSIS-29 psychological impact score

Table 62 presents summary statistics for the MSIS-29 psychological impact score at selected time points including the change from baseline to the last documented value in the respective time period; the full course can be found in post-text Table 6.4.2 (MSIS-29 psychological impact score) as well as corresponding changes from baseline over time in post-text Table 6.4.4 (changes from baseline in MSIS-29 psychological impact score).

In addition, post-Text Figure 6.4.6 displays the course of MSIS-29 psychological impact score as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, MSIS-29 psychological impact scores were (mean ± SD) 17.4 ± 6.0 (median 17.0) in STAY and 18.0 ± 6.4 in SWITCH-ON patients (median: 17.0). Up to last documented value, the MSIS-29 physical impact mean or median subscores did not relevantly changed from baseline (the median change was 0.0 in either cohort).

During the observational period the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts. Up to last documented value, the mean changes from baseline in MSIS-29 psychological impact score were by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the MSIS-29 psychological impact score at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 17.7 ± 6.2 (median 17.0) and similar to mean/median values in STAY and SWITCH-ON patients. Up to last visit, mean and median values of MSIS-29 psychological impact score only minimally increased (worsened) under subsequent therapy, the change from baseline to last visit was by -0.9 ± 4.9 (median -1.0). However, the small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in MSIS-29 psychological impact score, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 62: MSIS-29 – Psychological impact score (FAS)

Time point Psychological impact score	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	626	357	66
Mean ± SD	17.4 ± 6.0	18.0 ± 6.4	17.7 ± 6.2
Median (Q1; Q3)	17.0 (13.0; 21.0)	17.0 (13.0; 22.5)	17.0 (13.0; 22.0)
Min; Max	9.0; 34.0	9.0; 36.0	9.0; 32.0
Month 12			
N	538	200	42
Mean ± SD	16.9 ± 6.3	17.4 ± 6.1	17.5 ± 6.0
Median (Q1; Q3)	16.0 (11.0; 21.0)	17.0 (12.0; 21.0)	17.0 (14.0; 20.3)
Min; Max	9.0; 36.0	9.0; 35.0	9.0; 34.2
Month 24			
N	510	81	18
Mean ± SD	17.0 ± 6.2	17.4 ± 6.9	16.2 ± 5.4
Median (Q1; Q3)	16.0 (12.0; 21.0)	15.0 (12.0; 23.0)	15.0 (12.0; 20.0)
Min; Max	9.0; 36.0	9.0; 32.0	9.0; 29.0
Month 36			
N	379	2	-
Mean ± SD	17.0 ± 6.2	14.0 ± 1.4	-
Median (Q1; Q3)	16.0 (12.0; 21.0)	14.0 (13.0; 15.0)	-
Min; Max	9.0; 35.0	13.0; 15.0	-
Last value after baseline			
N	656	312	116
Mean ± SD	17.1 ± 6.2	17.8 ± 6.5	18.6 ± 6.1
Median (Q1; Q3)	16.0 (12.0; 21.0)	17.0 (12.0; 22.0)	18.0 (13.5; 23.0)
Min; Max	9.0; 35.0	9.0; 36.0	9.0; 36.0
Change from baseline at last value after baseline			
N	610	292	45
Mean ± SD	-0.4 ± 4.8	0.1 ± 5.0	-0.9 ± 4.9
Median (Q1; Q3)	0.0 (-3.0; 2.0)	0.0 (-2.0; 2.0)	-1.0 (-4.0; 3.0)
Min; Max	-16.0; 21.0	-15.0; 23.0	-13.0; 7.0

MSIS-29 = Multiple Sclerosis Impact Scale (29 items); FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation
The MSIS-29 psychological impact score ranges from 9 to 36. Higher scores indicated worse disability.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.4.2 and Table 6.4.4

8.3.5. Work Productivity and Activity Impairment

8.3.5.1. Percentage of work time missed due to MS

Table 63 presents summary statistics for the WPAI score **percentage of work time missed due to MS** at selected time points including the change from baseline to the last documented value in the respective time period; the full course can be found in post-text Table 6.5.1 (WPAI percent work time missed due to MS) and post-text Table 6.5.5 (changes from baseline in WPAI percent work time missed due to MS). Please note that only half of the patients in STAY and SWITCH-ON cohort provided data for this WPAI domain.

In addition, post-Text Figure 6.5.9 displays the course of the WPAI percentage of work time missed due to MS as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the percentage of work times missed due to MS was (mean ± SD) 6.1 ± 19.1 (median 0.0) in STAY and 8.1 ± 23.1 in SWITCH-ON patients (median: 0.0). Up to last documented value, the mean or median of the percentage of work time missed due to MS did not relevantly changed from baseline (by mean ± SD 0.6 ± 25.1 in STAY and by 2.5 ± 28.0 SWITCH-ON), the median changes were 0.0 in either cohort (as were 1st and 3rd quartile).

In the SWITCH-OFF subcohort, the percentage of work time missed due to MS at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 10.5 ± 29.5 (median 0.0); again median values and quartiles did not considerably change from baseline until last visit, the mean changes was by -3.6 ± 27.9. The small number of available values for this cohort should also be noted.

In any of the 3 cohorts, there were always distinctive individual changes in the percentage of work time missed due to MS, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 63: WPAI – Percentage of work time missed due to MS (FAS)

Time point % work time missed due to MS	STAY (N=698)	SWITCH-ON (N=396)	SWITCH-OFF (N=325)
Baseline			
N	329	181	32
Mean ± SD	6.1 ± 19.1	8.1 ± 23.1	10.5 ± 29.5
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Month 12			
N	299	106	18
Mean ± SD	5.5 ± 18.9	7.5 ± 22.4	15.1 ± 24.5
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 26.3)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 81.6
Month 24			
N	279	46	9
Mean ± SD	5.2 ± 19.2	9.8 ± 26.1	0.0 ± 0.0
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 0.0
Month 36			
N	226	3	-
Mean ± SD	5.2 ± 18.7	0.0 ± 0.0	-
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	-
Min; Max	0.0; 100.0	0.0; 0.0	-
Last value after baseline			
N	458	185	59
Mean ± SD	6.6 ± 21.5	9.0 ± 23.9	10.7 ± 25.6
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	0.0; 100.0	0.0; 100.0	0.0; 100.0
Change from baseline at last value after baseline			
N	313	140	15
Mean ± SD	0.6 ± 25.1	2.5 ± 28.0	-3.6 ± 27.9
Median (Q1; Q3)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Min; Max	-100.0; 100.0	-100.0; 100.0	-100.0; 26.3

MS = Multiple Sclerosis; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; WPAI = Work Productivity and Activity Impairment.
WPAI outcomes are expressed as impairment percentage (ranging from 0% to 100%), with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.5.1 and Table 6.5.5

8.3.5.2. Percentage of impairment while working due to MS

Table 64 presents summary statistics for the WPAI score **percentage of impairment while working due to MS** at selected time points including the change from baseline to the last documented value in the respective time period; the full course can be found in post-text Table 6.5.2 (WPAI percent impairment while working due to MS) and post-text Table 6.5.6 (changes from baseline in WPAI percent impairment while working due to MS). Please note that only half of the patients in STAY and SWITCH-ON cohort provided data for this WPAI domain.

In addition post-Text Figure 6.5.10 displays the course of the WPAI percentage of impairment while working due to MS as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the percentage of impairment while working due to MS was (mean ± SD) 28.1 ± 22.0 (median 20.0) in STAY and 29.8 ± 24.6 in SWITCH-ON patients (median: 20.0). Up to last documented value, the mean or median of the percentage of impairment while working due to MS only minimally changed from baseline by 1.0 ± 20.8 (STAY) and by 0.4 ± 18.0 (SWITCH-ON), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the percentage of impairment while working due to MS at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 30.9 ± 23.1 (median 30.0) and similar to mean/median values in STAY and SWITCH-ON patients; again mean or median values did not markedly change from baseline until last visit (by 2.2 ± 15.6, median 0.0). The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in the percentage of impairment while working due to MS, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 64: WPAI – Percentage of impairment while working due to MS (FAS)

Time point % impairment while working due to MS	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	357	194	33
Mean ± SD	28.1 ± 22.0	29.8 ± 24.6	30.9 ± 23.1
Median (Q1; Q3)	20.0 (10.0; 40.0)	20.0 (10.0; 40.0)	30.0 (10.0; 50.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 100.0
Month 12			
N	319	112	20
Mean ± SD	25.6 ± 21.4	27.6 ± 18.3	27.0 ± 22.3
Median (Q1; Q3)	20.0 (10.0; 30.0)	20.0 (10.0; 40.0)	20.0 (10.0; 35.0)
Min; Max	10.0; 100.0	10.0; 80.0	10.0; 80.0
Month 24			
N	298	48	9
Mean ± SD	27.5 ± 22.0	29.8 ± 23.9	35.6 ± 23.5
Median (Q1; Q3)	20.0 (10.0; 40.0)	20.0 (10.0; 40.0)	30.0 (20.0; 50.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 80.0
Month 36			
N	240	3	-
Mean ± SD	25.7 ± 19.9	43.3 ± 15.3	-
Median (Q1; Q3)	20.0 (10.0; 30.0)	40.0 (30.0; 60.0)	-
Min; Max	10.0; 100.0	30.0; 60.0	-
Last value after baseline			
N	477	201	63
Mean ± SD	30.1 ± 23.5	31.5 ± 22.3	36.0 ± 26.4
Median (Q1; Q3)	20.0 (10.0; 40.0)	30.0 (10.0; 50.0)	30.0 (10.0; 60.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 100.0
Change from baseline at last value after baseline			
N	334	151	18
Mean ± SD	1.0 ± 20.8	0.4 ± 18.0	2.2 ± 15.6
Median (Q1; Q3)	0.0 (-10.0; 10.0)	0.0 (-10.0; 10.0)	0.0 (0.0; 10.0)
Min; Max	-90.0; 90.0	-70.0; 60.0	-30.0; 40.0

MS = Multiple Sclerosis; FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; WPAI = Work Productivity and Activity Impairment.

WPAI outcomes are expressed as impairment percentage (ranging from 0% to 100%), with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.

For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.

Source: Post-text Table 6.5.2 and Table 6.5.6

8.3.5.3. Percentage of overall work impairment due to MS

Table 65 presents summary statistics for the WPAI score **percentage of overall work impairment due to MS** at selected time points including the change from baseline to the last documented value in the respective time period; the full course can be found in post-text Table 6.5.3 (WPAI percent overall work impairment due to MS) and post-text Table 6.5.7 (changes from baseline in WPAI percent overall work impairment due to MS).

In addition, post-Text Figure 6.5.11 displays the course of the WPAI percentage of overall work impairment due to MS as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

Please note that only a few patients provided data for this WPAI domain.

At baseline, the percentage (%) of overall work impairment due to MS was (mean ± SD) 50.5 ± 22.5 (median 44.8) (n=48) in STAY and 51.8 ± 24.3 in SWITCH-ON patients (median: 49.5) (n=27). Up to last documented value, the mean or median of the percentage (%) of overall work impairment due to MS, minimally decreases (by -2.8 ± 20.0, median -1.0) in STAY and minimally increased in SWITCH-OFF (by 4.1 ± 22.7, median 0.6).

In the SWITCH-OFF subcohort, the percentage of overall work impairment due to MS at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 61.8 ± 6.1 (median 65.2) (n=3). For calculation of the change from baseline, data of only one individual patient were available (decrease by -0.2)

In any of the 3 cohorts, there were always distinctive individual changes in the percentage of overall work impairment due to MS, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 65: WPAI – Percentage of overall work impairment due to MS (FAS)

Time point % overall work impairment due to MS	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	48	27	3
Mean ± SD	50.5 ± 22.5	51.8 ± 24.3	61.8 ± 6.1
Median (Q1; Q3)	44.8 (30.5; 69.2)	49.5 (31.9; 72.2)	65.2 (54.8; 65.5)
Min; Max	16.9; 97.6	16.8; 100.0	54.8; 65.5
Month 12			
N	34	16	7
Mean ± SD	51.0 ± 22.5	54.0 ± 23.8	62.1 ± 25.3
Median (Q1; Q3)	50.4 (28.0; 71.8)	44.9 (33.4; 75.0)	65.0 (36.0; 87.1)
Min; Max	19.7; 87.8	25.0; 99.2	23.8; 89.5
Month 24			
N	25	7	0
Mean ± SD	52.9 ± 26.0	55.4 ± 22.0	-
Median (Q1; Q3)	59.7 (28.6; 76.0)	58.6 (30.0; 73.9)	-
Min; Max	15.6; 96.0	29.7; 88.5	-
Month 36			
N	23	0	0
Mean ± SD	48.4 ± 20.1	-	-
Median (Q1; Q3)	46.9 (28.0; 60.0)	-	-
Min; Max	20.8; 88.0	-	-
Last value after baseline			
N	114	50	14
Mean ± SD	50.7 ± 22.6	55.2 ± 20.3	62.4 ± 19.6
Median (Q1; Q3)	50.6 (28.6; 68.0)	55.1 (38.8; 66.7)	64.0 (47.5; 77.9)
Min; Max	14.1; 96.0	21.3; 99.2	25.3; 89.5
Change from baseline at last value after baseline			
N	30	12	1
Mean ± SD	-2.8 ± 20.0	4.1 ± 22.7	-0.2 ± n.a.
Median (Q1; Q3)	-1.0 (-15.3; 10.6)	0.6 (-12.0; 15.7)	-0.2 (-0.2; -0.2)
Min; Max	-50.7; 40.1	-27.8; 56.2	-0.2; -0.2

MS = Multiple Sclerosis; FAS= Full Analysis Set; n.a. = Not applicable; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; WPAI = Work Productivity and Activity Impairment.
WPAI outcomes are expressed as impairment percentage (ranging from 0% to 100%), with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.5.3 and Table 6.5.7

8.3.5.4. Percentage of activity impairment due to MS

Table 66 presents summary statistics for the WPAI score **percentage of activity impairment due to MS** at selected time points including the change from baseline to the last documented visit in the respective time period; the full course overtime can be found in post-text Table 6.5.4 (WPAI percent activity impairment due to MS) and post-text Table 6.5.8 (changes from baseline in WPAI percent activity impairment due to MS).

