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Non-interventional Study Report

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PEARL (ProspEctive phArmacoeconomic cohoRt evaLuation)

A multicenter, prospective, non-interventional cohort study to collect health-economic and clinical parameters in patients with relapsing remitting multiple sclerosis (RRMS) treated with diverse approved first-line disease-modifying therapies over a time period of 24 months

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List of abbreviations

AE	Adverse Event
AMG	Arzneimittelgesetz (German Medicinal Products Act)
ARR	Annual Relapse Rate
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CGI	Clinical Global Impression
CRF	Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
DMP	Data Management Plan
DMT	Disease-Modifying Therapy
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQOL 5 Dimensions
FAS	Full Analysis Set
FSA	Freiwillige Selbstkontrolle für die Arzneimittelindustrie (Voluntary Self-Regulation of the Pharmaceutical Industry)
FU	Follow-Up
IFN	Interferon
HrQoL	Health-related Quality of Life
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NIS	Non-Interventional Study
nsADR	Non-Serious Adverse Drug Reaction
nsAE	Non-Serious Adverse Event
PEI	Paul-Ehrlich Institute
PT	Preferred Term (MedDRA)
PRIMUS	Patient-Reported Outcome Indices for Multiple Sclerosis
QoL	Quality of Life
RRMS	Relapsing Remitting Multiple Sclerosis
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard Deviation
SDV	Source Data Verification
SOC	System Organ Class (MedDRA)
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
TSQM-9	9-Item Treatment Satisfaction Questionnaire for Medication
UK NDS	United Kingdom Neurological Disability Scale
VAS	Visual Analogue Scale
VFA	Verband forschender Arzneimittelhersteller (German association of research-based pharmaceutical companies)
WHO	World Health Organization

1 Abstract

Title	PEARL (**P**rosp**E**ctive ph**A**rmacoeconomic coho**R**t eva**L**uation): A multicenter, prospective, non-interventional cohort study to collect health-economic and clinical parameters in patients with relapsing remitting multiple sclerosis (RRMS) treated with diverse approved first-line disease-modifying therapies over a time period of 24 months Main author: Stefan Viktor Vormfelde MD/PhD; Novartis Pharma GmbH Date of the abstract: 28 May 2014
Keywords	Non-interventional, relapsing remitting multiple sclerosis, first-line disease modifying therapy, health-economic parameters, health-related quality of life
Rationale and background	Multiple Sclerosis (MS) is the most common inflammatory disease of the central nervous system (brain and spinal cord), leading to demyelization and axonal damage. RRMS is the most common form of MS. It is characterized by repeatedly occurring neurological symptoms, which resolve either completely or partially. Thereby, RRMS causes a considerable impairment of the patients' health-related quality of life (HrQoL) already at the early stages of the disease. It temporarily deteriorates markedly and abruptly in case of a relapse and continuously worsens with the progression of the disease. The costs for the healthcare system and socio-economic burden are considerable.
Research question and objectives	The main objective of this study was to collect data to quantify the extent of resource utilization by patients with RRMS treated with approved first-line disease-modifying therapies (DMT, i.e. Interferon [IFN]-beta or glatiramer acetate) in daily outpatient practice in Germany. Additional aims were to describe the therapeutic effects of first-line DMTs on disease progression, clinical symptoms, HrQoL, productivity, compliance and treatment satisfaction. Additionally, data were collected regarding the frequency of switches between first-line DMTs, the reasons for switches and the impact on the clinical course of the disease.
Study design	The present study was a prospective, multi-center, non-interventional cohort study (NIS) of patients with RRMS treated with first-line DMTs (IFN-beta or glatiramer acetate). The observational period in PEARL was 24 months. In accordance with daily practice follow-up (FU) visits were documented about every 3 months, adding up to a maximum of nine visits possible in total.
Setting	PEARL was planned to include about 180 neurological practices or centers and about 1800 patients. The observation period was planned to start in September 2010, with the last data collection in April 2013. A total of 1778 patients were enrolled by 163 practices in Germany. Data collection started on 10 October 2010 (first patient first visit). The last visit (last patient last visit) was documented on 01 July 2013.
Subjects and study size, including dropouts	Patients of either sex with RRMS, who have already been treated with an approved first-line DMT (IFN-beta or glatiramer acetate) for at least 30 days, were to be documented.
Variables and data	**Effectiveness assessments**: CGI (Clinical Global Impression; severity and improvement), Expanded Disability Status Scale (EDSS), number of lesions,

sources	the patient questionnaires Patient-Reported Outcome Indices for Multiple Sclerosis (PRIMUS) activity, PRIMUS quality of life, EuroQOL 5 Dimensions (EQ-5D) and United Kingdom Neurological Disability Scale (UK NDS). **Patients' treatment satisfaction**: TSQM-9 questionnaire. **Patient compliance**: compliance patient questionnaire. **Pharmacoeconomic parameters**: patient resource questionnaire. **Infrastructure and management of treatment**: practice questionnaire. **Safety assessments**: Adverse Events (AE). AEs and Serious AEs (SAEs) were documented for all first-line DMTs. Follow-up information on SAEs of the Novartis product Extavia were more detailed than for the other therapies. The treating physician recorded all data in the CRF, including questionnaires.
Results	**Study patient characteristics** The descriptive statistical analysis was based on the documentation of 1705 patients. IFN-beta (Avonex: 23.17%; Rebif: 23.05%; Betaferon: 16.13%, Extavia: 8.86%) was more frequently prescribed than Copaxone (28.80%). The majority, of patients (72.55%), were female, 27.27% were male (missing data: 0.18%). The overall mean age was 42.5 ± 10.34 years (mean ± SD). The diagnosis as per ICD 10 was G35.10 (MS with primarily relapsing-remitting course: without acute exacerbation or progression) for the majority of patients overall (65.75%). Further diagnoses reported in more than 5% of patients were G35.1 (MS with primarily relapsing-remitting course; overall 10.67%), G35.9 (MS: not specified; 9.15%), G35.11 (MS with primarily relapsing-remitting course: with acute exacerbation or progression; 7.57%) and G35.0 (First manifestation of MS; 5.34%). All other ICD 10 diagnoses were reported in less than 5% of patients. For 53.36% of the patients with MRI, data on the number of lesions were missing at baseline. The proportion of patients with 3 to ≤9 T2 lesions was 18.35% and 19.64% with >9 T2 lesions. Gadolinium-enhancing lesions were reported for 32.77% of patients. The mean relapse rate in the last 12 months before start of PEARL was 0.52 ± 0.863. The intensity of the last MS relapse before start of PEARL based on the EDSS score was >1.5 to ≤2.5 points in 26.99%, >2.5 to ≤3.5 in 23.74% and ≤1.5 points in 20.49% cases. The majority, i.e. 59.67% of patients had sensory relapses, 36.91% had pyramidal relapses and 20.49% had visual relapses. All other types occurred in less than 15% of patients. The median time since start of first-line DMT was 2.6 years. The median observation period was 728.0 days. About 20% of the patients (Avonex: 20.51%, Betaferon: 18.91%, Copaxone: 19.55%, Extavia: 23.84%, Rebif: 20.10%) prematurely discontinued the study. A switch of therapy during the observation period was reported for 279 (16.36%) patients. The proportion of patients who terminated the therapy or for whom data on therapy switches were missing were as follows: Avonex 33.82%, Betaferon 22.45% Copaxone 28.57%, Extavia 37.93, Rebif 29.23%.

Results on pharmacoeconomic data – resource utilization

Pharmacoeconomic parameters were based on the analysis of the patient resource questionnaire.

About two-third of the patients were employed (baseline: 60.45%, last visit: 57.58%) with two-third of these patients being full-time employed (baseline: 59.75%, last visit: 59.83%). At baseline, 21.74% of patients reported that they were on sick leave due to MS within the three past months. At the last visit 13.32% of patients documented a sick leave due to MS in the last 3 months (baseline: mean duration 21.1 ± 26.01 days, median 10.0 days; last visit: mean duration 13.8 ± 17.19 days, median 9.5 days). A reduction of working hours due to MS was reported by 6.37% of patients at baseline and 2.90% at 24 month FU.

In the past 3 months before baseline, 86.20% of patients consulted a physician or other health care professional due to MS. MS-related hospitalization was reported for 4.74% of patients and 2.01% had to stay in a rehabilitation clinic. None of the patients had to stay in a nursing home. Ambulatory treatments in the hospital were documented for 3.08% of patients.

In the last 12 months before baseline, examinations due to MS were performed in 77.26% of patients. These were mainly blood examinations (56.78%) and MRTs (54.88%). At the 24 month FU, the percentage of patients with blood examinations in the past twelve months was 44.86% and 37.31% with MRT.

Manual injection was used by 87.39% of the patients at baseline and 29.42% at last visit, and an autoinjector was used by 67.44% of the patients at baseline and 67.53% at last visit. About 10% of the patients needed assistance with manual injection, e.g. provided by the partner or family.

A training on MS treatment was attended by 24.45% of patients in the past 3 months before baseline and 15.46% of patients in the past 3 months before last visit.

In the past 3 months before baseline, 34.99% of patients had purchased over-the-counter medications because of MS (mean expenses 43.0 ± 68.40 Euro). In the past 3 months before the last visit, the proportion of patients who had purchased over-the-counter medications because of MS was 31.10% (mean expenses 40.1 ± 58.15 Euro). Consumables due to MS were purchased by 10.60% of the patients in the past 3 months before baseline (mean expenses 29.4 ± 35.40 Euro) and by13.12% of the patients in the past 3 months before the last visit (mean expenses 32.6 ± 38.14 Euro).

MS-related expenses for equipment and devices in the past 12 months before baseline were documented by 8.11% of patients, thereof 57.66% were for walking aids and 34.31% for changes to the house. The expenses amounted to a mean of 3998.2 ± 8567.8 Euro and a median of 200.0 Euro. At 12 months and 24 months, expenses for equipment and devices were reported by about 5% of the patients, e.g. for walking aids and for use of a wheel chair.

Patients received assistance from family or friends (18.00% and 16.96%), from household help (4.50% and 5.45%), professionals (1.07% and 0.78%) and personal assistants (0.36% and 0.12%) in the past 3 months before baseline and before the last visit, respectively. For 1.18% and 1.08% of patients a mean work reduction of family members in the past 3 months before baseline and before the last visit, respectively, was reported. The

proportion of patients who received benefits from long term care insurances was 2.31% and 2.10% in the past 3 months before baseline and before the last visit,

Results on clinical effectiveness

The overall mean ARR was 0.39 ± 0.770 assessed over the two year study period (Avonex: 0.38 ± 0.814; Betaferon: 0.33 ± 0.633; Copaxone: 0.44 ± 0.784; Extavia: 0.41 ± 0.848; Rebif: 0.39 ± 0.767). For the 586 patients with MS relapses after start of PEARL, the median time from baseline to first relapse was 215.5 days (Avonex: 244.0, Betaferon: 193.0, Copaxone: 213.5, Extavia: 210.0, Rebif: 220.5). Over the two years, 20.14% of the patients were hospitalized. Most of them were treated with steroids (87.37%).