In addition post-Text Figure 6.5.12 displays the course of the WPAI percentage of activity impairment due to MS as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the percentage of activity impairment due to MS was (mean ± SD) 38.3 ± 24.7 (median 30.0 %) in STAY and 41.9 ± 26.7 in SWITCH-ON patients (median: 40.0). During the observational period the mean and median scores did not change remarkably in the STAY and SWITCH-ON cohorts. Up to last documented value, the mean changes from baseline in the percentage of activity impairment due to MS were by <1.0 (absolute value), the median change was by 0.0 in either cohort.

In the SWITCH-OFF subcohort, the percentage of activity impairment due to MS at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 40.9 ± 24.3 (median 40.0) and similar to mean/median values in STAY and SWITCH-ON patients; again mean or median values did not markedly change from baseline until last visit. Up to last documented value, the mean change was by <1.0 (absolute value), the median change was by 0.0 in the SWITCH-OFF cohort. The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in the percentage of activity impairment due to MS, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 66: WPAI – Percentage of activity impairment due to MS (FAS)

Time point % activity impairment due to MS	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	624	348	64
Mean ± SD	38.3 ± 24.7	41.9 ± 26.7	40.9 ± 24.3
Median (Q1; Q3)	30.0 (20.0; 60.0)	40.0 (20.0; 60.0)	40.0 (20.0; 60.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 90.0
Month 12			
N	533	193	40
Mean ± SD	36.1 ± 24.4	38.8 ± 25.7	38.5 ± 24.1
Median (Q1; Q3)	30.0 (10.0; 50.0)	30.0 (20.0; 60.0)	40.0 (15.0; 55.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 90.0
Month 24			
N	499	80	17
Mean ± SD	37.6 ± 24.9	41.9 ± 27.0	42.9 ± 25.7
Median (Q1; Q3)	30.0 (10.0; 60.0)	40.0 (15.0; 70.0)	40.0 (20.0; 70.0)
Min; Max	10.0; 100.0	10.0; 90.0	10.0; 80.0
Month 36			
N	373	3	0
Mean ± SD	35.6 ± 24.2	50.0 ± 20.0	-
Median (Q1; Q3)	30.0 (10.0; 50.0)	50.0 (30.0; 70.0)	-
Min; Max	10.0; 100.0	30.0; 70.0	-
Last value after baseline			
N	655	306	116
Mean ± SD	38.1 ± 24.8	41.2 ± 25.5	45.6 ± 26.3
Median (Q1; Q3)	30.0 (20.0; 50.0)	40.0 (20.0; 60.0)	45.0 (20.0; 70.0)
Min; Max	10.0; 100.0	10.0; 100.0	10.0; 100.0
Change from baseline at last value after baseline			
N	607	280	45
Mean ± SD	0.0 ± 21.0	-0.1 ± 20.7	-0.4 ± 18.7
Median (Q1; Q3)	0.0 (-10.0; 10.0)	0.0 (-10.0; 10.0)	0.0 (-10.0; 10.0)
Min; Max	-70.0; 90.0	-90.0; 80.0	-50.0; 60.0

MS = Multiple Sclerosis; FAS= Full Analysis Set; n.a. = Not applicable; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; WPAI = Work Productivity and Activity Impairment.
WPAI outcomes are expressed as impairment percentage (ranging from 0% to 100%), with higher numbers indicating greater impairment and less productivity, i.e. worse outcomes.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.5.4 and Table 6.5.8

8.3.6. Symbol Digit Modalities Test

The SDMT was used as a cognitive measure in MS patients.

Table 67 presents summary statistics for the **number of correct symbols in SDMT** at selected time points including the change from baseline at last documented value in the respective time period; the full course can be found in post-text Table 6.6.1 (SDMT) and post-text Table 6.6.2 (changes from baseline in SDMT).

In addition post-Text Figure 6.6.3 displays the course of the number of correct symbols in SDMT as boxplot graphs for the total FAS, and for the STAY, SWITCH-ON, and SWITCH-OFF subcohorts.

At baseline, the number of correct symbols in SDMT was (mean ± SD) 46.7 ± 13.3 (median 48.0) in STAY and 47.0 ± 14.2 in SWITCH-ON patients (median: 47.0). Up to last documented value, the mean or median of the number of correct symbols in SDMT minimally increased from baseline by 6.1 ± 11.3 symbols correct (median 5.0 symbols correct) in STAY and 2.1 ± 10.8 symbols correct (median 3.0 symbols correct) in SWITCH-ON cohort.

In the SWITCH-OFF subcohort, the number of correct symbols in SDMT at discontinuation of natalizumab (baseline value resulting from re-baselining) was mean ± SD 52.0 ± 19.4 (median 52.0) and somewhat higher compared with values in STAY and SWITCH-ON patients; the mean or median values did not markedly change from baseline until last visit (median change from re-baseline was 1.0 symbols correct). The small number of available values for this cohort should be noted.

In any of the 3 cohorts, there were always distinctive individual changes in the number of correct symbols in SDMT, deteriorations as well as improvement, at any visit during the observational period up to last visit.

Table 67: SDMT – Number of correct symbols in (FAS)

Time point SDMT number of correct symbols	**STAY (N=698)**	**SWITCH-ON (N=396)**	**SWITCH-OFF (N=325)**
Baseline			
N	555	304	54
Mean ± SD	46.7 ± 13.3	47.0 ± 14.2	52.0 ± 19.4
Median (Q1; Q3)	48.0 (38.0; 55.0)	47.0 (38.0; 56.0)	52.0 (41.0; 60.0)
Min; Max	0.0; 92.0	0.0; 118.0	0.0; 107.0
Month 12			
N	463	163	33
Mean ± SD	49.8 ± 14.4	49.4 ± 14.5	54.7 ± 14.4
Median (Q1; Q3)	50.0 (42.0; 58.0)	49.0 (40.0; 59.0)	54.0 (46.0; 61.0)
Min; Max	7.0; 110.0	0.0; 94.0	33.0; 103.0
Month 24			
N	424	61	14
Mean ± SD	52.3 ± 14.5	53.4 ± 14.9	58.0 ± 14.3
Median (Q1; Q3)	52.0 (44.0; 61.0)	54.0 (43.0; 60.0)	59.0 (48.0; 72.0)
Min; Max	13.0; 104.0	20.0; 107.0	27.0; 76.0
Month 36			
N	309	2	-
Mean ± SD	54.3 ± 14.9	48.5 ± 6.4	-
Median (Q1; Q3)	53.0 (45.0; 62.0)	48.5 (44.0; 53.0)	-
Min; Max	5.0; 108.0	44.0; 53.0	-
Last value after baseline			
N	590	256	90
Mean ± SD	52.6 ± 15.1	49.1 ± 15.2	52.2 ± 13.9
Median (Q1; Q3)	52.0 (44.0; 62.0)	50.0 (40.0; 58.5)	52.0 (46.0; 60.0)
Min; Max	5.0; 108.0	0.0; 107.0	17.0; 102.0
Change from baseline at last value after baseline			
N	526	230	34
Mean ± SD	6.1 ± 11.3	2.1 ± 10.8	-0.3 ± 10.0
Median (Q1; Q3)	5.0 (0.0; 11.0)	3.0 (-2.0; 8.0)	1.0 (-4.0; 4.0)
Min; Max	-57.0; 61.0	-46.0; 50.0	-31.0; 16.0

FAS= Full Analysis Set; Q1/Q3 = 1st/3rd Quartile; SD = Standard deviation; SDMT = Symbol Digit Modalities Test
SDMT outcomes are expressed as number of correct symbols, with higher numbers indicating less cognitive impairment, i.e. better outcomes.
For SWITCH-OFF cohort, Month 3, 6 etc. values were not scheduled but resulted from re-baselining.
Source: Post-text Table 6.6.1 and Table 6.6.2

9. SAFETY RESULTS

All spontaneously reported AEs received through the study regardless of whether the event was serious, labeled, or attributed to natalizumab were reported to regulatory authorities in accordance with applying regulations. Analyses of the adverse event data were based on the safety data (cutoff date 16-March-2020) provided by the Biogen's drug safety department.

9.1. Overview of adverse events

Table 68 provides an overall summary of the treatment emergent AE (TEAE) experience documented in the study. Please note that AEs starting before Visit 1 were not regarded as study events. This section and the following tables summarize AEs occurring during TRUST study (i.e., starting at or after Visit 1) up to 90 days after last application of natalizumab. In addition, Biogen's drug safety department might have considered some events which occurred > 90 days after natalizumab discontinuation treatment emergent as well on an individual basis.

Any treatment-emergent adverse event (TEAE) was reported in 882 out of 1191 patients (74.1%) [95% CI: 71.5–76.5%], any serious TEAE in 273 patients (22.9%) [95% CI: 20.6–25.4%], and any TEAE possibly related to natalizumab in 434 patients (36.4%) [95% CI: 33.7–39.2%]. Overall, 5 patients (0.4%) [95% CI: 0.1–1.0%] were reported with "fatal" TEAEs (SAE category "death"). Overall, 9 patients (0.8%) [95% CI: 0.3–1.4%] received a confirmed PML diagnosis. Serious infections occurred in at total of 52 patients (4.4%) [95% CI: 3.3–5.7%].

- The incidence of any TEAE was greater in STAY (77.7%, 542 patients) compared with SWITCH (72.2%, 286 patients). Please note that patients in the STAY cohort had a longer individual observation time than those of the SWITCH cohort.
- The incidences of any TEAEs possibly related to natalizumab were comparable in STAY and SWITCH cohorts (38.0% or 265 patients and 37.6% or 149 patients).
- The incidence of any TEAE leading to interruption or discontinuation of natalizumab was lower in STAY (6.2% or 43 patients) compared with SWITCH (22.5% or 89 patients).
- The incidence of any treatment emergent SAE was lower in STAY (22.2%, 155 patients) compared with SWITCH (25.0%, 99 patients).
- The 5 deaths and the 9 confirmed PML cases were in the SWITCH or INDETERMINABLE cohort.
- The incidence of any treatment emergent SAE possibly related to natalizumab was lower in STAY (6.0% or 42 patients) [95% CI: 4.4–8.0%] compared with SWITCH (11.4% or 45 patients) [95% CI: 8.4–14.9%]. The 95% CIs did not overlap.
- The incidence of any treatment emergent SAE leading to interruption or discontinuation of natalizumab was lower in STAY (0.9% or 6 patients) [95% CI: 0.3–1.9%] than in SWITCH (6.1% or 24 patients) [95% CI: 3.9–8.9%]. The 95% CIs did not overlap.
- The incidence of any treatment emergent serious infections was lower in STAY (3.0% or 21 patients) [95% CI: 1.9–4.6%] than in SWITCH (7.1% or 28 patients) [95% CI: 4.7–10.1%]. The 95% CIs did not overlap.