MRIs were reported for 11% to 14% of patients at each visit, meaning that a MRI was performed between the respective visit and the previous visit. At the last visit, 15.50% of patients have had an MRI reported since the previous visit. Data on the number of lesions was missing in the MRI reports (missing data at baseline: 53.36%, 12 months FU: 65.00%, 24 months FU: 62.04%). The proportion of patients with > 9 lesions over the course of the study was as follows: baseline: 19.64%, 12 months FU: 13.00%, 24 months FU: 9.49%. The proportion of patients with 3 to ≤9 lesions over the course of the study was as follows: baseline: 18.35%, 12 months FU: 12.50%, 24 months FU: 11.68%. Gadolinium enhancing lesions were present in 449 out of 1370 patients with MRI performed (32.77%) at baseline, in 35 out of 189 patients (18.52%) at the 12 months FU and in 20 out of 124 patients (16.13%) at the 24 months FU.

The EDSS is a method of quantifying disability in MS using a score from 0.0 (normal neurological exam) to 10.0 (death due to MS). The mean EDSS score was 2.3 ± 1.52 at baseline (Avonex: 2.3 ± 1.41, Betaferon: 2.2 ± 1.48, Copaxone: 2.4 ± 1.51, Extavia: 2.3 ± 1.53, Rebif: 2.2 ± 1.65) and 2.5 ± 1.64 at the last visit with possible EDSS assessment (Avonex: 2.5 ± 1.58, Betaferon: 2.4 ± 1.62, Copaxone: 2.5 ± 1.62, Extavia: 2.7 ± 1.66, Rebif: 2.5 ± 1.73). The mean difference from baseline to the last visit with possible EDSS assessment was 0.3 ± 0.87 (Avonex: 0.3 ± 0.83, Betaferon: 0.2 ± 0.78, Copaxone: 0.2 ± 0.91, Extavia: 0.4 ± 0.94, Rebif: 0.3 ± 0.92.

The CGI severity is rated on a 7-point scale using a range of responses from “normal, not at all ill” to “extremely ill”. The proportions of patients who reported to be “mildly ill” were: baseline 31.44% and last visit 30.23%. The proportions of patients reported to be “moderately ill” were: baseline 25.34% and last visit 28.80%. Overall, 77.20% showed “no change” of CGI (CGI improvement scale rated on a 7-point scale using a range of responses from “very much improved” to “very much worse”) at last visit. A total of 13.84% of patients were “minimally worse” and 4.28% of patients “minimally improved”.

Most frequently, physicians and patients rated the effectiveness at last visit (FU after 24 months or discontinuation visit) as “good” (physicians: 45.75%, patients: 44.79%) or “very good” (physicians: 34.71%, patients: 29.29%).

Results on patient reported effectiveness

The **TSQM-9** questionnaire measured the patients’ satisfaction with the treatment on 7-point- or 5-point scales with 1 being the most negative answer. The TSQM-9 score is the sum of all single TSQM-9 questions

ranging between 7 (low satisfaction) and 59 (high satisfaction). At baseline, the mean TSQM-9 score was 46.3 ± 7.47 and at last visit the mean TSQM-9 score was 45.2 ± 8.34. The mean difference from last visit to baseline was -1.1 ± 7.38.

The **UK NDS** questionnaire assessed neurological functions in 13 areas. For all subscores scales were used ranging from 0 (normal status) to 5 (total loss of function), with the exception of the cognition subscale ranging from 0 to 3. A total score was calculated from the individual subscores ranging from 0 to 63.

The mean total score was 8.1 ± 7.30 at baseline and 6.2 ± 6.65 at last visit. Individual mean sub-scores ranged from 0.1 ± 0.38 (swallowing score) to 1.9 ± 1.40 (fatigue score) at baseline and from 0.1 ± 0.34 (swallowing score) to 1.5 ± 1.36 (fatigue score) at last visit. Overall, the difference from last visit to baseline for the total score was -1.2 ± 4.95.

The **EQ-5D questionnaire** measured HrQoL covering the areas mobility, self-care, usual activities, pain / discomfort and anxiety / depression using a 3-point scale (no problems, some problems, extreme problems) for the descriptive system and a VAS ranging from 100 (best imaginable health state) to 0 (worst imaginable health state). The state of health compared to 12 months ago stayed 'roughly the same' for 66.55% at baseline and 71.17% at the last visit. At the last visit, the mean current health state on the VAS was 71.0 ± 18.7 compared to baseline 71.5 ± 18.6.

The **PRIMUS** is a questionnaire assessing QoL impairment (sum score ranging from 0 [no effect of the disease on QoL] to 45 [strong effect of the disease on QoL]) and activity impairment (sum score ranging from 0 [activity "could be done by oneself without difficulties"] to 38 [activity "could not be done by oneself"]) in MS patients. The mean **PRIMUS QoL** score was 8.4 ± 8.76 at baseline and, 7.4 ± 8.92 at the last visit. The mean **PRIMUS activity** score was 4.2 ± 5.16 at baseline and 4.5 ± 5.7 at the last visit.

On the **compliance questionnaire**, 83.71% of patients stated at baseline that they did not occasionally forget to take the MS medication. At the last visit, the proportion of patients was 81.22%. The mean number of days without medication in the last two weeks was 0.4 ± 1.23 before baseline and 1.6 ± 3.24 before the last visit.

Results on the practice questionnaire

A total of 167 **practice questionnaires** were documented. MS patients amounted to a mean of 17.5 ± 21.31% of patients in the physicians' practices. On average, the physicians saw 158 MS patients per quarter. The mean percentage of MS patients receiving first-line DMT was 64.3 ± 21.08%.

Staff, available at the study sites for the treatment of MS, included doctor's assistant (91.62%), nurse/MS nurse (62.87%) and neuropsychologist/ psychologist (23.35%; multiple response). The physicians cooperated with physiotherapists (95.21%), other specialists (87.43%), general practitioners (83.83%), and occupational therapists/ergotherapists (82.63%).

Physicians spent their time on: diagnosis (median 45.0 min), therapy initiation (median 30.0 min), and advice (median 20.0 min). Nurses spent their time for: therapy initiation (median 35.0 min), diagnosis (median 30.0 min), and FU examinations and advice (median 15.0 min each). The decision for prescription of first-line DMT was made by the physician (100.0%) and the patient (95.21%).

	The physicians documented that on average 81.8 ± 13.48% of patients displayed perfect compliance with therapy. The factor that had the highest influence on patient's compliance was personal motivation of the patient, followed by occurrence of new relapses, pain at injection, cutaneous side effects, difficulties with application, and influenza-like symptoms. On average, physicians were satisfied with the treatment situation of MS patients assessed on a scale rating from 1 = very dissatisfied to 5 = very satisfied (mean 3.4 ± 0.73), the therapy options for MS patients (mean 3.2 ± 0.72), the care for MS patients (mean 3.4 ± 0.84), and the cooperation with other professional groups for MS (mean 3.3 ± 0.87). **Results on safety** During this study, 1165 AEs were documented in 506 of 1705 patients (29.68%). In 300 patients (overall 17.60%; Avonex: 15.95%, Betaferon: 19.27%, Copaxone: 19.35%, Extavia: 15.89%, Rebif: 16.54%), a nsAE (no causality) was reported. An nsADR was documented in 240 patients (overall 14.08%; Avonex: 13.92%, Betaferon: 15.27%, Copaxone: 13.85%, Extavia: 14.57%, Rebif: 13.49%). A total of 70 patients (overall 4.11%; Avonex: 3.29%, Betaferon: 4.73%, Copaxone: 4.68%, Extavia: 4.64%, Rebif: 3.56%) had an SAE and for 31 patients (overall 1.82%; Avonex: 1.77%, Betaferon: 1.82%, Copaxone: 2.04%, Extavia: 3.97%, Rebif: 0.76%) at least one event met the criteria for a SADR. Two patients died during this study. The causality was not assessable in one fatal case (Avonex) and assessed as "improbable" in the other fatal case (pancreatitis and pancreatic carcinoma; Betaferon). The AE incidence per patient year was 0.17370 overall, 0.10299 for nsAEs, 0.02403 for SAEs, 0.08239 for nsADRs, and 0.01064 for SADRs. Regardless of seriousness or relationship, patients experienced AEs most frequently in the system organ classes nervous system disorders (overall: 7.68%, Avonex: 6.58%, Betaferon: 9.82%, Copaxone: 7.54%, Extavia: 9.27%, Rebif: 6.87%), infections and infestations (overall: 7.21%, Avonex: 5.57%, Betaferon: 8.00%, Copaxone: 8.55%, Extavia: 5.96%, Rebif: 7.12%), and general disorders and administration site conditions (overall: 6.33%, Avonex: 7.09%, Betaferon: 7.27%, Copaxone: 6.11%, Extavia: 6.62%, Rebif: 5.09%). At the PT level, the most frequently reported events were nasopharyngitis (overall: 2.46%, Avonex: 1.77%, Betaferon: 2.91%, Copaxone: 3.05%, Extavia: 1.32%, Rebif: 2.54%) and depression (overall: 2.46%, Avonex: 2.53%, Betaferon: 3.27%, Copaxone: 3.05%, Extavia: 1.99%, Rebif: 1.27%), followed by headache (overall: 1.64%, Avonex: 1.27%, Betaferon: 2.91%, Copaxone: 0.81%, Extavia: 2.65%, Rebif: 1.78%), maternal exposure during pregnancy (overall: 1.64%, Avonex: 1.52%, Betaferon: 1.09%, Copaxone: 2.04%, Extavia: 2.65%, Rebif: 1.27%), and sleep disorder (overall: 1.52%, Avonex: 2.03%, Betaferon: 1.45%, Copaxone: 1.22%, Extavia: 0.66%, Rebif: 1.78%)
Discussion	The PEARL study quantifies resource utilization and health status of RRMS-patients on first-line DMTs (i.e. IFN-beta or glatiramer acetate) in Germany over a two-year time period with a focus on routine outpatient practice.
Marketing Authorization Holder	Avonex®: Biogen Idec Betaferon®: Bayer HealthCare. Copaxone®: Teva Pharmaceuticals

	Extavia®: Novartis Pharma GmbH Rebif®: EMD Serono Inc, Pfizer
Name(s) and Affiliation(s) of Principal Investigator(s)	Prof Tjalf Ziemssen, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

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Rebif®: EMD Serono Inc, 1 Technology Pl, Rockland, MA 02370, USA; Pfizer, 235 East 42nd Street, NY 10017, USA

3 Investigators

The principal investigator was Prof Tjalf Ziemssen, Universitätsklinikum Carl Gustav Carus, Dresden, Germany. In total, 186 sites in Germany participated in this non-interventional study (NIS).

4 Milestones

Table 4-1 Study milestones

Milestone	Planned date	Actual date
Start of data collection	September 2010	14 October 2010
End of data collection	March 2013	01 July 2013
Final report of study results	August 2013	30 May 2014
Ethics approval	n.a.	06 October 2010

5 Rationale and background

Multiple Sclerosis (MS) is the most common inflammatory disease of the central nervous system (brain and spinal cord), leading to demyelization and axonal damage [Leitlinien für Diagnostik und Therapie 2008].