Table 68: Summary of treatment emergent adverse events (TRP)

Parameter	STAY (N=698) n (%) (95% CI)	SWITCH (N=396) n (%) (95% CI)	INDETERMI-NABLE (N=97) n (%) (95% CI)	Total (N=1191) n (%) (95% CI)
Any AE	542 (77.7) [74.4 - 80.7%]	286 (72.2) [67.5 - 76.6%]	54 (55.7) [45.2 - 65.8%]	882 (74.1) [71.5 - 76.5%]
Any AE possibly related to NTZ	265 (38.0) [34.4 - 41.7%]	149 (37.6) [32.8 - 42.6%]	20 (20.6) [13.1 - 30.0%]	434 (36.4) [33.7 - 39.2%]
Any AE leading to interruption or discontinuation of NTZ	43 (6.2) [4.5 - 8.2%]	89 (22.5) [18.5 - 26.9%]	5 (5.2) [1.7 - 11.6%]	137 (11.5) [9.7 - 13.5%]
Any SAE	155 (22.2) [19.2 - 25.5%]	99 (25.0) [20.8 - 29.6%]	19 (19.6) [12.2 - 28.9%]	273 (22.9) [20.6 - 25.4%]
Any SAE possibly related to natalizumab	42 (6.0) [4.4 - 8.0%]	45 (11.4) [8.4 - 14.9%]	9 (9.3) [4.3 - 16.9%]	96 (8.1) [6.6 - 9.8%]
Any SAE leading to interruption or discontinuation of NTZ	6 (0.9) [0.3 - 1.9%]	24 (6.1) [3.9 - 8.9%]	2 (2.1) [0.3 - 7.3%]	32 (2.7) [1.8 - 3.8%]
SAE category "death"	0 (0.0) [0.0 - 0.5%]	3 (0.8) [0.2 - 2.2%]	2 (2.1) [0.3 - 7.3%]	5 (0.4) [0.1 - 1.0%]
SAE category "life-threatening"	0 (0.0) [0.0 - 0.5%]	1 (0.3) [0.0 - 1.4%]	0 (0.0) [0.0 - 3.7%]	1 (0.1) [0.0 - 0.5%]
SAE category "(prolongation of) hospitalization"	124 (17.8) [15.0 - 20.8%]	83 (21.0) [17.1 - 25.3%]	11 (11.3) [5.8 - 19.4%]	218 (18.3) [16.1 - 20.6%]
SAE category "persistent disability"	0 (0.0) [0.0 - 0.5%]	1 (0.3) [0.0 - 1.4%]	0 (0.0) [0.0 - 3.7%]	1 (0.1) [0.0 - 0.5%]
SAE category "medically significant"	45 (6.4) [4.7 - 8.5%]	29 (7.3) [5.0 - 10.3%]	8 (8.2) [3.6 - 15.6%]	82 (6.9) [5.5 - 8.5%]
SAE category "congenital anomaly/birth defect"	0 (0.0) [0.0 - 0.5%]	0 (0.0) [0.0 - 0.9%]	0 (0.0) [0.0 - 3.7%]	0 (0.0) [0.0 - 0.3%]
Opportunistic infections	0 (0.0) [0.0 - 0.5%]	0 (0.0) [0.0 - 0.9%]	0 (0.0) [0.0 - 3.7%]	0 (0.0) [0.0 - 0.3%]
Serious infections	21 (3.0) [1.9 - 4.6%]	28 (7.1) [4.7 - 10.1%]	3 (3.1) [0.6 - 8.8%]	52 (4.4) [3.3 - 5.7%]
PML	0 (0.0) [0.0 - 0.5%]	8 (2.0) [0.9 - 3.9%]	1 (1.0) [0.0 - 5.6%]	9 (0.8) [0.3 - 1.4%]

AE = Adverse event; NTZ = Natalizumab TRP = Treated patients
Any AEs starting before Baseline (Visit 1) were not regarded as study events. Only AEs starting at or after Visit 1 up to 90 days after last application of NTZ were regarded treatment emergent in TRUST. In addition, Biogen's drug safety department might have considered some events which occurred > 90 days after NTZ discontinuation treatment emergent as well on an individual basis.
Source: Post-text Table 7.1

9.2. Description of adverse events

9.2.1. Adverse events

Table 69 summarizes all TEAEs (serious and non-serious) by SOC, by subcohort, and overall, together with the most common preferred terms (reported in overall ≥1.0% of patients) within each SOC, the complete tabulation of all TEAS including all preferred terms can be found in post-text Table 7.2. It should be noted that a patient having the same event more than once was counted only once in the incidence for that event.

The most commonly documented SOCs (TEAEs reported in overall ≥10% of patients) in the TRP were:

- **Infections and infestations** with overall 39.2% (467 patients)
  - The 2 most common preferred terms were “nasopharyngitis” with overall 21.7% or 259 patients and “urinary tract infection” with overall 6.0% or 72 patients.
- **Nervous system disorders** with overall 37.6% (448 patients)
  - The most common preferred terms were “multiple sclerosis relapse” with overall 22.2% or 264 patients, “headache” with overall 5.2% or 62 patients, and “dizziness” with overall 3.0% or 36 patients.
- **Musculoskeletal and connective tissue disorders** with overall 15.0% (179 patients).
  - The most common preferred terms were “back pain” with overall 2.4% or 29 patients, and “arthralgia” with overall 2.0% or 24 patients.
- **Psychiatric disorders** with overall 11.5% (137 patients).
  - The most common preferred terms were “depression” with overall 4.5% or 53 patients, and “sleep disorder” with overall 3.1% or 37 patients.
- **Gastrointestinal disorders** with overall 10.9% (130 patients).
  - The most common preferred term was “diarrhea” with overall 3.0% (36 patients).
- **General disorders and administration site** conditions with overall 10.7% or 127 patients.
  - The most common preferred terms were “fatigue” with overall 2.9% (35 patients), “gait disturbance” with overall 2.0% (24 patients), and “pyrexia” with overall 1.9% (23 patients).

With regard to analysis by STAY and SWITCH subcohorts, the differences in TEAE incidences were most pronounced (at least 1.0% between STAY and SWITCH cohorts) for the primary MedDRA SOCs (post-text Table 7.1):

- **“Infections and infestations”** (STAY 41.7% and SWITCH 37.4%),
  - On PT level, incidences most obviously differed for “nasopharyngitis” (STAY 24.5% and SWITCH 18.7%), “urinary tract infection” (STAY 8.3% and SWITCH 3.5%), “sinusitis” (STAY 3.0% and SWITCH 1.8%), “progressive multifocal leukoencephalopathy” (STAY 0.0%, SWITCH 2.0%) (see also Section 9.2.2.5),

"oral herpes" (STAY 2.3% and SWITCH 1.3%), "herpes zoster" (STAY 2.3% and SWITCH 1.0%), "gastroenteritis" (STAY 1.7% and SWITCH 0.0%), and "pneumonia" (STAY 0.1% and SWITCH 1.3%).

- "**Nervous system disorders**" (STAY 37.2% and SWITCH 41.2%),
  - On PT level, incidences most obviously differed for "multiple sclerosis relapse" (STAY 20.6% and SWITCH 26.5%), "restless legs syndrome" (STAY 2.3% and SWITCH 0.3%), and "carpal tunnel syndrome" (STAY 1.7% and SWITCH 0.5%).
- **"Musculoskeletal and connective tissue disorders"** (STAY 16.9% and 13.4% SWITCH),
  - On PT level, incidences most obviously differed for "back pain" (STAY 3.0% and 1.8% SWITCH), and "muscle spasms" (STAY 1.3% and 2.3% SWITCH).
- **"Gastrointestinal disorders"** (STAY 12.8% and 8.6% SWITCH),
  - On PT level, incidences most obviously differed for "diarrhoea" (STAY 3.3% and 2.3% SWITCH), and "gastrointestinal disorder" (STAY 1.3% and 0.0% SWITCH).
- **"Metabolism and nutrition disorders"** (STAY 11.2% and SWITCH 8.1%).
  - On PT level, incidences most obviously differed for "vitamin D deficiency" (STAY 8.5% and 5.3% SWITCH).
- "**Injury, poisoning and procedural complications**" (STAY 9.3% and SWITCH 8.3%).
  - On PT level, incidences most obviously differed for "fall" (STAY 4.2% and 1.8% SWITCH).
- **"Investigations"** (STAY 8.0% and SWITCH 4.5%).
  - There were no striking differences found between cohorts in terms of TEAE incidences (≥1.0%) within PTs referring to this SOC.
- **"Ear and labyrinth disorders"** (STAY 3.7% and SWITCH 2.5%).
  - There were no striking differences found between cohorts in terms of TEAE incidences (≥1.0%) within PTs referring to this SOC.
- **"Vascular disorders"** (STAY 2.0% and SWITCH 4.5%).
  - On PT level, incidences most obviously differed for "hypertension" (STAY 0.9% and 2.0% SWITCH).
- **"Renal and urinary disorders"** (STAY 3.6% and SWITCH 1.3%).
  - There were no striking differences found between cohorts in terms of TEAE incidences (≥1.0%) within PTs referring to this SOC.
- **"Endocrine disorders"** (STAY 2.4% and SWITCH 0.5%).

– There were no striking differences found between cohorts in terms of TEAE incidences (≥1.0%) within PTs referring to this SOC.

In addition to the above mentioned preferred terms, differences between STAY and SWITCH cohorts with regard to TEAE incidences (at least 1.0%) were found for the following preferred terms (without showing differences on primary SOC level):

- "Immune reconstitution inflammatory syndrome" (STAY 0.0% and 1.8% SWITCH).
- "Gait disturbance" (STAY 1.6% and 2.8% SWITCH).
- "Erectile dysfunction" (STAY 0.0% and 1.0% SWITCH).
- "Visual impairment" (STAY 0.3% and 1.3% SWITCH).

Table 69: All TEAEs by primary SOC and by most common (≥1.0% in the total population) preferred term (TRP) – multipage table

MedDRA primary SOC PT within SOC	**STAY (N=698)** **n (%)**	**SWITCH (N=396)** **n (%)**	**INDETERMI-NABLE (N=97)** **n (%)**	**Total (N=1191)** **n (%)**
Any TEAE	**542 (77.7)**	**286 (72.2)**	**54 (55.7)**	**882 (74.1)**
Infections and infestations	**291 (41.7)**	**148 (37.4)**	**28 (28.9)**	**467 (39.2)**
Nasopharyngitis	171 (24.5)	74 (18.7)	14 (14.4)	259 (21.7)
Urinary tract infection	58 (8.3)	14 (3.5)	-	72 (6.0)
Infection	20 (2.9)	12 (3.0)	2 (2.1)	34 (2.9)
Respiratory tract infection	20 (2.9)	12 (3.0)	2 (2.1)	34 (2.9)
Bronchitis	20 (2.9)	11 (2.8)	1 (1.0)	32 (2.7)
Sinusitis	21 (3.0)	7 (1.8)	2 (2.1)	30 (2.5)
Upper respiratory tract infection	18 (2.6)	8 (2.0)	2 (2.1)	28 (2.4)
Cystitis	16 (2.3)	8 (2.0)	2 (2.1)	26 (2.2)
Tonsillitis	15 (2.1)	7 (1.8)	-	22 (1.8)
Oral herpes	16 (2.3)	5 (1.3)	-	21 (1.8)
Gastrointestinal infection	15 (2.1)	5 (1.3)	-	20 (1.7)
Herpes zoster	16 (2.3)	4 (1.0)	-	20 (1.7)
Gastroenteritis	12 (1.7)	-	2 (2.1)	14 (1.2)
Influenza	10 (1.4)	2 (0.5)	1 (1.0)	13 (1.1)
Otitis media	10 (1.4)	2 (0.5)	-	12 (1.0)
Viral infection	7 (1.0)	4 (1.0)	1 (1.0)	12 (1.0)
Nervous system disorders	**260 (37.2)**	**163 (41.2)**	**25 (25.8)**	**448 (37.6)**
Multiple sclerosis relapse	144 (20.6)	105 (26.5)	15 (15.5)	264 (22.2)
Headache	40 (5.7)	20 (5.1)	2 (2.1)	62 (5.2)
Dizziness	23 (3.3)	13 (3.3)	-	36 (3.0)
Hypoaesthesia	12 (1.7)	5 (1.3)	4 (4.1)	21 (1.8)
Paraesthesia	9 (1.3)	6 (1.5)	2 (2.1)	17 (1.4)

MedDRA primary SOC PT within SOC	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETERMI-NABLE (N=97) n (%)	Total (N=1191) n (%)
Restless legs syndrome	16 (2.3)	1 (0.3)	-	17 (1.4)
Carpal tunnel syndrome	12 (1.7)	2 (0.5)	1 (1.0)	15 (1.3)
Muscle spasticity	5 (0.7)	6 (1.5)	1 (1.0)	12 (1.0)
Musculoskeletal and connective tissue disorders	**118 (16.9)**	**53 (13.4)**	**8 (8.2)**	**179 (15.0)**
Back pain	21 (3.0)	7 (1.8)	1 (1.0)	29 (2.4)
Arthralgia	16 (2.3)	7 (1.8)	1 (1.0)	24 (2.0)
Pain in extremity	12 (1.7)	7 (1.8)	1 (1.0)	20 (1.7)
Muscle spasms	9 (1.3)	9 (2.3)	1 (1.0)	19 (1.6)
Intervertebral disc protrusion	11 (1.6)	4 (1.0)	-	15 (1.3)
Arthropathy	10 (1.4)	3 (0.8)	-	13 (1.1)
Psychiatric disorders	**80 (11.5)**	**49 (12.4)**	**8 (8.2)**	**137 (11.5)**
Depression	31 (4.4)	21 (5.3)	1 (1.0)	53 (4.5)
Sleep disorder	24 (3.4)	11 (2.8)	2 (2.1)	37 (3.1)
Gastrointestinal disorders	**89 (12.8)**	**34 (8.6)**	**7 (7.2)**	**130 (10.9)**
Diarrhoea	23 (3.3)	9 (2.3)	4 (4.1)	36 (3.0)
Nausea	11 (1.6)	7 (1.8)	-	18 (1.5)
Vomiting	11 (1.6)	3 (0.8)	-	14 (1.2)
General disorders and administration site conditions	**75 (10.7)**	**41 (10.4)**	**11 (11.3)**	**127 (10.7)**
Fatigue	22 (3.2)	12 (3.0)	1 (1.0)	35 (2.9)
Gait disturbance	11 (1.6)	11 (2.8)	2 (2.1)	24 (2.0)
Pyrexia	16 (2.3)	5 (1.3)	2 (2.1)	23 (1.9)
Metabolism and nutrition disorders	**78 (11.2)**	**32 (8.1)**	**1 (1.0)**	**111 (9.3)**
Vitamin D deficiency	59 (8.5)	21 (5.3)	1 (1.0)	81 (6.8)
Injury, poisoning and procedural complications	**65 (9.3)**	**33 (8.3)**	**2 (2.1)**	**100 (8.4)**
Fall	29 (4.2)	7 (1.8)	1 (1.0)	37 (3.1)
Skin and subcutaneous tissue disorders	**52 (7.4)**	**33 (8.3)**	**5 (5.2)**	**90 (7.6)**
Rash	8 (1.1)	5 (1.3)	1 (1.0)	14 (1.2)
Investigations	**56 (8.0)**	**18 (4.5)**	**1 (1.0)**	**75 (6.3)**
Respiratory, thoracic and mediastinal disorders	**39 (5.6)**	**23 (5.8)**	**3 (3.1)**	**65 (5.5)**
Cough	15 (2.1)	10 (2.5)	1 (1.0)	26 (2.2)
Blood and lymphatic system disorders	**24 (3.4)**	**10 (2.5)**	**3 (3.1)**	**37 (3.1)**
Ear and labyrinth disorders	**26 (3.7)**	**10 (2.5)**	**1 (1.0)**	**37 (3.1)**

MedDRA primary SOC PT within SOC	STAY (N=698) n (%)	SWITCH (N=396) n (%)	INDETERMI-NABLE (N=97) n (%)	Total (N=1191) n (%)
Vascular disorders	**14 (2.0)**	**18 (4.5)**	**-**	**32 (2.7)**
Hypertension	6 (0.9)	8 (2.0)	-	14 (1.2)
Renal and urinary disorders	**25 (3.6)**	**5 (1.3)**	**1 (1.0)**	**31 (2.6)**
Eye disorders	**16 (2.3)**	**9 (2.3)**	**2 (2.1)**	**27 (2.3)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**17 (2.4)**	**8 (2.0)**	**2 (2.1)**	**27 (2.3)**
Reproductive system and breast disorders	**17 (2.4)**	**9 (2.3)**	**1 (1.0)**	**27 (2.3)**
Immune system disorders	**16 (2.3)**	**10 (2.5)**	**-**	**26 (2.2)**
Cardiac disorders	**16 (2.3)**	**9 (2.3)**	**-**	**25 (2.1)**
Endocrine disorders	**17 (2.4)**	**2 (0.5)**	**-**	**19 (1.6)**
Pregnancy, puerperium and perinatal conditions	**9 (1.3)**	**4 (1.0)**	**2 (2.1)**	**15 (1.3)**
Surgical and medical procedures	**8 (1.1)**	**4 (1.0)**	**1 (1.0)**	**13 (1.1)**
Congenital, familial and genetic disorders	**3 (0.4)**	**2 (0.5)**	**-**	**5 (0.4)**
Hepatobiliary disorders	**4 (0.6)**	**1 (0.3)**	**-**	**5 (0.4)**
Social circumstances	**1 (0.1)**	**-**	**-**	**1 (<0.1)**

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; SOC = System Organ Class; TRP = Treated patients
Source: Post-text Table 7.2

9.2.1.1. Treatment emergent adverse events possibly related to natalizumab

Table 70 summarizes all TEAEs (serious and non-serious) **possibly related to natalizumab** by SOC. "Possibly related" means any other causality assessment than "not related" or "unlikely". Table 71 presents the most common preferred terms (reported in overall ≥3 patients [≥0.25% of patients]); the complete tabulation of all TEAEs possibly related to natalizumab including all preferred terms can be found in post-text Table 7.5.

The most commonly documented SOCs (reported in overall ≥3.0% of patients) in the TRP were:

- "Infections and infestations" with overall 15.5% (185 patients).
- "Nervous system disorders" with overall 13.3% (158 patients).
- "General disorders and administration site conditions" with overall 3.9% (46 patients).
- "Musculoskeletal and connective tissue disorders" with overall 3.3% (39 patients).

The most commonly documented preferred terms (reported in overall ≥1.0% of patients) in the TRP were: "multiple sclerosis relapse" (8.4% or 100 patients), "nasopharyngitis" (6.6% or 79 patients), "urinary tract infection" (2.4% or 29 patients), "headache" (1.5% or 18 patients), "oral

herpes" (1.2% or 14 patients), "depression" (1.0% or 12 patients), "gait disturbance" (1.0% or 12 patients), and "respiratory tract infection" (1.0% or 12 patients).

Table 70: All TEAEs possibly related to natalizumab by primary SOC (TRP)

MedDRA Primary system organ class	Total, (N=1191), n (%)
Any TEAE possibly related to natalizumab	**434 (36.4)**
Infections and infestations	185 (15.5)
Nervous system disorders	158 (13.3)
General disorders and administration site conditions	46 (3.9)
Musculoskeletal and connective tissue disorders	39 (3.3)
Investigations	34 (2.9)
Psychiatric disorders	32 (2.7)
Skin and subcutaneous tissue disorders	32 (2.7)
Gastrointestinal disorders	28 (2.4)
Blood and lymphatic system disorders	22 (1.8)
Metabolism and nutrition disorders	18 (1.5)
Respiratory, thoracic and mediastinal disorders	15 (1.3)
Immune system disorders	14 (1.2)
Injury, poisoning and procedural complications	12 (1.0)
Renal and urinary disorders	11 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (0.8)
Cardiac disorders	8 (0.7)
Pregnancy, puerperium and perinatal conditions	6 (0.5)
Eye disorders	5 (0.4)
Reproductive system and breast disorders	5 (0.4)
Vascular disorders	5 (0.4)
Ear and labyrinth disorders	4 (0.3)
Surgical and medical procedures	4 (0.3)
Endocrine disorders	3 (0.3)
Congenital, familial and genetic disorders	1 (<0.1)
Hepatobiliary disorders	1 (<0.1)
Social circumstances	1 (<0.1)

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; TRP = Treated patients.
Possibly related means other causality than "not related" or "unlikely".
Source: Post-text Table 7.5

Table 71: All TEAEs possibly related to natalizumab by most common (≥3 patients or 0.25% in the total population) preferred term (TRP) – multipage table

MedDRA preferred term	Total, (N=1191) n (%)
Any TEAE possibly related to natalizumab	**434 (36.4)**
Multiple sclerosis relapse	100 (8.4)
Nasopharyngitis	79 (6.6)
Urinary tract infection	29 (2.4)
Headache	18 (1.5)
Oral herpes	14 (1.2)
Depression	12 (1.0)
Gait disturbance	12 (1.0)
Respiratory tract infection	12 (1.0)
Fatigue	11 (0.9)
Sleep disorder	11 (0.9)
Arthropathy	10 (0.8)
Muscle disorder	10 (0.8)
Bronchitis	9 (0.8)
Cough	9 (0.8)
Dizziness	9 (0.8)
Herpes zoster	9 (0.8)
Progressive multifocal leukoencephalopathy	9 (0.8)
Upper respiratory tract infection	8 (0.7)
Hypoaesthesia	7 (0.6)
Immune reconstitution inflammatory syndrome	7 (0.6)
Leukocytosis	7 (0.6)
Lymphocytosis	7 (0.6)
Sinusitis	7 (0.6)
Tonsillitis	7 (0.6)
Vitamin D deficiency	7 (0.6)
Arthralgia	6 (0.5)
Diarrhoea	6 (0.5)
Infection	6 (0.5)
Influenza	6 (0.5)
Secondary progressive multiple sclerosis	6 (0.5)
Abortion spontaneous	5 (0.4)
Cystitis	5 (0.4)
Fall	5 (0.4)
Gastrointestinal disorder	5 (0.4)
Pyrexia	5 (0.4)
Alanine aminotransferase increased	4 (0.3)

MedDRA preferred term	Total, (N=1191) n (%)
Constipation	4 (0.3)
Dermatitis atopic	4 (0.3)
Herpes virus infection	4 (0.3)
Magnetic resonance imaging abnormal	4 (0.3)
Muscle spasticity	4 (0.3)
Otitis media	4 (0.3)
Pain in extremity	4 (0.3)
Paraesthesia	4 (0.3)
Viral infection	4 (0.3)
Abdominal pain	3 (0.3)
C-reactive protein increased	3 (0.3)
Dysaesthesia	3 (0.3)
Erythema	3 (0.3)
Gamma-glutamyltransferase increased	3 (0.3)
Hypersensitivity	3 (0.3)
Hypokalaemia	3 (0.3)
Lymphadenopathy	3 (0.3)
Lymphocyte count increased	3 (0.3)
Migraine	3 (0.3)
Mobility decreased	3 (0.3)
Muscle spasms	3 (0.3)
Pain	3 (0.3)
Palpitations	3 (0.3)
Pruritus	3 (0.3)
Rash	3 (0.3)
Thrombocytopenia	3 (0.3)
Trigeminal neuralgia	3 (0.3)
Visual impairment	3 (0.3)

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; TRP = Treated patients

Possibly related means other causality than “not related” or “unlikely”.

Source: Post-text Table 7.5

9.2.2. Serious adverse events

9.2.2.1. Deaths

Table 7.4.1 provides a listing per patient of all patients who died during TRUST observational study (i.e., event starting at or after Visit 1 and up to 90 days after natalizumab discontinuation),

Overall, 5 patients were reported with fatal TEAEs during the TRUST observational study.

- Death 1: MedDRA preferred term “completed suicide” (outcome: fatal, causality: not related).
- Death 2: MedDRA preferred term “road traffic accident” (outcome: fatal, causality: unknown).
- Death 3: MedDRA preferred term “death” (outcome: fatal, causality: not related) was reported; in the same patient concurrent “pancreatic carcinoma” (outcome: not recovered, causality: not assessed) was reported (data on file).
- Death 4: MedDRA preferred term “optic glioma” (outcome: fatal, causality: related).
- Death 5: MedDRA preferred term “death” (outcome: fatal, causality: unknown) was reported; in the same patient concurrent “progressive multifocal leukoencephalopathy” (outcome: not recovered, causality: related) was reported (data on file).

In one of the cases, the causality with natalizumab was assessed as “related” (preferred term “optic glioma”), in two other cases as “unknown”, the preferred terms were “fatal car accident” and “death” (please note that the latter patient was also reported with related unresolved PML at the same time, see also section 9.2.2.3).

9.2.2.2. All serious adverse events

Table 72 summarizes all serious TEAEs (including fatal events and PML) by SOC, by subcohort, and overall, together with the most common preferred terms within each SOC (reported in overall at least 2 patients); the complete tabulation of all serious TEAEs including all preferred terms can be found in post-text Table 7.3. It should be noted that a patient having the same event more than once was counted only once in the incidence for that event.

Overall, 273 patients (22.9%) experienced at least one TEAE that was serious. The proportions of patients with at least one serious TEAE were greater among SWITCH patients (25.0%, or 99 patients) compared with STAY (22.2%, or 155 patients) or INDETERMINABLE (19.6%, or 19 patients) patients.

The most commonly documented SOCs for serious TEAEs (reported in overall ≥2.0% of patients) were:

- **“Nervous system disorders”** with overall 9.1% (108 patients).
  - The most common preferred term was “multiple sclerosis relapse” with overall 5.5% or 66 patients.
- **“Infections and infestations”** with overall 4.4% (52 patients).
  - the most common preferred term was “progressive multifocal leukoencephalopathy” overall 0.8% or 9 patients.
- **“Injury, poisoning and procedural complications”** with overall 2.5% (30 patients).
  - The most common preferred term was “fall” with overall 0.7% (8 patients).
- **“Psychiatric disorders”** with overall 2.2% (26 patients).

– The most common preferred term was “depression” with overall 0.8% (9 patients).