Relapsing Remitting Multiple Sclerosis (RRMS) is the most common form of MS. It is characterized by repeatingly occurring neurological symptoms, which resolve either completely or partially.

MS compromises muscle control and strength. It affects vision and sensory functions, especially the sense of balance, and impairs the cognitive ability.

Thereby, MS causes a considerable impairment of the patients' health-related quality of life (HrQoL) already at the early stages of the disease. It temporarily deteriorates markedly and abruptly in case of a relapse and continuously worsens with the progression of the disease. The impairment of HrQoL also has considerable impact on the social environment of the patient, i.e. family, friends and caregivers.

When evaluating cost of illness, the direct disease-related costs as well as the indirect disease costs have to be considered. The direct disease-related costs include the medication costs for disease modification and treatment of acute relapses, hospitalizations, out-patient care by

other medical disciplines, benefits according to the catalogue of non-physician care, aides, in- and out-patient rehabilitation measures and ambulatory caregivers. The indirect costs include sick leave, retirement, handicapped-accessible facilities or reconstruction, as well as decreased productivity of caregiving relatives [Kobelt 2006].

The costs of MS for the healthcare system and socio-economic burden are considerable. Previous retrospective studies on cost structures mention between 8.8 to 12.5 billion Euros per year for Europe, which corresponds to 0.1% of the total European gross national income [Kobelt 2005].

6 Research question and objectives

The main objective of this study was to collect data to quantify the extent of resource utilization by patients with RRMS treated with approved first-line disease-modifying therapies (DMT, i.e. Interferon [IFN]-beta or glatiramer acetate) in daily outpatient practice in Germany.

Additional aims were to describe the therapeutic effects of first-line DMTs on disease progression, clinical symptoms, HrQoL, productivity, compliance and treatment satisfaction. Additionally, data were collected regarding the frequency of therapy switches between first-line DMTs, the reasons for switches and the impact on the clinical course of the disease.

In detail the study objectives were:

- The analysis of pharmacoeconomic data, obtained under daily practice conditions, of RRMS patients treated with first-line DMTs (IFN-beta or glatiramer acetate),:
    - data on prescription and choice of treatment collected by the treating physician
    - data on direct and indirect resource utilization collected by standardized patient interviews and questionnaires on work productivity.
- The exploration of patient profiles for first-line DMTs (IFN-beta or glatiramer acetate) in the treatment of RRMS.
- Analysis of the patients' self-assessment of HrQoL by RRMS patients treated with first-line DMTs (IFN-beta or glatiramer acetate) by patient questionnaires: Patient-Reported Outcome Indices for Multiple Sclerosis (PRIMUS) activity, PRIMUS QoL, EuroQOL 5 Dimensions (EQ-5D); analysis of compliance by compliance questionnaire for patients and analysis of treatment satisfaction by patient questionnaire: 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9).
- Assessment of the course of the disease of RRMS patients treated with first-line DMTs (IFN-beta or glatiramer acetate) regarding clinical outcome parameters obtained by the treating physician (Expanded Disability Status Scale [EDSS], Clinical Global Impression [CGI] and MS relapses), as well as by the patients' self-assessment (PRIMUS activity, PRIMUS QoL, EQ-5D, United Kingdom Neurological Disability Scale [UK NDS]).
- Collection of data on the frequency and reasons for a switch between first-line DMTs (IFN-beta or glatiramer acetate) in the treatment of MS patients.

- Description of pharmacoeconomic and effectiveness parameters of patients with and without switches between first-line DMT (IFN-beta or glatiramer acetate).

7 Amendments and updates to the protocol

Not applicable.

8 Research methods

8.1 Study design

The present study was a prospective, multi-center, non-interventional cohort study (NIS) of patients with RRMS treated with diverse first-line DMTs (IFN-beta or glatiramer acetate).

Diagnostic measures and medically indicated examinations under daily practice routine were to be documented. Patients were to be treated with commercially available product in accordance with the respective summaries of product characteristics (SmPCs).

The period to be observed in PEARL was 24 months. In accordance with daily practice follow-up (FU) visits were documented about every 3 months, adding up to a maximum of nine visits possible in total.

This NIS was performed under the following regulations:

- the Arzneimittelgesetz (AMG) section 4, paragraph 23, sentence 3.
- the Freiwillige Selbstkontrolle für die Arzneimittelindustrie (FSA; Voluntary Self-Regulation of the Pharmaceutical Industry) -Code
- the joint recommendations of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute (PEI) for planning, implementation and analysis of an observational study
- the Verband forschender Arzneimittelhersteller (VFA; German Association of Research-based pharmaceutical companies) - Recommendations for the improvement of the quality and transparency of NISs.

According to the recommendations of BfArM and PEI for planning, implementation and analysis of an observational study as well as the VFA - recommendations for the improvement of the quality and transparency of NIS, the ethics committee, responsible for the study center of the principal investigator, was consulted.

8.2 Setting

PEARL was planned to include about 180 neurological practices or centers and about 1800 patients. The observation period was planned to start in September 2010, with the last data collection in April 2013.

A total of 1778 patients were enrolled by 163 practices in Germany. Data collection started on 10 October 2010 (first patient first visit). The last patient was enrolled on 20 September 2012. The last visit (last patient last visit) was documented on 01 July 2013.

Case Report Forms (CRFs) received after 15 July 2013 could not be included in the statistical evaluation. In total, 9 visits of 5 patients were not included in the evaluation.

8.3 Subjects

About 1800 patients of either sex with a diagnosis of RRMS, who have already been treated with an approved first-line DMT (IFN-beta or glatiramer acetate) for at least 30 days, were to be documented. Only patients meeting these criteria should be included after they had signed an informed consent form. Patients meeting contraindications stated in the respective SmPCs should not be included. No further selection criteria were applied. Therapeutic decision had to be independent of the inclusion into the NIS and based solely on the medical necessity for treatment. Patients were enrolled in consecutively in each study center.

8.4 Variables

8.4.1 Patient characteristics

At start of observation, the patient informed consent and enrollment, demographic patient characteristics, and anamnesis including MS anamnesis had to be documented. Current first-line DMT and changes thereof, concomitant drug and non-drug MS therapies had to be documented at start of observation and subsequently every 3 months. Weight had to be documented at start of observation and every 12 months. Premature discontinuation of therapy had to be reported at the FU visits.

8.4.2 Pharmacoeconomic data

Pharmacoeconomic parameters were based on the analysis of the patient resource questionnaire. These were to be filled out at start of observation and subsequently every 3 months.

8.4.3 Clinical effectiveness

Effectiveness assessments were based mainly on the evaluation of the CGI (severity and improvement), the change of the total EDSS score, occurrence of MS relapses and the number of lesions. Changes in the scores over the course of the study were assessed by calculation of differences to baseline or shift-tables.

MS relapses since previous visit and premature discontinuation of therapy had to be reported at each FU visit. CGI had to be documented at start of observation and subsequently every 3 months and EDSS was documented at start of observation and every 6 months. In case of a performed MRI at the respective visit, the number of lesions was to be documented.

8.4.4 Patient questionnaires

The patient questionnaires PRIMUS activity, PRIMUS QoL, EQ-5D and UK NDS were analyzed as additional measures of effectiveness. Changes in the scores over the course of the study were assessed by calculation of differences to baseline. The patients' therapy satisfaction was measured with the TSQM-9 questionnaire. Patients' compliance derived primarily from the compliance patient questionnaire.

The patient questionnaires for compliance and the TSQM-9 were to be filled out at start of observation and subsequently every 3 months, PRIMUS activity, PRIMUS QoL and EQ-5D were to be recorded at start of observation and every 6 months and the UK NDS was to be filled out at start of observation and every 12 months.

8.4.5 Practice questionnaire

Data regarding the infrastructure and management of treatment for patients with MS was based on the practice questionnaire filled out once by each participating physician.

8.4.6 Safety

8.4.6.1 Adverse events

Safety assessments were based on the analysis of Adverse Events (AE). AEs and Serious AEs (SAEs) occurring during the observation period had to be documented irrespective of administered first-line DMT. FU information on SAEs of the Novartis product Extavia were more detailed than for the other therapies. AEs were to be documented at each FU visit.

An AE was defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

Each AE was to be documented in the documentation form by type of event, start, duration, intensity, and causal relationship to the administered therapy, as well as the outcome and potential counteractive measures.

In general, SAE and non-serious AEs (nsAE) were differentiated. For the purpose of the statistical analysis, events were further distinguished according to their relationship to study drug.

SAEs were defined as all events which:

- result in death or
- are life threatening, or
- require in-patient hospitalization or prolongation of existing hospitalization, or
- result in persistent or significant disability or incapacity, or
- are a congenital anomaly/birth defect, or
- are medically important events, meaning events that might jeopardize the patient but none of the other criteria is met

Inpatient hospitalization was not to be considered an SAE, if any of the following was the case:

- pre-planned hospitalizations (before inclusion in the NIS)
- elective hospitalizations for treatment of preexisting diseases, without relationship to the condition under treatment or to the study medication.

- outpatient hospital treatments, which did not lead to hospitalization (in this context it had to be checked, if one of the other criteria was present, e.g. in case of a life-threatening event).
- hospital treatment, that is part of the normal treatment or control of the disease examined in this NIS and that was not caused by a worsening of the disease.

Seriousness assessment was only based on the presence of any of the above mentioned formal criteria whether or not considered related to the medicinal product.

Non-serious MS relapses that were documented on the documentation form page "New MS relapses" were automatically registered as AE, without further documentation on the "AE" page. With the exception of abnormally severe and unexpected (life-threatening or fatal) MS relapses, the progression of MS, including relapses was only to be documented on the documentation form page "New MS relapses" and not on the "SAE" form.

All documents were checked immediately after receipt by Kantar Health GmbH as regards content, formal completion, plausibility, consistency, and the presence of (S)AEs as well as AEs of special interest and MS relapses. Additionally, the patient documentations were examined by the CRO if data regarding AEs had been entered into the appropriate page and all CRF pages were carefully screened for hidden AEs.

In case of AE or the suspicion of one, the documents were separated and the information entered into the event database under the original wording and coding according to the Medical Dictionary for Regulatory Activities (MedDRA).

Inpatient hospitalizations that did not meet the SAE criteria were registered as nsAEs. In cases where it was not clear, when the hospitalization was planned, or whether it met the SAE criteria, the case was reported as SAE.

8.4.6.2 Vital signs

Blood pressure and heart rate were documented at start of observation and subsequently every at every FU visit.

8.5 Data sources and measurement

This NIS used paper CRFs only. The investigator collected historic data (demographic and anamnestic characteristics) from medical records if available.

Vital signs, AEs, MS relapses, CGI and EDSS score were documented by the physician in the medical record during visits performed under routine practice and the respective information was transferred into the CRF.