With regard to analysis by STAY and SWITCH subcohorts, the differences in serious TEAE incidences were most pronounced (at least 1.0% between STAY and SWITCH cohorts) for the following primary MedDRA SOCs (post-text Table 7.5):

- **“Nervous system disorders”** (STAY 7.6% and SWITCH 12.1%),
  - On PT level, inter-cohort incidences most obviously differed for the PT “multiple sclerosis relapse” (STAY 4.0% and SWITCH 8.6%).
- **“Infections and infestations”** (STAY 3.0% and SWITCH 7.1%),
  - On PT level, incidences most obviously differed for “progressive multifocal leukoencephalopathy” (STAY 0.0%, SWITCH 2.0%, and INDETERMINABLE 1.0%) (see also Section 9.2.2.5), and “pneumonia” (STAY 0.0% and SWITCH 1.3%).
- **“General disorders and administration site conditions”** (STAY 1.3% and 2.5% SWITCH),
  - On PT level, incidences most obviously differed for “gait disturbance” (STAY 0.4% and 1.3% SWITCH),
- **“Immune system disorders”** (STAY 0.3% and SWITCH 1.8%).
  - On PT level, incidences most obviously differed for “Immune reconstitution inflammatory syndrome” (STAY 0.0% and 1.8% SWITCH).

Table 72: All serious TEAEs by primary SOC and by most common (≥2 patients in the total population) preferred term (TRP) – multipage table

MedDRA primary SOC Preferred term within SOC	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Any serious TEAE	**155 (22.2)**	**99 (25.0)**	**19 (19.6)**	**273 (22.9)**
Nervous system disorders	**53 (7.6)**	**48 (12.1)**	**7 (7.2)**	**108 (9.1)**
Multiple sclerosis relapse	28 (4.0)	34 (8.6)	4 (4.1)	66 (5.5)
Epilepsy	5 (0.7)	3 (0.8)	1 (1.0)	9 (0.8)
Multiple sclerosis	4 (0.6)	2 (0.5)	-	6 (0.5)
Uhthoff's phenomenon	3 (0.4)	3 (0.8)	-	6 (0.5)
Dizziness	3 (0.4)	1 (0.3)	-	4 (0.3)
Headache	4 (0.6)	-	-	4 (0.3)
Hypoaesthesia	2 (0.3)	1 (0.3)	-	3 (0.3)
Cognitive disorder	1 (0.1)	1 (0.3)	-	2 (0.2)
Generalised tonic-clonic seizure	2 (0.3)	-	-	2 (0.2)
Monoparesis	1 (0.1)	1 (0.3)	-	2 (0.2)
Muscle spasticity	1 (0.1)	1 (0.3)	-	2 (0.2)
Tension headache	2 (0.3)	-	-	2 (0.2)
Trigeminal neuralgia	2 (0.3)	-	-	2 (0.2)

MedDRA primary SOC Preferred term within SOC	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Infections and infestations	**21 (3.0)**	**28 (7.1)**	**3 (3.1)**	**52 (4.4)**
Progressive multifocal leukoencephalopathy	-	8 (2.0)	1 (1.0)	9 (0.8)
Appendicitis	4 (0.6)	1 (0.3)	-	5 (0.4)
Pneumonia	-	5 (1.3)	-	5 (0.4)
Infection	2 (0.3)	2 (0.5)	-	4 (0.3)
Urinary tract infection	2 (0.3)	2 (0.5)	-	4 (0.3)
Sepsis	1 (0.1)	2 (0.5)	-	3 (0.3)
Urosepsis	2 (0.3)	1 (0.3)	-	3 (0.3)
Bronchitis	-	2 (0.5)	-	2 (0.2)
Cytomegalovirus infection	2 (0.3)	-	-	2 (0.2)
Nasopharyngitis	-	2 (0.5)	-	2 (0.2)
Tonsillitis	2 (0.3)	-	-	2 (0.2)
Injury, poisoning and procedural complications	**20 (2.9)**	**10 (2.5)**	**-**	**30 (2.5)**
Fall	6 (0.9)	2 (0.5)	-	8 (0.7)
Contusion	3 (0.4)	1 (0.3)	-	4 (0.3)
Foot fracture	3 (0.4)	1 (0.3)	-	4 (0.3)
Road traffic accident	2 (0.3)	1 (0.3)	-	3 (0.3)
Craniocerebral injury	1 (0.1)	1 (0.3)	-	2 (0.2)
Ligament sprain	1 (0.1)	1 (0.3)	-	2 (0.2)
Lumbar vertebral fracture	2 (0.3)	-	-	2 (0.2)
Post lumbar puncture syndrome	1 (0.1)	1 (0.3)	-	2 (0.2)
Radius fracture	1 (0.1)	1 (0.3)	-	2 (0.2)
Psychiatric disorders	**13 (1.9)**	**11 (2.8)**	**2 (2.1)**	**26 (2.2)**
Depression	5 (0.7)	4 (1.0)	-	9 (0.8)
Suicidal ideation	1 (0.1)	2 (0.5)	-	3 (0.3)
Anxiety	1 (0.1)	1 (0.3)	-	2 (0.2)
Depression suicidal	1 (0.1)	-	1 (1.0)	2 (0.2)
Gastrointestinal disorders	**14 (2.0)**	**8 (2.0)**	**1 (1.0)**	**23 (1.9)**
Inguinal hernia	1 (0.1)	2 (0.5)	-	3 (0.3)
Abdominal adhesions	1 (0.1)	1 (0.3)	-	2 (0.2)
Gastric ulcer	1 (0.1)	1 (0.3)	-	2 (0.2)
Gastritis	2 (0.3)	-	-	2 (0.2)
Gastrointestinal disorder	1 (0.1)	-	1 (1.0)	2 (0.2)
Umbilical hernia	2 (0.3)	-	-	2 (0.2)
General disorders and administration site conditions	**9 (1.3)**	**10 (2.5)**	**2 (2.1)**	**21 (1.8)**
Gait disturbance	3 (0.4)	5 (1.3)	-	8 (0.7)
Death	-	-	2 (2.1)	2 (0.2)

MedDRA primary SOC Preferred term within SOC	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Pyrexia	1 (0.1)	1 (0.3)	-	2 (0.2)
Musculoskeletal and connective tissue disorders	**14 (2.0)**	**6 (1.5)**	**1 (1.0)**	**21 (1.8)**
Intervertebral disc protrusion	4 (0.6)	2 (0.5)	-	6 (0.5)
Osteoarthritis	1 (0.1)	1 (0.3)	-	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**11 (1.6)**	**8 (2.0)**	**2 (2.1)**	**21 (1.8)**
Ependymoma	1 (0.1)	1 (0.3)	-	2 (0.2)
Malignant melanoma	-	2 (0.5)	-	2 (0.2)
Investigations	**11 (1.6)**	**3 (0.8)**	**1 (1.0)**	**15 (1.3)**
Eosinophil count increased	2 (0.3)	-	-	2 (0.2)
Liver function test increased	2 (0.3)	-	-	2 (0.2)
Lymphocyte count increased	2 (0.3)	-	-	2 (0.2)
Pregnancy, puerperium and perinatal conditions	**8 (1.1)**	**4 (1.0)**	**2 (2.1)**	**14 (1.2)**
Abortion spontaneous	4 (0.6)	1 (0.3)	2 (2.1)	7 (0.6)
Cervical incompetence	1 (0.1)	1 (0.3)	-	2 (0.2)
Premature labour	1 (0.1)	1 (0.3)	-	2 (0.2)
Renal and urinary disorders	**6 (0.9)**	**3 (0.8)**	**1 (1.0)**	**10 (0.8)**
Ureterolithiasis	2 (0.3)	1 (0.3)	-	3 (0.3)
Nephrolithiasis	1 (0.1)	1 (0.3)	-	2 (0.2)
Surgical and medical procedures	**7 (1.0)**	**2 (0.5)**	**1 (1.0)**	**10 (0.8)**
Caesarean section	2 (0.3)	1 (0.3)	-	3 (0.3)
Vascular disorders	**5 (0.7)**	**5 (1.3)**	**-**	**10 (0.8)**
Deep vein thrombosis	1 (0.1)	1 (0.3)	-	2 (0.2)
Cardiac disorders	**4 (0.6)**	**5 (1.3)**	**-**	**9 (0.8)**
Mitral valve incompetence	-	2 (0.5)	-	2 (0.2)
Immune system disorders	**2 (0.3)**	**7 (1.8)**	**-**	**9 (0.8)**
Immune reconstitution inflammatory syndrome	-	7 (1.8)	-	7 (0.6)
Respiratory, thoracic and mediastinal disorders	**4 (0.6)**	**5 (1.3)**	**-**	**9 (0.8)**
Dyspnoea	-	2 (0.5)	-	2 (0.2)
Ear and labyrinth disorders	**5 (0.7)**	**2 (0.5)**	**1 (1.0)**	**8 (0.7)**
Deafness unilateral	1 (0.1)	1 (0.3)	1 (1.0)	3 (0.3)
Sudden hearing loss	2 (0.3)	-	-	2 (0.2)
Vertigo	1 (0.1)	1 (0.3)	-	2 (0.2)
Reproductive system and breast disorders	**7 (1.0)**	**1 (0.3)**	**-**	**8 (0.7)**
Ovarian cyst	3 (0.4)	-	-	3 (0.3)

MedDRA primary SOC Preferred term within SOC	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Cervical dysplasia	2 (0.3)	-	-	2 (0.2)
Skin and subcutaneous tissue disorders	**3 (0.4)**	**2 (0.5)**	**-**	**5 (0.4)**
Hepatobiliary disorders	**2 (0.3)**	**1 (0.3)**	**-**	**3 (0.3)**
Cholelithiasis	1 (0.1)	1 (0.3)	-	2 (0.2)
Metabolism and nutrition disorders	**2 (0.3)**	**1 (0.3)**	**-**	**3 (0.3)**
Blood and lymphatic system disorders	**2 (0.3)**	**-**	**-**	**2 (0.2)**
Congenital, familial and genetic disorders	**1 (0.1)**	**1 (0.3)**	**-**	**2 (0.2)**
Endocrine disorders	**1 (0.1)**	**-**	**-**	**1 (<0.1)**
Eye disorders	**1 (0.1)**	**-**	**-**	**1 (<0.1)**

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; SOC = System Organ Class; TRP = Treated patients
Source: Post-text Table 7.3

Overall, 21 patients experience serious TEAEs pertaining to the primary SOC “neoplasms benign, malignant and unspecified (incl cysts and polyps)” of that 2 patients were reported (preferred terms) with “ependymoma”, 2 patients with “malignant melanoma”, and 1 patient each with “acoustic neuroma”, “benign ovarian tumour”, “breast cancer”, “cervix carcinoma”, “female reproductive neoplasm”, “intraductal proliferative breast lesion”, “invasive ductal breast carcinoma”, “leiomyoma”, “meningioma”, “neurofibroma”, “optic glioma”, “pancreatic carcinoma”, “papillary thyroid cancer”, “prostate cancer”, “rectal adenoma”, “squamous cell carcinoma of the vulva”, “uterine leiomyoma” (multiple events per patient possible).

Among the 15 patients in total who experienced serious TEAEs pertaining to the primary SOC “investigations” were 2 patients each with serious “eosinophil count increased”; “liver function test increased”; “lymphocyte count increased”; and 1 patient each with serious “alanine aminotransferase increased”; “blood bilirubin increased”; “C-reactive protein increased”; “clostridium test positive”; “cytology abnormal”; “gamma-glutamyltransferase increased”; “haematocrit decreased”; “haemoglobin decreased”; “hepatic enzyme increased”; “investigation”; “legionella test positive”; “mean cell haemoglobin decreased”; “mean cell volume abnormal”.

9.2.2.3. Progressive multifocal leukoencephalopathy

Table 7.4.2 refers to an adverse event listing per patient of all patients who developed PML during their participation in the TRUST observational study and received a confirmed PML diagnosis.

Overall, 9 patients received a confirmed diagnosis of treatment-emergent PML during the TRUST observational study. Of the 9 PML events, all were serious, all but one (the causality of which was assessed as “unknown”) were regarded as related to natalizumab treatment. The outcome of PML was not recovered in two patients (of which one patient died a year later but

final cause of death was not provided), and recovered in the remaining 7 PML events (data on file, information received from drug safety department).

Patients were assigned to the following pre-defined PML risk classes and types according to their baseline data by drug safety department:

- High risk type 1: anti-JCV antibody status "positive" and natalizumab exposure at baseline > 24 months and prior immunosuppressive treatment;
- High risk type 2: anti-JCV antibody index >1.5 and natalizumab exposure at baseline > 24 months;
- Low risk type 1: anti-JCV antibody status "negative" and exposure ≤ 60 months and no prior immunosuppressive treatment;
- Low risk type 2: anti-JCV antibody index 0.4 to 0.9 and natalizumab exposure ≤ 60 months.

The following immunosuppressive therapies were regarded as relevant for assigning patients to pre-defined PML risk classes: Novantron/Onkotrone, Endoxan, Aubagio, Mabthera, Bendatrexat, Lantarel, Metex, or Lemtrada.

The following PML case narratives contain additional information which is not included in the clinical data base and which was provided by the drug safety department (safety data base, data on file).