Patient questionnaires regarding resource utilization (patient resource questionnaire), QoL (PRIMUS activity, PRIMUS quality of life, EQ-5D), disability (UK NDS), treatment satisfaction (TSQM-9) and compliance (compliance patient questionnaire.), as well as information on AEs were directly obtained from the patient. The original questionnaires were validated and German translations of the respective questionnaires were used. For UK NDS a modified version was used.

8.6 Bias

As this is a non-interventional study with the limitations inherent to observational studies, this study will not generate unbiased results. To ensure that no selection bias affects the results of the study, patients were enrolled in a consecutive order in each study center.

8.7 Study size

The number of neurologists in Germany was estimated to be about 4300. Of these, about 1300 are practitioners. Patients with MS are normally treated as out-patients in neurological practices or centers. The planned participation of about 180 neurological practices/centers corresponded to 10% to 15% of the practices and centers. To ensure regional representativeness, the interested practices and enters were enrolled differentiatedly by region.

The prevalence of MS in Germany was estimated to 150 cases per 100,000 inhabitants, adding to a total number of 122,000 MS patients. Of these, about 70%, i.e. 85,000 patients, receive a first-line DMT. Assuming an enrollment of 10 patients per practice, data of 1800 patients were to be documented. This number seemed sufficient to document the most commonly prescribed first-line DMT.

8.8 Data transformation

No data transformations were performed.

Permissible clarifications were performed for obviously implausible data.

For handling of quantitative data see Section 8.9.

8.9 Statistical methods

Main summary measures

Descriptive analysis of the data was performed using summary statistics for categorical and continuous data. Continuous data were described by mean, standard deviation (SD), minimum, median, maximum, 25, 75, percentiles and number of non-missing values. In addition, continuous data were categorized in a clinically meaningful way.

Categorical data including categories of continuous data were presented in frequency tables containing absolute and relative frequencies (one-way or more complex tables). These tables included the total number of observations and the number of missing values as additional categories. Multiple response data were presented as distribution of single entries.

Statistical methods applied to the study

The statistical evaluation was done descriptively. For variables with predictive validity (first-line DMT, therapy switch) appropriate strata were created and the results were displayed within the strata as well. The output tables were prepared using the statistical software program SAS® Version 9.3 for Windows.

For coding of plain text, the coding systems are summarized in Table 8-1.

Table 8-1: Coding Systems

Specification of concomitant diseases	MedDRA (MedDRA Version 16.0)
Specification of concomitant medication	WHO drug reference list (version 06/2013)
Adverse events	MedDRA (MedDRA Version 16.0)
Relevant concomitant non-medical MS treatments	Free text coding
Other reasons for premature discontinuation of documentation	Free text coding
Staff, available at the study sites for the treatment of MS	Free text coding

Further details of the analysis were described in the SAP (Version 1.0 of 26 Sep 2013).

Methods used to examine subgroups and interactions

The following subgroups were created and used for stratified analysis in general: First-line DMT (Avonex, Betaferon, Copaxone, Extavia, Rebif). For a specified subset of tables the stratification into patients who switched between first-line DMTs during the observation period versus patients who did not switch were also considered (for details see SAP). Additional stratifications for single tables are specified in the SAP.

According to the SAP (Version 1.0 of 26 Sep 2013) a subset of the Full Analysis Set (FAS), including all patients who fulfill the label for Gilenya, could be defined. Since the number of lesions is one of the criteria needed for classification and due to the low number of documented MRIs at the respective visits, only few patients could be allocated to the Gilenya Label Set. Therefore, no analyses on this set were performed.

Missing data

Implausible data, which could remain after validation processing, were set to missing. The number of patients with missing data was presented as separate category. Percentages were calculated as proportion of each category including the category of missing values.

In order to account for the effect of premature withdrawals, the data for all patients at the last completed visit were summarized in the form of a final FU (last visit).

Sensitivity analyses

No sensitivity analyses were performed.

Any amendment to the plan of data analysis included in the study protocol, with a rationale for the change

Not applicable.

8.10 Quality control

For all participating study centers on-site monitoring was to be performed after the inclusion of three patients, but at the latest two months after the inclusion of the first patient. Guidelines for data protection were followed (EU directive 95/46/EC and general national guidelines). For 10% of the participating study centers on-site monitoring was planned to be performed after end of observation. The results of the monitoring visits were documented in the monitoring report.

The basis for all data management processes were the relevant Kantar Health Standard operation procedure (SOPs). All data management quality assurance processes were laid down in a project specific data management plan (DMP) and were specified for the individual phases of data management:

- Check of the documentation forms before data capture
- Plausibility checks in the context of the data capture
- Data query plan specifying all questions that result in queries for the study center
- Implementation of an audit trail according to FDA CFR21. Part 11 Standard
- Reconciliation of the documentation forms and database in the context of a database audit
- Securing data integrity by documented data base closure
- Data handling report for the handling of inconsistent data present after database closure that are relevant to the analysis. The data handling report is an integral part of the statistical analysis plan (SAP)

After receiving the CRFs they were screened immediately (within 24 hours) for (S)AEs or hidden (S)AEs. FU procedures and reporting for AE reports and the cumulative AE report are based on the SOPs of Novartis Pharma GmbH.

Data were captured using single data entry supported by integrated data entry checks for plausibility. After data entry predefined basic data regarding demography and FU evaluations were checked according to a query logic described in the data edit check catalogue. Queries were generated automatically and sent to the physician for resolution and completion. In case of failure to respond a reminder was sent quarterly. The processing of incomplete or missing documentation of (hidden) AEs was performed according to Novartis SOPs.

9 Results

9.1 Participants

In total, 186 sites participated in this NIS. Of these, 163 sites (87.63%) had enrolled at least one patient and 167 sites (89.78%) had filled out the practice questionnaire (Appendix, Table 1.1).

A total of 1784 patients were entered in the study database. Of these, six were not enrolled due to violation of the following inclusion criteria (multiple response): The informed consent form was not signed (3 patients), no diagnosis of RRMS (4 patients) and the first-line DMT was not specified at baseline (5 patients). Therefore, 1778 patients (99.66%) were enrolled in this NIS (Appendix, Table 1.2).

The FAS consisted of 1705 patients out of the 1778 enrolled patients, as 73 patients (4.11%) were excluded due to lacking FU information (Appendix, Table 1.3).

IFN-beta (Avonex: 395 patients, 23.17%; Rebif: 393 patients, 23.05%; Betaferon: 275 patients, 16.13%, Extavia: 151 patients, 8.86%) was more frequently prescribed than Copaxone (491 patients, 28.80%) (Appendix, Table 4.1).

9.2 Descriptive data

9.2.1 Demographic and anamnestic data

The majority, i.e. 1237 (72.55%), of patients were female, 465 patients (72.55%) were male: (missing data for 3 patients, 0.18%).

A summary of the demographic and biometric parameters of the patients stratified by first-line DMT is given in Table 9-1.

Table 9-1: Demographic and biometric parameters (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
Age [years]						
n	1532	353	255	448	137	339
Missing	173	42	20	43	14	54
Mean	42.5	43.6	43.1	42.3	41.9	41.4
SD	10.34	10.40	10.76	10.05	10.85	10.04
Median	43.0	44.1	43.9	42.9	42.2	41.9
Height [cm]						
n	1682	395	271	481	143	392
Missing	23	0	4	10	8	1
Mean	170.9	169.8	171.8	171.0	170.7	171.5
SD	8.87	8.50	10.03	8.35	8.97	8.89
Median	170.0	169.0	171.0	170.0	169.0	170.0
Weight [kg]						
n	1681	395	271	480	143	392
Missing	24	0	4	11	8	1
Mean	74.6	73.4	73.9	74.8	77.8	74.9
SD	16.33	15.43	15.89	16.62	18.49	16.21
Median	72.0	70.0	72.0	73.0	75.0	72.0
Body mass index [kg/m^2]						
n	1681	395	271	480	143	392
Missing	24	0	4	11	8	1
Mean	25.5	25.4	25.0	25.5	26.7	25.4
SD	5.05	4.84	4.61	5.27	6.01	4.81
Median	24.5	24.5	24.0	24.5	25.2	24.6

kg = kilogram, cm = centimeter, BMI = Body mass index, m = meter, n = number of patients; SD = standard deviation
Source: Appendix, Table 2.2

The overall mean age was 42.5 ± 10.34 years (mean ± SD), the mean height 170.9 ± 8.87 cm, the mean weight 74.6 ± 16.33 kg and the mean body mass index (BMI) 25.5 ± 5.05 kg/m2.

Table 9-2 presents a summary of age at the initial visit.

Table 9-2: Age (categorized) (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Patients (FAS)	1705 (100.00%)	395 (100.00%)	275 (100.00%)	491 (100.00%)	151 (100.00%)	393 (100.00%)
Missing	173 (10.15%)	42 (10.63%)	20 (7.27%)	43 (8.76%)	14 (9.27%)	54 (13.74%)
≤20 years	7 (0.41%)	2 (0.51%)	0 (0.00%)	2 (0.41%)	2 (1.32%)	1 (0.25%)
>20 to ≤30 years	200 (11.73%)	39 (9.87%)	39 (14.18%)	57 (11.61%)	20 (13.25%)	45 (11.45%)
>30 to ≤40 years	380 (22.29%)	82 (20.76%)	50 (18.18%)	118 (24.03%)	34 (22.52%)	96 (24.43%)
>40 to ≤50 years	558 (32.73%)	120 (30.38%)	92 (33.45%)	171 (34.83%)	49 (32.45%)	126 (32.06%)
>50 to ≤60 years	327 (19.18%)	93 (23.54%)	60 (21.82%)	87 (17.72%)	26 (17.22%)	61 (15.52%)
>60 to ≤70 years	56 (3.28%)	16 (4.05%)	14 (5.09%)	13 (2.65%)	5 (3.31%)	8 (2.04%)
>70 to ≤80 years	4 (0.23%)	1 (0.25%)	0 (0.00%)	0 (0.00%)	1 (0.66%)	2 (0.51%)
>80 years	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 2.3

Age categories were as follows: >40 to ≤50 years old (32.73%), >30 to ≤40 years (22.29%) and >50 to ≤60 years (19.18%).

A summary of BMI by categories at the initial visit is given in Appendix, Table 2.4.

9.2.2 Diagnosis/ Anamnesis

9.2.2.1 Diagnosis

All 1705 patients in the FAS had a diagnosis of RRMS (Appendix, Table 3.1).

The diagnosis as per ICD 10 was G35.10 (MS with primarily relapsing-remitting course: without acute exacerbation or progression) for 1121 patients (65.75%). Further reported in more than 5% of patients, were G35.1 (MS with primarily relapsing-remitting course; overall 10.67%), G35.9 (MS: not specified; 9.15%), G35.11 (MS with primarily relapsing-remitting course: with acute exacerbation or progression; 7.57%) and G35.0 (First manifestation of MS; 5.34%). All other ICD 10 diagnoses were reported in less than 5% of patients (Appendix, Table 3.2).

Summary of time periods in the diagnosis of MS is presented in Table 9-3.

Table 9-3: Summary of time periods (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
Time since first confirmed MS diagnosis [years]						
n	1664	383	273	481	146	381
Missing	41	12	2	10	5	12
Mean	7.2	7.9	8.0	6.9	6.1	6.7
SD	6.03	6.12	6.59	5.74	6.14	5.73
Median	5.7	6.4	6.2	5.5	4.1	5.6
Time from first symptoms to MS diagnosis [years]						
n	1529	348	252	449	129	351
Missing	176	47	23	42	22	42
Mean	2.6	2.5	3.0	2.7	2.0	2.5
SD	4.54	4.83	5.11	4.63	3.73	3.94
Median	0.5	0.3	0.7	0.7	0.3	0.5
Time since start of MS treatment [years]						
n	1633	379	263	473	141	377
Missing	72	16	12	18	10	16
Mean	5.2	5.6	5.9	4.8	4.0	5.2
SD	4.34	4.45	4.80	3.97	4.31	4.24
Median	3.9	4.5	4.6	3.7	2.5	3.9

n = number of patients; SD = standard deviation
Source: Appendix, Table 3.3, Table 3.4 and Table 3.5

For the overall population, the median time from first symptoms to MS diagnosis was 0.5 years and the median time since first confirmed MS diagnosis was 5.7 years. The median time since start of MS treatment was 3.9 years. The time since start of the first-line DMT is presented in Table 9-6.

9.2.2.2 Magnetic resonance imaging (MRI)

The date of the last MRI was known for 1548 patients. For these, the median time since last MRI was 332.0 days. An MRI with contrast media was documented for 1370 patients (88.50%; Appendix, Table 3.6).The number of lesions in MRI for the total population as well as for the different first-line DMTs is presented in Table 9-4.

Table 9-4: Number of patients with lesions in MRI

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
T2 weighted lesions*						

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total	1548 (100.00%)	362 (100.00%)	250 (100.00%)	449 (100.00%)	129 (100.00%)	358 (100.00%)
Missing	826 (53.36%)	192 (53.04%)	118 (47.20%)	240 (53.45%)	69 (53.49%)	207 (57.82%)
None	18 (1.16%)	7 (1.93%)	3 (1.20%)	1 (0.22%)	0 (0.00%)	7 (1.96%)
1 to ≤2	75 (4.84%)	19 (5.25%)	18 (7.20%)	19 (4.23%)	4 (3.10%)	15 (4.19%)
3 to ≤9	284 (18.35%)	64 (17.68%)	50 (20.00%)	83 (18.49%)	26 (20.16%)	61 (17.04%)
>9	304 (19.64%)	72 (19.89%)	52 (20.80%)	90 (20.04%)	29 (22.48%)	61 (17.04%)
Multiple	41 (2.65%)	8 (2.21%)	9 (3.60%)	16 (3.56%)	1 (0.78%)	7 (1.96%)
Gadolinium enhancing lesions**						
Total	1370 (100.00%)	326 (100.00%)	219 (100.00%)	396 (100.00%)	108 (100.00%)	321 (100.00%)
Yes	449 (32.77%)	113 (34.66%)	65 (29.68%)	139 (35.10%)	37 (34.26%)	95 (29.60%)

MRI = magnetic resonance imaging;: N = number of patients; % = percentage of patients
* Patients with performed MRI
** Patients with performed MRI with contrast media (N=1370)
Source: Appendix, Table 3.8 and Table 3.7

For 53.36% of the patients with MRI, data on the number of lesions were missing at baseline. The proportion of patients with 3 to ≤9 T2 lesions was 18.35% and 19.64% with >9 T2 lesions.

Gadolinium-enhancing lesions were reported for 32.77% of patients.

9.2.2.3 MS relapses

The intensity of the last MS relapse before start of PEARL based on the EDSS score was >1.5 to ≤2.5 points in 26.99%,, >2.5 to ≤3.5 in 23.74% and ≤1.5 points in 20.49% cases. The majority, i.e. 59.67% of patients had sensory relapses, 36.91% had pyramidal relapses and 20.49% had visual relapses. All other types occurred in less than 15% of patients.

The mean relapse rate in the last 12 months before start of PEARL was 0.52 ± 0.863. (Appendix, Table 3.9.1).

Most patients had either no relapses (1058 patients, 62.05%) or one relapse (430 patients, 25.22%) A total of 141 patients (8.27%) had two relapses, 44 patients (2.58%) had more than two relapses and for 32 patients (1.88%) data on the number of relapses was missing (Appendix, Table 3.9.2).

For 615 patients with MS relapse in the last 12 months before start of PEARL, the median time from last relapse to initial visit was 144.5 days (Betaferon / Extavia: 129.5, Copaxone: 138.0, Avonex: 156.0, Rebif: 166.0). The duration of the relapse was more than 15 days for 210 patients (34.15%) and duration of hospitalization was 6 to 10 days for 69 patients (11.22%) or 4 to 5 days (10.73%). Patients were treated with steroids (544 patients, 88.46%; Appendix, Table 3.10).

The characterization of last MS relapse before start of PEARL is presented in Table 9-5.

Table 9-5: Characterization of last MS relapse before start of PEARL (N=615; patients with relapse in the last 12 months before start of PEARL)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Patients (FAS)	615 (100.00%)	140 (100.00%)	89 (100.00%)	180 (100.00%)	56 (100.00%)	150 (100.00%)
Relapse intensity (increase in EDSS Score)						
Missing	20 (3.25%)	5 (3.57%)	1 (1.12%)	8 (4.44%)	1 (1.79%)	5 (3.33%)
≤1.5	126 (20.49%)	29 (20.71%)	22 (24.72%)	37 (20.56%)	8 (14.29%)	30 (20.00%)
>1.5 to ≤2.5	166 (26.99%)	36 (25.71%)	23 (25.84%)	48 (26.67%)	22 (39.29%)	37 (24.67%)
>2.5 to ≤3.5	146 (23.74%)	31 (22.14%)	22 (24.72%)	46 (25.56%)	11 (19.64%)	36 (24.00%)
>3.5 to ≤4.5	86 (13.98%)	21 (15.00%)	12 (13.48%)	24 (13.33%)	7 (12.50%)	22 (14.67%)
>4.5 to ≤5.5	51 (8.29%)	15 (10.71%)	7 (7.87%)	9 (5.00%)	4 (7.14%)	16 (10.67%)
>5.5 to ≤6.5	15 (2.44%)	3 (2.14%)	1 (1.12%)	7 (3.89%)	2 (3.57%)	2 (1.33%)
>6.5	5 (0.81%)	0 (0.00%)	1 (1.12%)	1 (0.56%)	1 (1.79%)	2 (1.33%)
Characterization of MS relapse (multiple response)						
Visual	128 (20.81%)	20 (14.29%)	22 (24.72%)	35 (19.44%)	15 (26.79%)	36 (24.00%)
Pyramidal	227 (36.91%)	56 (40.00%)	28 (31.46%)	61 (33.89%)	21 (37.50%)	61 (40.67%)
Sensory	367 (59.67%)	90 (64.29%)	52 (58.43%)	105 (58.33%)	29 (51.79%)	91 (60.67%)
Cerebral	63 (10.24%)	16 (11.43%)	9 (10.11%)	12 (6.67%)	6 (10.71%)	20 (13.33%)
Brain stem	83 (13.50%)	14 (10.00%)	21 (23.60%)	21 (11.67%)	5 (8.93%)	22 (14.67%)
Cerebellar	71 (11.54%)	16 (11.43%)	13 (14.61%)	18 (10.00%)	8 (14.29%)	16 (10.67%)
Intestinal tract and bladder	37 (6.02%)	7 (5.00%)	4 (4.49%)	14 (7.78%)	1 (1.79%)	11 (7.33%)
Outcome of MS relapse						
Missing	4 (0.65%)	2 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.79%)	1 (0.67%)
Complete remission	234 (38.05%)	53 (37.86%)	36 (40.45%)	74 (41.11%)	24 (42.86%)	47 (31.33%)
Extensive remission	218 (35.45%)	53 (37.86%)	31 (34.83%)	58 (32.22%)	17 (30.36%)	59 (39.33%)
Partial remission	88 (14.31%)	18 (12.86%)	9 (10.11%)	30 (16.67%)	9 (16.07%)	22 (14.67%)
Light remission	26 (4.23%)	3 (2.14%)	9 (10.11%)	6 (3.33%)	3 (5.36%)	5 (3.33%)
No remission	5 (0.81%)	2 (1.43%)	1 (1.12%)	1 (0.56%)	0 (0.00%)	1 (0.67%)
Attack ongoing	40 (6.50%)	9 (6.43%)	3 (3.37%)	11 (6.11%)	2 (3.57%)	15 (10.00%)

N = number of patients; % = percentage of patients; EDSS = Expanded Disability Status Scale
Source: Appendix, Table 3.10

The intensity of the last MS relapse based on the increase in the EDSS score was >1.5 to ≤2.5 points (26.99%), >2.5 to ≤3.5 points (23.74%) and ≤1.5 points (20.49%). Sensory relapses were reported for 59.67% of patients, pyramidal relapses for 36.91% and 20.49% had visual relapses. All other types occurred in less than 15% of patients. Relapses completely remitted in 38.05% of patients or extensively remitted in 35.45%.

9.2.3 Type of First-line disease modifying therapy at Baseline

The median time since start of first-line DMT was 2.6 years (Appendix, Table 4.2.1). The median time since start of MS treatment in general was 3.9 years as presented in Table 9-3.

The time since start of first-line DMT is given in Table 9-6.

Table 9-6: Time since start of first-line DMT (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total	1705 (100.00%)	395 (100.00%)	275 (100.00%)	491 (100.00%)	151 (100.00%)	393 (100.00%)
Missing	54 (3.17%)	13 (3.29%)	3 (1.09%)	17 (3.46%)	5 (3.31%)	16 (4.07%)
<0.5 years	226 (13.26%)	55 (13.92%)	26 (9.45%)	72 (14.66%)	37 (24.50%)	36 (9.16%)
≥0.5 to <1 year	198 (11.61%)	39 (9.87%)	26 (9.45%)	52 (10.59%)	32 (21.19%)	49 (12.47%)
≥1 to <2 years	272 (15.95%)	60 (15.19%)	19 (6.91%)	81 (16.50%)	59 (39.07%)	53 (13.49%)
≥2 to <3 years	224 (13.14%)	42 (10.63%)	48 (17.45%)	71 (14.46%)	5 (3.31%)	58 (14.76%)
≥3 to <5 years	263 (15.43%)	66 (16.71%)	48 (17.45%)	93 (18.94%)	5 (3.31%)	51 (12.98%)
≥5 to <7 years	159 (9.33%)	43 (10.89%)	27 (9.82%)	46 (9.37%)	2 (1.32%)	41 (10.43%)
≥7 to <10 years	197 (11.55%)	46 (11.65%)	42 (15.27%)	48 (9.78%)	5 (3.31%)	56 (14.25%)
≥10 years	112 (6.57%)	31 (7.85%)	36 (13.09%)	11 (2.24%)	1 (0.66%)	33 (8.40%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 4.2.2

The time since start of first-line DMT ranged from less than half year to more than ten years with patients from each group in each category.