Confirmed PML case 1

This female patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 93 months. This patient had not received immunosuppressive pretherapy, the last prior therapy before natalizumab was Betaferon/Extavia (duration unknown). This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV index unknown) at baseline (visit 1); at visit 2, anti-JCV antibody was "positive" and the anti-JCV antibody index was very high (1853). Although the patient was informed on PML risk, the patient wished to continue with natalizumab. After consultation with the expert team, it was decided to have MRI and JCV tests at 3-month intervals. With the 2nd MRI performed, PML was suspected and finally confirmed in the following month, natalizumab was permanently discontinued. The last natalizumab infusion was administered about 6 weeks prior to PML suspicion (at Visit 2 within TRUST). The patient recovered from PML (data on file).

Confirmed PML case 2

This female patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 99 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Copaxone (duration 4 months). This patient entered TRUST with a "positive" anti-JCV antibody status and a very high anti-JCV index of 4426 at baseline (visit 1). The patient was assigned to PML risk class "high risk type 2". With the 2nd MRI performed, PML was suspected and natalizumab was permanently discontinued without subsequent MS treatment. PML was finally confirmed about 3.5 months later. This patient recovered from PML on an unknown date.

In addition, this patient was reported experiencing serious "immune reconstitution inflammatory syndrome" (IRIS) (data on file).

Confirmed PML case 3

This female patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 117 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Copaxone (duration 3 months), further prior MS treatment was Rebif. This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV antibody index unknown) at baseline (visit 1); no further JCV test results were available. The patient was assigned to PML risk class "other than low or high risk". During the study, the treating neurologist suspected PML and natalizumab was permanently discontinued. The last natalizumab infusion was administered about 6 weeks prior to PML suspicion. Finally, PML was confirmed about 3 months later. The patient recovered from PML after approximately 1 year.

In addition, this patient was reported having concurrent serious IRIS (data on file).

Confirmed PML case 4

This male patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 94 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Betaferon/Extavia (duration 7 months), further prior MS treatment included Copaxone and Rebif. This patient entered TRUST with a positive anti-JCV antibody status (anti-JCV antibody index unknown) at baseline (visit 1); no further JCV test results were available. The patient was assigned to PML risk class "other than low or high risk". In the 2nd MRI performed, PML was suspected and finally confirmed in the following month; natalizumab was permanently discontinued and the patient switched to Copaxone. The last natalizumab infusion was administered about 6 weeks prior to PML suspicion. The patient recovered from PML about 5 months later.

In addition, this patient was reported having concurrent serious IRIS (data on file).

Confirmed PML case 5

In this female patient, the total duration of natalizumab therapy without interruptions was 52 months. This patient had not received previous immunosuppressive therapy, prior MS therapy before natalizumab was unknown. This patient entered TRUST without any JCV test results being available. The patient was assigned to PML risk class "other than low or high risk". After enrollment, PML was suspected due to clinical signs and symptoms and finally confirmed in the following month by the treating neurologist in a hospital (not the treating investigator). No MRI images were available for this patient. The last natalizumab infusion was administered about 6 weeks prior to PML suspicion and the patient switched to Copaxone after PML diagnosis had been confirmed. The patient recovered from PML.

In addition, this patient was reported having concurrent serious IRIS (data on file).

Confirmed PML case 6

In this female patient, the total duration of natalizumab therapy without interruptions was 52 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Copaxone (duration 36 months), there was no further prior MS

treatment. This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV antibody index 2.59) at baseline (visit 1); after entering TRUST further JCV test results were available at 6 time points covering a time period of about 18 months, the anti-JCV antibody status was always "positive" and anti-JCV antibody index was always between 3.56 and 3.60. The patient was assigned to PML risk class "other than low or high risk". During this time period, PML developed and natalizumab was permanently discontinued without subsequent MS treatment. The PML outcome was "not recovered". In the following year this patient died. The cause of death was not specified (data on file).

Confirmed PML case 7

In this female patient, the total duration of natalizumab therapy without interruptions was 23 months. This patient had received previous immunosuppressive therapy (see below past MS treatment), the last prior therapy before natalizumab was Copaxone (duration 85 months), further prior MS treatment included Novantron/Onkotrone and "other". This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV antibody index 3.35) at baseline (visit 1); no further JCV test results were available. The patient was assigned to PML risk class "other than low or high risk". In the 2nd MRI performed, PML was suspected and finally confirmed in the subsequent month and natalizumab was permanently discontinued. The last natalizumab infusion was administered 4 weeks prior to PML suspicion. The PML outcome was not recovered.

In addition, this patient was suspected having concurrent serious IRIS (data on file).

Confirmed PML case 8

This female patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 84 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Copaxone (duration 2 months), no further prior MS treatment. This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV antibody index 3246) at baseline (visit 1); the second JCV test result revealed positive anti-JCV antibody status (anti-JCV antibody index 2.99); no further JCV test results were available. The patient was assigned to PML risk class "high risk (type 2)". In a routine MRI performed, PML was strongly suspected and finally confirmed about 4 weeks later; natalizumab was permanently discontinued. The patient recovered from PML about 2 years later.

In addition, this patient was reported having concurrent serious IRIS and MS relapse (data on file).

Confirmed PML case 9

This female patient had a history of longstanding natalizumab treatment, the total duration of natalizumab therapy without interruptions was 112 months. This patient had not received previous immunosuppressive therapy, the last prior therapy before natalizumab was Copaxone (duration 60 months), no further prior MS treatment. This patient entered TRUST with a "positive" anti-JCV antibody status (anti-JCV antibody index 0.85) at baseline (visit 1); the second JCV test result revealed "positive" anti-JCV antibody status (anti-JCV antibody index 0.88); third JCV test was not done; fourth JCV test result revealed "positive" anti-JCV antibody status (anti-JCV antibody index 0.910); no further JCV test results were available.

The patient was assigned to PML risk class "other than low or high risk". In the 5th routine MRI performed, PML was strongly suspected and finally confirmed 4 weeks later; natalizumab was permanently discontinued. The last natalizumab infusion was administered about 6 weeks prior to PML suspicion. The patient recovered from PML 3 months later.

In addition, this patient was reported having concurrent serious IRIS, and developed during the PML infection also a serious "pneumonia" and serious "sepsis" two months after PML onset (outcomes unknown) (data on file).

9.2.2.4. Opportunistic infections

Physicians could document opportunistic infections by selecting a pre-specified drop-down entry in the comorbidities section of the eCRF. No opportunistic infections were documented by the study centers in the eCRF by using this tool.

9.2.2.5. Serious infections

Table 73 summarizes all serious infections (including fatal events and PML) by preferred term, by subcohort, and overall, together. Serious infections were defined as all serious TEAE referring to the primary MedDRA SOC "infections and infestations".

Based on this definition, serious infections occurred in overall 4.4% (52 patients) of all TRP patients, the proportions were numerically lower among STAY 3.0% (21 patients) compared with SWITCH 7.1% (28 patients).

The between-group differences were most pronounced for the most common preferred term "**progressive multifocal leukoencephalopathy**" with overall 0.8% or 9 patients (of that STAY 0.0%, SWITCH 2.0% or 8 patients, and INDETERMINABLE 1.0% or 1 patients), and for "**pneumonia**" with overall 0.4% or 5 patients (of that STAY 0.0%, SWITCH 1.3% or 5 patients, and INDETERMINABLE 0.0%).

Among the patients with serious infections reported there was also 1 patient (<0.1%) each reported with (preferred terms) "herpes zoster", "ophthalmic herpes zoster", "latent tuberculosis" and "tuberculosis".

Table 73: All serious treatment emergent infections by preferred term (TRP) – multipage table

MedDRA primary SOC PT within SOC	**STAY (N=698)**	**SWITCH (N=396)**	**INDETERMI-NABLE (N=97)**	**Total (N=1191)**
Any serious infection	**21 (3.0)**	**28 (7.1)**	**3 (3.1)**	**52 (4.4)**
Infections and infestations	**21 (3.0)**	**28 (7.1)**	**3 (3.1)**	**52 (4.4)**
Progressive multifocal leukoencephalopathy	-	8 (2.0)	1 (1.0)	9 (0.8)
Appendicitis	4 (0.6)	1 (0.3)	-	5 (0.4)
Pneumonia	-	5 (1.3)	-	5 (0.4)
Infection	2 (0.3)	2 (0.5)	-	4 (0.3)
Urinary tract infection	2 (0.3)	2 (0.5)	-	4 (0.3)
Sepsis	1 (0.1)	2 (0.5)	-	3 (0.3)
Urosepsis	2 (0.3)	1 (0.3)	-	3 (0.3)

MedDRA primary SOC PT within SOC	STAY (N=698)	SWITCH (N=396)	INDETERMI-NABLE (N=97)	Total (N=1191)
Bronchitis	-	2 (0.5)	-	2 (0.2)
Cytomegalovirus infection	2 (0.3)	-	-	2 (0.2)
Nasopharyngitis	-	2 (0.5)	-	2 (0.2)
Tonsillitis	2 (0.3)	-	-	2 (0.2)
Bronchitis bacterial	1 (0.1)	-	-	1 (<0.1)
Ear infection	-	1 (0.3)	-	1 (<0.1)
Endocarditis	-	1 (0.3)	-	1 (<0.1)
Erysipelas	-	1 (0.3)	-	1 (<0.1)
Escherichia pyelonephritis	1 (0.1)	-	-	1 (<0.1)
Escherichia urinary tract infection	-	1 (0.3)	-	1 (<0.1)
Gastrointestinal fungal infection	-	1 (0.3)	-	1 (<0.1)
Herpes zoster	1 (0.1)	-	-	1 (<0.1)
Latent tuberculosis	-	1 (0.3)	-	1 (<0.1)
Lung abscess	-	1 (0.3)	-	1 (<0.1)
Myelitis	-	1 (0.3)	-	1 (<0.1)
Ophthalmic herpes zoster	-	-	1 (1.0)	1 (<0.1)
Otitis media	1 (0.1)	-	-	1 (<0.1)
Peritonitis	1 (0.1)	-	-	1 (<0.1)
Peritonsillar abscess	-	1 (0.3)	-	1 (<0.1)
Pilonidal cyst	1 (0.1)	-	-	1 (<0.1)
Pyelonephritis	-	-	1 (1.0)	1 (<0.1)
Pyelonephritis acute	-	1 (0.3)	-	1 (<0.1)
Sinusitis	1 (0.1)	-	-	1 (<0.1)
Staphylococcal abscess	-	1 (0.3)	-	1 (<0.1)
Streptococcal abscess	-	1 (0.3)	-	1 (<0.1)
Tinea versicolour	-	1 (0.3)	-	1 (<0.1)
Tuberculosis	1 (0.1)	-	-	1 (<0.1)
Viral infection	1 (0.1)	-	-	1 (<0.1)

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; SOC = System Organ Class; TRP = Treated patients
Source: Post-text Table 7.3

9.2.2.6. Pregnancies

Overall, 103 patients (data on file clinical data base) became pregnant during the study as documented in the eCRF.

Among the 14 patients with serious TEAEs pertaining to the primary SOC "**pregnancy, puerperium and perinatal conditions**" there were 7 patients with PT "abortion spontaneous", and 2 patients with "cervical incompetence", 2 patients with "premature labour", 1 patient with "placental insufficiency", and 1 patient with "premature separation of placenta".

9.2.2.7. All adverse events leading to permanent discontinuation of natalizumab

Table 74 summarizes all TEAEs (serious and non-serious) that lead to permanent discontinuation of natalizumab by SOC together with the most common preferred terms (reported in overall ≥2 patients); the complete tabulation of all TEAEs leading to discontinuation of natalizumab including all preferred terms can be found in post-text Table 7.6.

The most commonly documented SOCs (reported in overall ≥1.0% patients) for TEAEs leading to permanent discontinuation of natalizumab in the TRP were:

- **"Nervous system disorders"** with overall 3.9% (47 patients).
  - The most common preferred term was "multiple sclerosis relapse" with overall 2.1% or 25 patients.
- **"Infections and infestations"** with overall 3.2% (38 patients).
  - The most common preferred terms were "nasopharyngitis" with overall 1.0% or 12 patients and "progressive multifocal leukoencephalopathy" with 0.8% or 9 patients.