The median time since last prescription of the first-line DMT was 8.0 days (Appendix, Table 4.3).

Use of an autoinjector was documented for 1166 patients (68.39%). Presented by group the proportions are as follows: Avonex: 144 patients, 36.46%; Betaferon: 224 patients, 81.45%; Copaxone: 368 patients, 74.95%; Extavia: 112 patients, 74.17%; Rebif: 318 patients, 80.92%) (Appendix, Table 4.4).

About 30% of the patients participated in a patient program (486 patients, 28.50%; Appendix, Table 4.5).

9.2.4 Prior and concomitant diseases and treatments

9.2.4.1 Prior diseases

For a total of 127 patients (7.45%) relevant prior diseases were documented (Avonex: 6.08%, Betaferon: 8.73%, Copaxone: 8.96%, Extavia: 3.31%, Rebif: 7.63%).

The most common relevant prior diseases belonged to the System Organ Class (SOC) psychiatric disorders (overall: 2.35%), followed by benign, malignant and unspecified neoplasms (including cysts and polyps) (overall: 1.41%) and nervous system disorders

(overall: 1.17%). The most common Preferred Term (PT) was depression (overall: 1.41%). (Appendix, Table 5.1.1).

9.2.4.2 Concomitant diseases

Relevant concomitant diseases were documented for 43.93% of patients overall and for 42.53% of patients receiving Avonex, 45.45% of patients receiving Betaferon, 45.62% of patients receiving Copaxone, 41.06% of patients receiving Extavia, and 43.26% of patients receiving Rebif.

Overall, concomitant diseases were most frequently documented in the SOC psychiatric disorders (overall: 15.07%, Avonex: 13.42%, Betaferon: 15.27%, Copaxone: 16.70%, Extavia: 11.92%, Rebif: 15.78%), followed by nervous system disorders (overall: 9.97%, Avonex: 9.37%, Betaferon: 8.73%, Copaxone: 11.20%, Extavia: 6.62%, Rebif: 11.20%) and vascular disorders (overall: 9.68%, Avonex: 8.35%, Betaferon: 11.64%, Copaxone: 9.98%, Extavia: 13.91%, Rebif: 7.63%). At the PT level, the most frequently reported concomitant diseases were depression (overall: 10.56%, Avonex: 10.13%, Betaferon: 9.82%, Copaxone: 12.63%, Extavia: 4.64%, Rebif: 11.20%) and hypertension (overall: 9.09%, Avonex: 7.59%, Betaferon: 10.91%, Copaxone: 9.57%, Extavia: 13.25%, Rebif: 7.12%) (Appendix, Table 5.1.2).

9.2.4.3 Concomitant non-MS medications

About a third of patients (overall: 652 patients, 38.24%; Avonex: 39.24%, Betaferon: 38.55%, Copaxone: 38.49%, Extavia: 33.77%, Rebif: 38.42%) received non-MS concomitant medications at study entry (Appendix, Table 5.2.1).

For 643 patients (37.71%) any concomitant non-MS medication during the observation period was specified. Most frequently, patients received non-MS medication of the ATC-classification nervous system (18.47%) and cardiovascular system (13.19%). On ATC level 4, the most common non-MS specific medications were thyroid hormones (6.51%) and selective serotonin reuptake inhibitors (6.45%) (Appendix, Table 5.2.2).

9.2.4.4 MS specific concomitant medications

MS-specific concomitant medication at study entry was documented for 751 patients overall (44.05%; Avonex: 44.05%, Betaferon: 48.36%, Copaxone: 39.71%, Extavia: 47.02%, Rebif: 45.29%; Appendix, Table 5.3.1).

For 852 patients (49.97%) any relevant concomitant medications for MS treatment during the complete observation period were specified. Most frequently, patients received relevant concomitant MS medication of the ATC-classification systemic hormonal preparations, excluding sex hormones and insulins (24.04%), followed by dermatologicals (22.63%), nervous system (22.22%), and sensory organs (21.99%). A similar distribution was also observed for the subgroups Betaferon, Copaxone and Rebif. For Avonex systemic hormonal preparations, excl. sex hormones and insulins (21.77%), cardiovascular system (20.75%), and nervous system (20.50%) were the most common relevant concomitant medications, and for Extavia dermatologicals (23.17%), systemic hormonal preparations, excl. sex hormones and insulins (22.51%), sensory organs (21.19%) were the most common relevant concomitant medications (Appendix, Table 5.3.2).

9.2.4.5 Concomitant non-medical MS treatments

Concomitant non-medical MS treatments were documented for about 10% of patients (overall: 188 patients, 11.03%; Avonex: 10.89%, Betaferon: 13.09%, Copaxone: 10.59%, Extavia: 8.61%, Rebif: 11.20%). Most frequently, these were remedial gymnastics (6.80%), followed by physiotherapy (3.40%) and occupational therapy (1.35%; Appendix, Table 5.3.3).

9.2.5 Premature discontinuation of therapy

For about 20% of the patients (overall: 20.18%; Avonex: 20.51%, Betaferon: 18.91%, Copaxone: 19.55%, Extavia: 23.84%, Rebif: 20.10%) premature discontinuation of documentation was recorded (Appendix, Table 6.3).

The time to premature discontinuation of documentation is presented in Table 9-7.

Table 9-7: Time to premature discontinuation of documentation in days in patients with documentation of premature discontinuation (N=344)

	Type of First-line disease modifying therapy at Baseline					
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
n	305	71	46	91	31	66
Missing	39	10	6	5	5	13
Mean	398.8	406.4	459.8	336.2	458.5	406.2
SD	228.70	229.58	222.25	209.34	220.08	246.36
Median	379.0	421.0	458.5	302.0	408.0	385.5

n = number of patients; SD= standard deviation
Source: Appendix, Table 6.4

The median time from initial visit to premature discontinuation of documentation was 379.0 days (Avonex: 421.0 days, Betaferon: 458.5 days, Copaxone: 302.0 days, Extavia: 408.0 days, Rebif: 385.5 days).

The reasons for premature discontinuation of documentation reported in >10% of the patients are summarized in Table 9-8.

Table 9-8: Reasons for premature discontinuation of documentation (cutoff > 10%; Multiple Response)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total	344 (100.00%)	81 (100.00%)	52 (100.00%)	96 (100.00%)	36 (100.00%)	79 (100.00%)
Change to other therapy*	54 (15.70%)	13 (16.05%)	11 (21.15%)	11 (11.46%)	5 (13.89%)	14 (17.72%)
Switch to Gilenya*	51 (14.83%)	18 (22.22%)	4 (7.69%)	15 (15.63%)	3 (8.33%)	11 (13.92%)
Lost to follow up*	45 (13.08%)	9 (11.11%)	9 (17.31%)	8 (8.33%)	7 (19.44%)	12 (15.19%)
Change of physician	40 (11.63%)	6 (7.41%)	4 (7.69%)	15 (15.63%)	3 (8.33%)	12 (15.19%)
Patient's decision (unspecified)	36 (10.47%)	12 (14.81%)	12 (23.08%)	6 (6.25%)	3 (8.33%)	3 (3.80%)
Pregnancy / Desire to have children*	21 (6.10%)	3 (3.70%)	2 (3.85%)	7 (7.29%)	4 (11.11%)	5 (6.33%)
Relapse / Progression of disease*	17 (4.94%)	3 (3.70%)	2 (3.85%)	6 (6.25%)	4 (11.11%)	2 (2.53%)
Adverse event	16 (4.65%)	1 (1.23%)	6 (11.54%)	6 (6.25%)	0 (0.00%)	3 (3.80%)

* Free text coding
N = number of patients; % = percentage of patients
Source: Appendix, Table 6.5

Overall, the reasons for premature discontinuation most frequently were “change to other therapy” (15.70%), followed by “switch to Gilenya” (14.83%) and “lost to follow up” (13.08%).

9.2.6 Course of the first-line disease modifying therapy

The modification of first-line DMT since the previous visit is presented in Table 9-9.

Table 9-9: Modification of first-line disease modifying therapy since the previous visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
Patients with modification	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
FU after 3 months	51 / 1656 (3.08%)	7 / 385 (1.82%)	4 / 268 (1.49%)	22 /469 (4.69%)	3 / 147 (2.04%)	15 (3.88%)
FU after 6 months	73 / 1564 (4.67%)	21 / 370 (5.68%)	13 / 259 (5.02%)	13 / 434 (3.00%)	4 / 136 (2.94%)	22 / 365 (6.03%)
FU after 9 months	39 / 1481 (2.63%)	4 / 343 (1.17%)	5 / 248 (2.02%)	12 / 418 (2.87%)	8 / 129 (6.20%)	10 / 343 (2.92%)
FU after 12 months	50 / 1432 (3.49%)	11 / 333 (3.30%)	8 / 243 (3.29%)	11 / 402 (2.74%)	8 / 125 (6.40%)	12 / 329 (3.65%)
FU after 15 months	35 / 1340 (2.61%)	8 / 312 (2.56%)	9 / 223 (4.04%)	12 / 379 (3.17%)	3 / 115 (2.61%)	3 / 311 (0.96%)
FU after 18 months	43 /1279 (3.36%)	13 / 299 (4.35%)	4 / 217 (1.84%)	10 / 358 (2.79%)	5 / 106 (4.72%)	11 / 299 (3.68%)
FU after 21 months	29 / 1184 (2.45%)	5 / 269 (1.86%)	4 / 200 (2.00%)	7 / 338 (2.07%)	5 / 100 (5.00%)	8 / 277 (2.89%)
FU after 24 months	28 / 1114 (2.51%)	5 / 247 (2.02%)	3 / 197 (1.52%)	13 / 324 (4.01%)	3 / 92 (3.26%)	4 / 254 (1.57%)
Last Visit	158 / 1684 (9.38%)	37 / 391 (9.46%)	21 / 274 (7.66%)	49 / 479 (10.23%)	17 / 149 (11.41%)	34 / 391 (8.70%)

N = number of patients; % = percentage of patients, FU = follow-up
Note: Missing values are not presented (range 0.00% to 2.68%)
Source: Appendix, Table 7.1

Modification of the first-line DMT between two visits was documented in up to 4.67% of patients. With respect to the last visit, 9.38% of patients had a modification of the first-line DMT since the previous visit.

A switch of therapy during the observation period was reported for 279 out of the 1705 patients (16.36%). No difference was observed between patients that were in a patient program and patients that were not (Appendix, Table 7.2.1).

The proportion of patients who terminated the therapy or for whom data on therapy switches were missing were as follows: Avonex 33.82%, Betaferon 22.45% Copaxone 28.57%, Extavia 37.93, Rebif 29.23% (Appendix, Table 7.2.2).

A shift table of the first-line DMT at baseline visit versus last documented visit is presented in Appendix, Table 7.3 and a listing of patients with documented therapy switches in Appendix, Table 7.4.

Of the total 1705 patients, 40 patients (2.35%) had one therapy interruption and three (0.18%) had two interruptions (Appendix, Table 7.5).

9.3 Outcome data

9.3.1 Number of documentations

The number of documentations for the main outcome data can be found in Section 9.4.1 for pharmacoeconomic parameters, in Table 9-13 for MS relapses, in Table 9-16 for performed MRIs, in Table 9-19 for the EDSS score, in Appendix, Table 9.11 and Table 9.2.1 for CGI (severity and improvement) and in Appendix, Table 9.7.1 and Table 9.8.1 for the physicians' and patients' assessment of efficacy.

The number of documentations for the patient questionnaires is presented in Section 9.4.3 and for the practice questionnaires in Section 9.4.4.

The number of patients with documented FU visit is presented in Table 9-10.

Table 9-10: Number of patients with documented follow-up visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline	1705	395	275	491	151	393
3 month FU	1656	385	268	469	147	387
6 month FU	1564	370	259	434	136	365
9 month FU	1481	343	248	418	129	343
12 month FU	1432	333	243	402	125	329
15 month FU	1340	312	223	379	115	311
18 month FU	1279	299	217	358	106	299
21 month FU	1184	269	200	338	100	277
24 month FU	1114	247	197	324	92	254
Last Visit	1684	391	274	479	149	391

N = number of patients; % = percentage of patients; FU = follow-up
Note: For 21 patients a reported AE was the only FU information. Therefore, these patients do not have a last visit.
Source: Appendix, Table 6.0

Of the 1705 patients at baseline, 1114 patients had documentation of the 24 months FU visit and for 1684 patients the data at the last completed visit were summarized in the form of a final FU (last visit).

9.3.2 Observation period

The median observation period was 728.0 days (Appendix, Table 6.1).

The median time of the FU examinations in relation to start of PEARL is provided in Appendix, Table 6.2.

9.4 Main results

9.4.1 Pharmacoeconomic results

Pharmacoeconomic parameters were based on the analysis of the patient resource questionnaire. Resource utilization was documented at start of observation and subsequently every 3 months.

The resource utilization questionnaires were filled out by a total of 1699 patients at any visit. For the majority of patients the resource utilization questionnaires were also available at all FU visits (Appendix, Table Sub 7.0).

Employment

The employment status of MS patients is summarized in Table 9-11.

Table 9-11: Employment status

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N / Patient FAS (%)	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
Baseline						
Current employment *	1021 / 1689 (60.45%)	231 /392 (58.93%)	167 / 270 (61.85%)	299 / 488 (61.27%)	89 / 148 (60.14%)	235 / 391 (60.10%)
Full-time employed **	610 / 1021 (59.75%)	126 / 231 (54.55%)	110 / 167 (65.87%)	175 / 299 (58.53%)	59 / 89 (66.29%)	140 / 235 (59.57%)
Sick leave **	222 / 1021 (21.74%)	47 / 231 (20.35%)	36 / 167 (21.56%)	66 / 299 (22.07%)	28 / 89 (31.46%)	45 / 235 (19.15%)
FU after 6 months						
Current employment *	880 / 1546 (56.92%)	211 / 365 (57.81%)	149 / 255 (58.43%)	247 / 431 (57.31%)	74 / 134 (55.22%)	199 / 361 (55.12%)
Full-time employed **	521 / 880 (59.20%)	121 / 211 (57.35%)	106 / 149 (71.14%)	141 / 247 (57.09%)	47 / 74 (63.51%)	106 / 199 (53.27%)
Sick leave **	106 / 880 (12.05%)	25 / 211 (11.85%)	23 / 149 (15.44%)	31 / 247 (12.55%)	11 / 74 (14.86%)	16 / 199 (8.04%)
FU after 12 months						
Current employment *	826 / 1396 (59.17%)	200 / 323 (61.92%)	143 / 236 (60.59%)	228 / 393 (58.02%)	65 / 121 (53.72%)	190 / 323 (58.82%)
Full-time employed **	485 / 826 (58.72%)	105 / 200 (52.50%)	98 / 143 (68.53%)	134 / 228 (58.77%)	44 / 65 (67.69%)	104 / 190 (54.74%)
Sick leave **	95 / 826 (11.50%)	27 / 200 (13.50%)	18 / 143 (12.59%)	23 / 228 (10.09%)	8 / 65 (12.31%)	19 / 190 (10.00%)
FU after 18 months						
Current employment *	707 / 1256 (56.29%)	169 295 (57.29%)	127 / 215 (59.07%)	202 / 353 (57.22%)	52 / 100 (52.00%)	157 / 293 (53.58%)
Full-time employed **	422 / 707 (59.69%)	89 / 169 (52.66%)	91 / 127 (71.65%)	119 / 202 (58.91%)	32 / 52 (61.54%)	91 / 157 (57.96%)
Sick leave **	82 / 707 (11.60%)	10 / 169 (5.92%)	17 / 26 (13.39%)	26 / 202 (12.87%)	8 / 52 (15.38%)	21 / 157 (13.38%)
FU after 24 months						
Current employment *	655 / 1099 (59.60%)	150 / 246 (60.98%)	115 / 194 (59.28%)	187 / 319 (58.62%)	50 / 88 (56.82%)	153 / 252 (60.71%)
Full-time employed **	386 / 655 (58.93%)	80 / 150 (53.33%)	79 / 115 (68.70%)	107 / 187 (57.22%)	30 / 50 (60.00%)	90 / 153 (58.82%)
Sick leave **	64 / 655 (9.77%)	13 / 150 (8.67%)	10 / 115 (8.70%)	19 / 187 (10.16%)	8 / 50 (16.00%)	14 / 153 (9.15%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N / Patient FAS (%)	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
Last Visit						
Current employment *	961 / 1669 (57.58%)	226 / 391 (57.80%)	162 / 272 (59.56%)	265 / 472 (56.14%)	83 / 146 (56.85%)	225 / 388 (57.99%)
Full-time employed **	575 / 961 (59.83%)	124 / 226 (54.87%)	112 / 162 (69.14%)	155 / 265 (58.49%)	52 / 83 (62.65%)	132 / 225 (58.67%)
Sick leave **	128 / 961 (13.32%)	29 / 226 (12.83%)	18 / 162 (11.11%)	37 / 265 (13.96%)	16 / 83 (19.28%)	28 / 225 (12.44%)

* Patients with filled resource questionnaire
** Patients with current employment
Source: Appendix Table Sub 7.4, Table Sub 7.7 and Table Sub 7.8.

Current employment was documented for 60.45% of patients at baseline and 57.58% at last visit) with full-time employment for 59.75% at baseline and 59.83% at last visit.

About a third were part-time employed with a mean percentage of 53.3 ± 21.04 at baseline (Appendix, Table Sub 7.7).

At baseline, 21.74% of patients reported that they were on sick leave due to MS within the past 3 months and at the last visit 13.32% of patients documented a sick leave due to MS in the last 3 months. Sick leaves amounted to a mean of 21.1 ± 26.01 days (median 10.0 days) and 13.8 ± 17.19 days (median 9.5 days), respectively. The mean number of sick days per visit is documented in the Appendix, Table Sub 7.8. A reduction of working hours due to MS was reported by 6.37% of patients at baseline and 2.90% at 24 month FU. For these, the work reduction was a mean of 51.9 ± 24.30% (median 50.0%) at baseline and 49.4 ± 23.94% (median 50.0%) at the 24 month FU (Appendix, Table Sub 7.9).

A change in the type of employment within the past year due to MS (baseline: 4.31%, 24 month FU: 1.22%; Appendix, Table Sub 7.10) or a wage reduction due to MS (baseline: 10.48%, 24 month FU: 5.50%; Appendix, Table Sub 7.11) was reported.

Within the past 7 days before baseline, 8.62% of patients with current employment were absent from work due to MS. The absence lasted for a mean of 22.6 ± 16.11 hours (median 20.0 hours; Appendix, Table Sub 7.12). Time absent from work within the past seven days due to non-MS reasons (holiday, spare time, etc.) was documented at baseline for 15.96% of patients with current employment. For these, the average time absent from work was 18.3 ± 13.78 hours (median 15.0 hours). Results for the last visit can be found in Appendix, Table Sub 7.13.

In the past seven days before baseline, patients with current employment worked on average for 30.4 ± 14.87 hours (median 35.0 hours). Results for the last visit can be found in Appendix, Table Sub 7.14.

The influence of MS on productivity on a scale from 0 (no effect at all) to 10 (massive effect) for patients with current employment was a mean of 2.1 ± 2.85 (median 1.0) at baseline (Appendix, Table Sub 7.15.1). The rating by category is presented in Appendix, Table Sub 15.2.

General situation

The majority of patients lived together with family, spouse or mate (baseline: 76.38%; 12 months FU: 77.08%, 24 months FU: 74.89%; Appendix, Table Sub 7.1). About half of the patients had a completed professional **education** (baseline: 53.64%, 12 months FU: 47.13%, 24 months FU: 51.96%; Appendix, Table Sub 7.2) and about half of the patients documented their **current occupation** as employed (baseline: 51.75%, 12 months FU: 52.51%, 24 months FU: 51.14%; Appendix, Table Sub 7.3.1).

An average **disability pension** due to MS of 72.9 ± 21.44% (median 70.0%) was documented at baseline and of 77.1 ± 22.47% (median 80.0%) at last visit (Appendix, Table Sub 7.3.2).

At baseline, 94.02% of patients were reported to have a public health insurance (Appendix, Table Sub 7.5).

About a third of patients (32.98%) at baseline provided care for other family members. On a scale from 0 (no worry) to 10 (maximum worry), patients had a mean rating of

3.7 ± 3.01 (median 3.0) regarding their worry to be able to provide this care in the future. Results for the 24 months FU visit can be found in Appendix, Table Sub 7.6).

Relapses

The number of MS relapses derived from the resource utilization questionnaire is provided in Appendix, Table Sub 7.16.1. The mean number of relapses treated with steroids in patients with relapses during the last 3 months was 0.9 ± 0.48 (median 1.0; Appendix, Table Sub 7.16.2) and the mean number of days in hospital due to a relapse in the past 3 months was 1.6 ± 3.69 days (median 0.0; Appendix, Table Sub 7.16.3).

Hospitalizations / rehabilitation clinics / nursing homes

MS-related hospitalization was reported for 4.74% of patients. For these the mean number of hospitalizations was 1.5 ± 1.46 (median 1.0) and the mean number of days in hospital was 8.8 ± 9.12 days (median 6.5 days). For 71 patients a mean of 8.6 ± 9.08 days (median 6.0 days) in the neurologic ward and for seven patients 5.3 ± 5.09 days (median 4.0 days) in another ward were documented (Appendix, Table Sub 7.17.1).

In the past 3 months before baseline, 34 patients (2.01%) had to stay in a rehabilitation clinic. The mean number of stays was 1.3 ± 1.64 (median 1.0) and the mean number of days 26.7 ± 7.40 days (median 28.0 days). Results for the last visit can be found in Appendix, Table Sub 7.17.2.

None of the patients throughout the study stayed in a nursing home (Appendix, Table Sub 7.17.3).