Table 74: All TEAEs leading to permanent discontinuation of natalizumab by primary SOC and by most common (≥2 patient in the total population) preferred term (TRP) – multipage table

MedDRA SOC PT within SOC	**Total (N=1191)** **n (%)**
Any TEAE leading to discontinuation of natalizumab	**112 (9.4)**
Nervous system disorders	**47 (3.9)**
Multiple sclerosis relapse	25 (2.1)
Secondary progressive multiple sclerosis	5 (0.4)
Dizziness	3 (0.3)
Hypoaesthesia	2 (0.2)
Multiple sclerosis	2 (0.2)
Progressive multiple sclerosis	2 (0.2)
Uhthoff's phenomenon	2 (0.2)
Infections and infestations	**38 (3.2)**
Nasopharyngitis	12 (1.0)
Progressive multifocal leukoencephalopathy	9 (0.8)
Bronchitis	3 (0.3)
Infection	3 (0.3)
Urinary tract infection	3 (0.3)
Respiratory tract infection	2 (0.2)
Upper respiratory tract infection	2 (0.2)
General disorders and administration site conditions	**11 (0.9)**
Gait disturbance	5 (0.4)
Fatigue	2 (0.2)
Pyrexia	2 (0.2)

MedDRA SOC PT within SOC	Total (N=1191) n (%)
Musculoskeletal and connective tissue disorders	**7 (0.6)**
Psychiatric disorders	**7 (0.6)**
Depression	5 (0.4)
Sleep disorder	2 (0.2)
Investigations	**6 (0.5)**
C-reactive protein increased	2 (0.2)
Skin and subcutaneous tissue disorders	**5 (0.4)**
Immune system disorders	**4 (0.3)**
Immune reconstitution inflammatory syndrome	3 (0.3)
Ear and labyrinth disorders	**3 (0.3)**
Eye disorders	**3 (0.3)**
Visual impairment	2 (0.2)
Metabolism and nutrition disorders	**3 (0.3)**
Pregnancy, puerperium and perinatal conditions	**3 (0.3)**
Gastrointestinal disorders	**2 (0.2)**
Injury, poisoning and procedural complications	**2 (0.2)**
Renal and urinary disorders	**2 (0.2)**
Respiratory, thoracic and mediastinal disorders	**2 (0.2)**
Vascular disorders	**2 (0.2)**
Blood and lymphatic system disorders	**1 (<0.1)**
Cardiac disorders	**1 (<0.1)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (<0.1)**

TEAE = Treatment emergent adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; SOC = System Organ Class; TRP = Treated patients
Source: Post-text Table 7.6

10. DISCUSSION AND OVERALL CONCLUSIONS

This non-interventional observational study was conducted at 160 study centers located in Germany. The first subject was documented on 20 August 2014 and the last subject's last documentation was on 12 December 2019. Overall, 1191 subjects (enrolled at 157 study centers) provided IC and received at least one dose of natalizumab after study inclusion, and were thus suitable for evaluation in the TRP. The planned individual study duration was 36 months regardless of whether natalizumab was discontinued before regular end of study at Month 36.

For the data analyses, the 1191 TRP patients were assigned to STAY (698 patients) (i.e., continued natalizumab therapy until the end of study at Month 36), SWITCH (396 patients) (i.e., patients discontinued natalizumab before the end of study at Month 36), and INDETERMINABLE (97 patient) subcohorts. Two (2) TRP subjects did not fulfill all selection criteria, and thus, the FAS comprised 1189 patients (698 STAY, 396 SWITCH, and 95 INDETERMINABLE).

In addition, the FAS patients were 1:1 propensity score matched for STAY versus SWITCH for the outcome parameters ARR and EDSS worsening; the resulting PSM comprised 580 patients: 290 in STAY and 290 in SWITCH cohort. In addition, for the evaluation of the parameter "EDSS worsening", a second PSM2 (326 STAY and 326 SWITCH patients) was created without considering the baseline EDSS score for propensity score matching.

Overall, 396 patients (33.2%) of the TRP set discontinued natalizumab therapy at any time up to study end at Month 36. The most common reasons were "PML risk" (46.7%), "requested by patient" (13.4%), and "positive anti-JCV antibody test" (12.1%), no reason was specified in 17.9% of patients.

The observational time per patient was 36.3 ± 1.8 months in the STAY cohort; and 20.4 ± 9.8 months in switch patients before natalizumab discontinuation (SWITCH-ON; N=396), and 12.7 ± 10.7 months after natalizumab discontinuation (SWITCH-OFF; N=325).

Baseline data and demography

The patients' mean ± SD age was 39.1 ± 10.0 years ranging from 18.0 to 76.0 years. Multiple sclerosis is generally more prevalent in women and this was consistent with our study population with the majority of patients being women (72.5%). Demographic data differed between the subcohorts, with a slightly greater proportion of women and slightly lower patients' mean age in STAY compared with SWITCH cohort.

The time interval between the onset of first MS symptoms and start of study was 11.2 ± 7.1 years, the mean time between MS diagnosis and start of study was 9.8 ± 6.3 years, with no striking differences between the STAY and SWITCH cohorts.

Before starting natalizumab, most patients already had received prior treatment due to MS, only 160 patients (13.4%) had been treatment naïve. The mean number of prior MS therapies was 1.3 ± 0.9 (maximum up to 5 prior MS therapies), without remarkable differences between subcohorts. The most common previous treatments were glatiramer acetate ("Copaxone", 34.5%), and interferons such as "Avonex" (31.2%), "Rebif" (30.8%) or "Betaferon/Extavia" (22.2%). The proportions with a specific previous MS treatment were largely comparable across STAY and SWITCH subcohorts.

Natalizumab treatment

The **number of prior natalizumab infusions** as well as the duration of prior **natalizumab treatment before study inclusion** showed a very broad range in the total population (from 9 to 122 prior natalizumab infusions corresponding to a treatment duration of 11.8 to 146.4 months). Overall, patients had received median 31.0 natalizumab infusion (Q1=17.0 infusions; Q3=65.0 infusions) prior to study inclusion, corresponding to a median treatment duration of 36.1 month (Q=17.2 months; Q3=76.5 months). The number prior natalizumab infusions was slightly greater in the STAY cohort (median 32.0 infusions) compared with the SWITCH cohort (median 29.5 infusions); as expected, the duration of prior natalizumab treatment was also slightly longer in the STAY cohort (median 36.9 months vs. 33.3 months).

The mean number of **natalizumab infusions after study inclusion** was 34.1 ± 5.3 infusion in the STAY and 15.9 ± 9.5 infusions in the SWITCH cohort.

Analysis of the **infusion intervals** revealed that of the overall 30331 infusions intervals documented in this study, 36.5% were ≥4.5 weeks thereby pointing to a possible EID, with a

minimally greater proportion among SWITCH patients (37.5% of the 5886 infusion intervals) compared with STAY patients (36.2% of the 23101 infusion intervals).

The time on natalizumab treatment was evaluated using Kaplan-Meier estimates. In this study, the Kaplan-Meier estimated **time on natalizumab from treatment start** was relatively long with 10.3 years for the median and 6.5 years for the 25% quartile; in the SWITCH cohort it was markedly shorter (about 4.5 years).

In the total PSM, the Kaplan-Meier estimated time on natalizumab from treatment start was somewhat shorter than in the total TRP (median was 8.2 years; 25% quartile 4.1 years).

The estimated time on natalizumab since treatment start decreased with increasing PML risk; it was highest in the "no PML risk" group (median about 12.0 years) and lowest in the "high PML risk" group (median about 9.5 years).

The Kaplan-Meier estimated median **time on natalizumab since study entry** was 3.6 years for the total population, 1.5 years for the SWITCH cohort, and 3.0 years for the total PSM.

Again, the median time on natalizumab since study entry decreased with increasing **PML risk**, as it could be expected: The estimated median time on natalizumab was about 3.2 years each for "intermediate" and "low PML risk", about 2.1 years for "high PML risk" (not estimable for the "no PML risk" subgroup).

To adjust **the duration of natalizumab treatment since treatment start for non-safety discontinuations** we performed a competing risk analysis. Overall, 235 of the 1191 TRP patients discontinued natalizumab due to safety reasons (i.e., positive anti-JCV antibody test, PML risk, or AE), further 161 patients discontinued treatment due to non-safety reasons (competing events, i.e., reasons other than those mentioned before, which includes not specified reasons), 795 patients were censored (i.e., stayed on natalizumab treatment). After 2 years of natalizumab treatment, the **cumulative incidence of discontinuations due to safety reasons** was 0.9%, and it increased to 4.7% after 3 years and to 11.1% after 5 years; after 10 years of natalizumab treatment it was 27.2%.

A logistic regression model including backward selection identified the following **prognostic factors for natalizumab discontinuation:** The duration of exposure to natalizumab including time before study start in days (patients with a shorter treatment exposure were more likely to discontinue natalizumab. However, this finding might be biased since patients who discontinue have inherently a shorter treatment duration); Last EDSS score before discontinuation/end of study (patients with higher EDSS before discontinuation were more likely to discontinue natalizumab); EID (patients assigned to "EID not calculable" were 6.07 times as likely to be discontinued from natalizumab than patients assigned to "EID yes". This finding is probably biased by treatment duration. Only in patients with a relatively long treatment duration, an EID could be detected at all. Thus, only patients with a long treatment duration had the possibility to be assigned to the "EID yes" subgroup); PML risk at baseline (patients entering the study with a high / intermediate / low PML risk were 8.10 / 4.38 / 2.24 times as likely to be discontinued from natalizumab than patients classified as "no PML risk").

The "duration of disease since diagnosis in years" which was identified as a prognostic factor in the full model without backward selection (were patients with a longer duration of disease were

more likely to discontinue natalizumab) was not identified in the model with backward selection (nevertheless, the p-value very close to the 0.05 threshold).

Number of MS relapses and annualized relapse rate

The number of MS relapses and the estimated ARR were calculated using the FAS. It should be recognized that the data on the number relapses for the specified time periods were documented using different data collection methods. The information on the number of relapses before study entry were retrospectively collected as a single summary value, whilst the number of relapses occurring after study entry were based on prospective data collection which was performed continuously at each data collection visit.

During **the last 12 months prior to initiating natalizumab,** only 8.1% of the patients in the FAS were relapse-free with similar proportions in STAY and SWITCH cohorts. Patients with 1, 2, or >2 relapses within the last 12 months prior start of natalizumab were relatively equally distributed among the relapse frequency categories (1, 2, >2 relapses) and comparable across STAY and SWITCH cohorts.

After start of natalizumab (until study entry), the proportion of relapse-free patients markedly increased to nearly two thirds of patients across all cohorts (total 64.9%).

From after study enrollment to natalizumab discontinuation, 79.5% of patients in the STAY and 76.0% in the SWITCH cohort were relapse-free: **after natalizumab discontinuation,** 78.5% of patients in the SWITCH cohort remained relapse-free.

The **ARR was adjusted for the covariates** gender, baseline EDSS, disease duration, number of previous DMTs, and treatment duration. The **estimated ARR after start of natalizumab but prior to study enrollment** was 0.127 relapses per year and slightly decreased to 0.100 relapses per year for the time interval **from study inclusion to natalizumab discontinuation/last visit**. **After discontinuation of natalizumab**, the estimated ARR markedly increased to 0.269 relapses per year. Non-overlapping 95% CIs indicated statistically meaningful differences between the ARR after natalizumab discontinuation and the ARRs for both preceding time intervals. The results for estimated ARRs in the total PSM were largely consistent the results in the total FAS, but with numerically higher values for ARRs compared to FAS.

The estimated ARRs for the time interval from start of natalizumab but prior to study enrollment were similar in STAY and SWITCH patients (0.131 and 0.133, respectively). The ARR from study inclusion until natalizumab discontinuation/last visit was considerably lower in the STAY (0.078) than in the SWITCH cohort (0.175), the 95% CIs did not overlap. In the SWITCH cohort, the ARR further markedly increased to 0.274 after natalizumab discontinuation.

In both cohorts, the ARR estimates using the PSM largely confirmed the qualitative findings from the FAS. The only exception was that the ARR estimate for the interval from start of natalizumab until study enrollment, which was lower in the PSM STAY cohort (0.129) than in the PSM SWITCH cohort (0.170), but overlapping 95% CIs indicated that this difference might not be statistically relevant.

The estimated ARRs for the time interval from start of natalizumab until study enrollment were minimally higher in patients with EID than in patients without (0.132 and 0.118, respectively). The estimated ARRs from study inclusion until last visit were lower and comparable in both populations (EID yes vs. EID no with 0.084 and 0.076, respectively). After discontinuation of

natalizumab, the estimated ARRs increased in both populations (to 1.441 and 0.233; EID yes vs. EID no, respectively) and the ARR in was markedly higher in patients with EID compared to the subgroup without, but the 95% CI was quite wide indicating that this estimate was uncertain and not very precise. Despite some numerical differences compared to the FAS, the ARR estimates in the PSM largely confirmed the qualitative findings from the FAS.

Expanded Disability Status Scale

At start of natalizumab, the retrospectively collected EDSS was (mean ± SD) 3.0 ± 1.5 in STAY and 3.2 ± 1.8 in SWITCH-ON patients (median: 3.0 in both cohorts). At study entry, the EDSS was numerically lower in STAY cohort (2.7 ± 1.6, median 2.5) compared with SWITCH-ON cohort (3.1 ± 1.8, median 3.0), and SWITCH-OFF subcohort (3.1 ± 1.8, median 3.0). There were no relevant mean or median changes from baseline in any of the cohorts throughout the study course (LOCF).

The proportions of patients with an EDSS worsening at any time point during the study were lower among STAY patients (6.6%) compared with SWITCH-ON (9.2%) or SWITCH-OFF (7.9%) patients. The results after propensity score matching (PSM2), were consistent with the FAS results (EDSS worsening in 4.7% of STAY, 9.3% of SWITCH-ON and 7.5% of SWITCH-OFF patients).

With regard to subgroups by EID, the proportions of patients with an EDSS worsening were lowest among patients with EID (5.0%) compared with patients without EID (8.2%) or patients where EID was not calculable (11.1%). Results with the PSM2 confirmed FAS results (EID yes 2.7%; EID no 6.3% EID not calculable 12.9%).

With regard to subgroups by baseline PML risk, the proportions of patients with EDSS worsening were lowest among patients with “no PML risk” (8.3%) and highest among patients “high PML risk” (11.1%).

In the PSM, the proportions of patients with a worsening in EDSS were lower among patients with or “no” or “intermediate PML risk” (7–8%) compared with “low” (10.3%) or “high PML risk” patients (11.9%).

MS Symptoms

Overall, 74.9% of patients entered the study with at least one MS symptom present at baseline, in about half of the patients even more than one symptom was present. The most frequent MS symptom present at study entry was “dys-/hyperesthesia” with 31.4%.

Overall, in 25.7% of patients at least one MS symptom improved (STAY 26.1% and SWITCH 28.8%), and in 30.2% at least one MS symptom worsened after study start (STAY 27.9% and SWITCH 36.1%); the most common ones were (for both categories, improved and worsened) “dys-/hyperesthesia” and “fatigue”, with only minor differences between STAY and SWITCH patients.

Overall, in 49.2% of the patients at least one MS symptom newly occurred after study start. (STAY 49.4% and 52.5% SWITCH), the most common ones were “other” (20.2%), “fatigue” (15.4%), “dys-/hyperesthesia” (12.6%), “bladder/intestinal disorders” (10.2%), and “depression” (6.2%), with only minor differences between STAY and SWITCH patients.

John-Cunningham-Virus tests

In almost all patients who entered the TRUST study a JCV test result was available. The mean duration of the time interval between JCV tests was similar across all cohorts (mean 5.2 to 5.7 months), whilst the median value was greater in the STAY (5.2 months) than in SWITCH-ON (3.7 months) or SWITCH-OFF (3.2 months) cohorts.

Among the STAY patients, 70.8% entered the study with an anti-JCV antibody index <0.4 ("negative" indicating "no PML risk") compared to 35.7% of SWITCH-ON patients. Conversely, among the SWITCH-ON patients, 44.4% entered the study with an anti-JCV antibody index >1.5 ("positive" indicating "high PML risk") compared with 13.2% of STAY patients.

At baseline, the anti-JCV antibody index was 0.6 ± 0.9 in STAY, 1.5 ± 1.3 in SWITCH-ON, and 2.4 ± 1.1 in the SWITCH-OFF cohort, i.e., at natalizumab discontinuation. Mean and median values of the anti-JCV antibody index did not relevantly change over time in STAY, whilst they mildly increased in SWITCH-ON, and mildly decreased in SWITCH-OFF cohorts (LOCF).

Of the 703 patients who tested "negative" for anti-JCV antibody status at baseline, 102 patients had a seroconversion to "positive" at their last visit.

MRI scans

Before natalizumab discontinuation, the duration of the time interval between MRI check-ups was mildly greater among STAY (8.0 ± 6.4 months, median 6.3 months) compared with SWITCH patients (7.0 ± 5.4 months, median 5.8 months). After natalizumab discontinuation, the duration of the time interval between MRI scans was (7.3 ± 4.2 months, median 6.2 months) in SWITCH patients.

Patient reported outcomes

Generally, the PROs, which comprised TSQM-9, FSMC, HADS, MSIS-29, and WPAI-MS, did not change remarkably over time in any of the cohorts (STAY, SWITCH-ON, or SWITCH-OFF). With the exception of the FSMC (which indicated moderate fatigue at study entry based on sum score mean and median values) and some of the WPAI-MS domains (which e.g., revealed a percent activity impairment due to MS of mean 38-42%), all PROs showed relatively favorable results and patient's conditions already at study entry. Nevertheless, in all 3 cohorts distinctive individual changes in all PROs were noted during study course, deteriorations as well as improvements.

The number of correct symbols in SDMT mildly improved in the STAY and SWITCH-ON cohorts, whilst it did not notably change in SWITCH-OFF cohort, but it should be noted that the baseline-values in the SWITCH-OFF cohort (resulting from re-baselining) was already somewhat better compared with both latter cohorts.

Safety

Regarding tolerability of natalizumab, the overall incidence of any TEAE amounted to 74.1%, and in 22.9% of patients any serious TEAE occurred. Treatment emergent serious infections occurred in overall 4.4% of patients. In 36.4% of patients, at least on TEAE with a possible relationship to natalizumab was documented.

There were several numerical differences between STAY and SWITCH with regard to AE incidences, but these findings were presumably biased by differences in duration of observation (considerably longer in STAY compared with SWITCH patients), and more over by the definitions applicable for cohort assignment itself as AEs are a common reason to stop a drug therapy.

The 3 most common SOCs affected by TEAEs in the total population were “infections and infestations” (39.2%), “nervous system disorders” (37.6%), and “musculoskeletal and connective tissue disorders” (15.0%).

The 3 most common SOCs affected by TEAEs possibly related to natalizumab in the total population were “infections and infestations” (15.5%), “nervous system disorders” (13.3%), and “general disorders and administration site condition” (3.9%). On a preferred term level, the most common TEAEs possibly related to natalizumab were “multiple sclerosis relapse” (8.4%), “nasopharyngitis” (6.6%), “urinary tract infection” (2.4%), “headache” (1.5%), “oral herpes” (1.2%), “depression” (1.0%), “gait disturbance” (1.0%), and “respiratory tract infection” (1.0%) which were either consistent with the underlying MS disease or the known safety profile of natalizumab.

Overall, 5 (0.4%) treatment emergent deaths were reported, of which one case (“optic glioma”) was assessed as causally related to natalizumab.

Overall, 9 patients (0.8%) had a confirmed diagnosis of treatment emergent PML (7 recovered, and 2 with PML outcome “not recovered”. Of these two, one patient died later from an unspecified cause). Of the 9 confirmed PML events, all but one (the causality of which was assessed as “unknown”) were regarded as related to natalizumab treatment.

Evaluation of adverse events and the data generally supported the established safety profile of natalizumab. No new significant safety findings were noted and the benefit-risk profile of natalizumab remained positive.

Overall conclusion

- This non-interventional, observational, German, multicenter study included a large and heterogeneous sample of RRMS patients on ongoing treatment with natalizumab according to prescription information for at least 12 months.
- The patient sample broadly varied with regard to MS disease history, duration and exposure to previous natalizumab treatment before study enrollment. The majority of patients had longstanding MS disease (≥10 years) and more than 2 years natalizumab treatment duration at enrollment into TRUST. The Kaplan-Meier estimated median time on natalizumab from treatment start including the study period was 10.3 years.
- Almost all patients (≥96%) entered the study with an anti-JCV antibody test result (status or index) available at baseline, 37% of patients had a “positive” anti-JCV antibody status. The median duration of time intervals between anti-JCV tests was shorter among SWITCH compared with STAY patients.
- The MRI scans during natalizumab treatment were performed at approximately 6-month intervals (median duration between subsequent intervals).

- The proportion of relapse-free patients considerably increased after initiating natalizumab, was stable during study, and remained on the same level in the SWITCH cohort after discontinuation of natalizumab treatment, whilst ARR increased after permanent natalizumab discontinuation.
- The most frequent reason for permanent natalizumab discontinuation was PML risk.
- With the exception of the fatigue questionnaire and some WPAI scores, all PROs showed relatively favorable results and good patient's conditions already at study enrollment. Generally, neither the EDSS nor the PROs changed remarkably over time in any of the cohorts (STAY, SWITCH-ON/OFF)
- Overall 9 patients experienced confirmed PML during study participation.
- Evaluation of adverse events and the data generally supported the established safety profile of natalizumab. No new significant safety findings were noted and the benefit-risk profile of natalizumab remained positive.

11. REFERENCE LIST

1. Ziemssen T, Gass A, Wuerfel J, Bayas A, Tackenberg B, Limmroth V, et al. Design of TRUST, a non-interventional, multicenter, 3-year prospective study investigating an integrated patient management approach in patients with relapsing-remitting multiple sclerosis treated with natalizumab. BMC Neurol. 2016;16:98.
2. Schultheiss T, Kempcke R, Kratzsch F, Eulitz M, Pette M, Reichmann H, et al. [Multiple sclerosis management system 3D. Moving from documentation towards management of patients]. Nervenarzt. 2012;83(4):450-7.
3. Ziemssen T, Kempcke R, Eulitz M, Grossmann L, Suhrbier A, Thomas K, et al. Multiple sclerosis documentation system (MSDS): moving from documentation to management of MS patients. J Neural Transm (Vienna). 2013;120 Suppl 1:S61-6.
4. Ryerson Z. Natalizumab Extended Interval Dosing Is Associated with a Reduction in Progressive Multifocal Leukoencephalopathy (PML) Risk in the Touch® Registry; ACTRIMS 2018 - Late Breaking News Posters. Mult Scler. 2018;24(1_suppl):118-40.
5. 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.
6. Hobart J, Cano S. Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods. Health Technol Assess. 2009;13(12):iii, ix-x, 1-177.
7. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001;124(Pt 5):962-73.

8. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. Health Technol Assess. 2004;8(9):iii, 1-48.

9. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics. 1993;4(5):353-65.

10. Reilly MC. Reilly Associates WPAI; http://www.reillyassociates.net/WPAI_Scoring.html.

11. Gass A, Wuerfel J, Ziemssen T, Bayas A, Tackenberg B, Limmroth V, et al. TRUST – Evaluation of baseline data focusing on optional MRI-safety surveillance for progressive multifocal leukoencephalopathy (PML) in relapsing remitting multiple sclerosis patients treated with natalizumab (Poster P028; TY-GER-0675a). 90 Kongress der Deutschen Gesellschaft für Neurologie, 20-23 September; Leipzig, Germany 2017.

12. Hartung HP, Gass A, Wuerfel J, Bayas A, Tackenberg B, Limmroth V, et al. TRUST – Evaluation of baseline data to investigate an integrated approach for optimised patient management in multiple sclerosis patients treated with natalizumab (EP1720). 7th Joint ECTRIMS-ACTRIMS Meeting , 25-28 October 2017; Paris, France 2017.

13. Hartung HP, Gass A, Wuerfel J, Bayas A, Tackenberg B, Limmroth V, et al. Baseline data of TRUST – A study to evaluate an integrated approach for optimised patient management in multiple sclerosis patients treated with natalizumab (Poster P029; TY-GER-0675). 90 Kongress der Deutschen Gesellschaft für Neurologie I 20-23 September; Leipzig, Germany 2017.

14. Mäurer M, Bayas A, Tackenberg B, Haas J, Limmroth V, Stangel M, et al. TRUST – Interim analysis of the utilisation of expert advice to support optimised patient management in multiple sclerosis patients treated with natalizumab (Poster P030; TY-GER-0675b). 90 Kongress der Deutschen Gesellschaft für Neurologie I 20-23 September; Leipzig, Germany 2017.

15. Ziemssen T, Gass A, Limmroth V, Bayas A, Haas J, Linker R, et al. TRUST: a Study to Evaluate an Integrated Approach for Optimized Patient Management in Multiple Sclerosis Patients Treated with Natalizumab – First Analysis of Baseline Data (P2.147). 68th Annual Meeting of the American Academy of Neurology April 15-21; Vancouver, Canada 2016.

12. APPENDICES

Appendix A

Listing of Ethics Committees

A central ethics committee approval/favorable opinion were obtained from the ethics committee responsible for the Scientific Expert of this observational study, therefore a listing of ECs is not available.

Scientific Expert / Institution Name	Name / Address of Ethics Committee
[redacted]	Ethikkommission der Med. Fakultät der HHU Düsseldorf, Kinderklinik Geb. 13.41 Moorenstr. 5, 40225 Düsseldorf, Germany.

Appendix B

Listing of Investigators

Scientific Expert / Institution Name
[redacted]

A list of all participating investigators is located in the Sponsor's study file.

Study advisory committee

The members of the study advisory committee were (listed alphabetically by last name):

[redacted]

Appendix C

Statistical Analysis Plan

The final SAP is filed separately in the Sponsor's study file and will be provided upon request.

Appendix D

Scientific Expert Signature Page

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of Study GER-TYS-14-10626 (TRUST) "A 3-year, non-interventional, prospective, multicenter study to investigate the impact of an integrated patient management including biomarkers, magnetic resonance imaging and expert advice on disease activity in relapsing remitting multiple sclerosis patients treated with Tysabri® over the last 12 months."

[redacted] [redacted]

Scientific Expert's Signature Date

Scientific Expert's Name: [redacted]

Scientific Expert's Affilition: [redacted]

Appendix E

Analysis Tables, Listings and Figures

The Analysis Tables, Listings and Figures (version 30-November-2020) are filed separately in the Sponsor's study file and will be provided upon request.