Ambulant treatments and examinations

Ambulant treatments in the hospital were documented for 52 patients (3.08%). The mean number of ambulant treatments was 1.7 ± 1.63 (median 1.0), the mean number of days of ambulant treatment was 3.2 ± 4.56 days (median 2.0), the mean number of days of ambulant treatment in neurologic ward was 2.9 ± 2.72 days (median 2.0 days) and the mean number of days of ambulant treatment in another ward was 1.2 ± 0.75 days (median 1.0 days; Appendix, Table Sub 7.18.1).

In the past 3 months before baseline, 9 patients (0.53%) had documented ambulant treatments in a rehabilitation clinic. The mean number of stays was 1.3 ± 0.50 (median 1.0) and the mean number of days 19.0 ± 8.07 days (median 21.0 days). Results for the last visit can be found in Appendix, Table Sub 7.18.2.

None of the patients throughout the study had ambulant treatments in a nursing home (Appendix, Table Sub 7.18.3).

Consultation of physician or other health care professional

In the past 3 months before baseline, 86.20% of patients consulted a physician or other health care professional due to MS (Appendix, Table Sub 7.19.1). These were physical therapists in a private practice (mean 2.89 ± 7.083 consultations), neurologists in private practices (mean 1.51 ± 1.878 consultations) and general practitioners in a private practices (mean 0.60 ± 1.443 consultations; Appendix, Table Sub 7.19.2.1 and 7.19.2.2).

Patients had only alternative treatments (acupuncture or alternative cures) due to MS (Appendix, Table Sub 7.20.1 and 7.20.2).

Examinations

In the last 12 months before baseline, examinations due to MS were performed for 77.26% of patients (Appendix, Table Sub 7.21.1). MRIs were performed for 927 patients (54.88%), with a mean number of 1.4 ± 0.72 MRIs. A mean number of 1.2 ± 0.93 CTs were performed in 50 patients (2.96%), a mean number of 1.2 ± 0.86 lumbar punctures in 158 patients (9.35%), a mean number of 2.6 ± 2.03 blood examinations in more than half of the patients (959 patients; 56.78%), and a mean number of 2.2 ± 1.50 other examinations in 217 patients (12.85%). In the past twelve months before 24 month FU, MRIs were performed for 410 patients (37.31%); CTs for 19 patients (1.73%); lumbar punctures for 4 patients (0.36%), blood examinations for 493 patients (44.86%) and other examinations for 89 patients (8.10%) (Appendix, Table Sub 7.21.2).

Injection of MS medication

Manual injection was used by 87.39% of the patients at baseline and 29.42% at last visit, and an autoinjector was used by 67.44% of the patients at baseline and 67.53% at last visit. About 70% (baseline: 69.63%, last visit: 69.56%) were able to use both systems. About 10% of the patients (baseline: 10.89%, last visit: 9.65%) needed assistance with manual injection (Appendix, Table Sub 7.22.2). About 40% of patients needed help with each injection (baseline: 39.88%, last visit: 42.05%), about 25% for less than half of the injections (baseline: 24.93%, last visit: 22.85%; Appendix, Table Sub 7.22.3). The assistance was provided by the partner or family (baseline: 62.17%, last visit: 66.23%; Appendix, Table Sub 7.22.4).

Training programs

About a quarter of the patients (24.45%) had participated in a training about MS treatment in the last 3 months before baseline. These trainings were led completely by a nurse in more than half of the cases (56.66%). In the last 3 months before the last visit, 15.46% of patients had participated in a training and the trainings were completely led by a nurse in about 40% of the cases (37.60%; Appendix, Table Sub 7.23).

About a third of the patients (32.68%) at baseline had participated in a company sponsored care program. The person who looked after the patients was the nurse and service center for half of the patients (46.92%) and the service center only (27.17%). On average, patients had 1.8 ± 1.58 contacts. Results for the last visit can be found in Appendix, Table Sub 7.24.

Over-the-counter medications, consumables and devices

About a third of the patients (34.99%) at baseline had purchased over-the-counter medications against MS in the past 3 months. The expenses amounted to a mean of 43.0 ± 68.40 Euro. In the past 3 months before the last visit, the proportion of patients who had purchased over-the-counter medications because of MS was 31.10% (mean expenses 40.1 ± 58.15 Euro). Most frequently, these medications were purchased on the patient's own initiative (49.58%), followed by the recommendation by a medical specialist (39.93%) (Appendix, Table Sub 7.25).

Consumables due to MS were purchased by 10.60% of the patients in the past 3 months before baseline (mean expenses 29.4 ± 35.40 Euro) and by13.12% of the patients in the past 3 months before the last visit (mean expenses 32.6 ± 38.14 Euro).(Appendix, Table Sub 7.26).

Expenses for equipment and devices due to MS in the past 12 months were documented by 137 patients (8.11%) at baseline. Of these, the most frequently reported expenses were expenses for walking aids (57.66%), followed by changes to the house (34.31%), and expenses for other (20.44%). The expenses amounted to a mean of 3998.2 ± 8567.8 Euro and a median of 200.0 Euro and were funded by the patient's own expense in half of the patients (48.18%). At the 12 month FU and 24 months, expenses for equipment and devices were documented by about 5% of the patients (12 month FU: 5.59%, 24 month FU: 5.00%), with the most frequently reported expenses being expenses for walking aids (12 month FU: 53.85%, 24 month FU: 50.91%), followed by the current use of wheel chair (12 month FU: 30.77%, 24 month FU: 23.64%; Appendix, Table Sub 7.27).

Need for assistance

In the past 3 months before baseline, 18 patients (1.07%) needed professional assistance. In the past 3 months before the last visit, 13 patients (0.78%) needed professional assistance. The number of visits amounted to a mean of 2.6 ± 2.34 visits per week and 3.1 ± 3.02 hours per week (Appendix, Table Sub 7.28.

Assistance from a household help was received by 76 patients (4.50%) in the past 3 months before baseline and by 91 patients (5.45%) in the past 3 months before the last visit. The number of visits amounted to a mean of 1.4 ± 1.04 visits per week and 3.6 ± 2.30 hours per week (Appendix, Table Sub 7.29.

Assistance from a personal assistant was provided for 6 patients (0.36%) within the past 3 months before baseline and for 2 patients (0.12%) in the past 3 months before the last visit. The number of visits amounted to a mean of 2.0 ± 2.00 visits per week and 4.0 ± 6.24 hours per week (Appendix, Table Sub 7.30).

A total of 304 patients (18.00%) received assistance from family or friends in the past 3 months before baseline, as well as 283 patients (16.96%) in the past 3 months before the last visit. Of these patients, 91.45% received part-time care, with a mean of 4.2 ± 4.47 visits per week (Appendix, Table Sub 7.31.

For 20 patients (1.18%) a mean work reduction of family members in the past 3 months before baseline of 14.2 ± 11.18 hours per week was reported. In the past 3 months before the last visit, this was reported by 18 patients (1,08%) with a mean reduction of 9.1 ± 10.93 hours per week (Appendix, Table Sub 7.32).

The mean degree of disability was 36.5 ± 30.12% (median 40.0%) at baseline and 37.7 ± 29.90% (median 50.0%) at last visit (Appendix, Table Sub 7.33).

In the past 3 months before baseline, 39 patients (2.31%) received benefits from long term care insurances (2.10% in the past 3 months before the last visit). For the needs assessment of care, these patients received a mean of 1.3 ± 0.69 visits by a medical care giver, amounting to 74.0 ± 47.09 minutes. Of the patients, for whom data were available, 37.48% were not categorized in a care level (Appendix, Table Sub 7.34).

About a third of patients (27.12%) at baseline applied for, or received an ID for the severely handicapped in the past 3 months before baseline. Of these patients, 45,63% had no marks. Results for the last visit can be found in Appendix, Table Sub 7.35.

9.4.2 Clinical effectiveness results

9.4.2.1 Documentation of MS relapses

The mean and median numbers of MS relapses since the previous visit is presented in Table 9-12.

Table 9-12: Mean number of MS relapses since the previous visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
FU after 6 months						
n	1564	370	259	434	136	365
Mean (SD)	0.11 (0.335)	0.10 (0.321)	0.11 (0.340)	0.13 (0.347)	0.10 (0.305)	0.11 (0.341)
FU after 12 months						
n	1432	333	243	402	125	329
Mean (SD)	0.09 (0.306)	0.13 (0.356)	0.07 (0.249)	0.07 (0.251)	0.12 (0.350)	0.10 (0.330)
FU after 18 months						
n	1279	299	217	358	106	299
Mean (SD)	0.08 (0.283)	0.08 (0.291)	0.07 (0.262)	0.09 (0.301)	0.08 (0.299)	0.07 (0.263)
FU after 24 months						
n	1114	247	197	324	92	254
Mean (SD)	0.05 (0.230)	0.04 (0.197)	0.04 (0.198)	0.08 (0.272)	0.03 (0.179)	0.05 (0.238)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
Last visit						
n	1684	391	274	479	149	391
Mean (SD)	0.11 (0.330)	0.11 (0.334)	0.08 (0.285)	0.12 (0.335)	0.13 (0.373)	0.10 (0.332)

n = number of patients; FU = follow-up; SD = standard deviation.
To avoid overly long text tables, only n, mean (SD) and median are presented here.
Source: Appendix, Table 8.2

Considering the mean values, the number of MS relapses was 0.11±0.335 MS relapses at the 6 months FU, 0.09±0.306 MS relapses at the 12 months FU, 0.08±0.283 MS relapses at the 18 months FU, and 0.05±0.230 MS relapses at the 24 months FU.

The absolute and relative frequencies of patients with new MS relapses since the previous visit are presented in Table 9-13.

Table 9-13: The absolute and relative frequencies of patients with new MS relapses since the previous visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N / Patient FAS (%)	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
FU after 3 months	159 / 1656 (9.60%)	32 / 385 (8.31%)	23 / 268 (8.58%)	56 / 469 (11.94%)	13 / 147 (8.84%)	35 / 387 (9.04%)
FU after 6 months	168 / 1564 (10.74%)	36 / 370 (9.73%)	27 / 259 (10.42%)	53 / 434 (12.21%)	14 / 136 (10.29%)	38 / 365 (10.41%)
FU after 9 months	129 / 1481 (8.71%)	21 / 343 (6.12%)	15 / 248 (6.05%)	43 / 418 (10.29%)	16 / 129 (12.40%)	34 / 343 (9.91%)
FU after 12 months	129 / 1432 (9.01%)	42 / 333 (12.61%)	16 / 243 (6.58%)	27 / 402 (6.72%)	14 / 125 (11.20%)	30 / 329 (9.12%)
FU after 15 months	118 / 1340 (8.81%)	28 / 312 (8.97%)	22 / 223 (9.87%)	37 / 379 (9.76%)	8 / 115 (6.96%)	23 / 311 (7.40%)
FU after 18 months	92 / 1279 (7.19%)	21 / 299 (7.02%)	16 / 217 (7.37%)	29 / 358 (8.10%)	7 / 106 (6.60%)	19 / 299 (6.35%)
FU after 21 months	81 / 1184 (6.84%)	18 / 269 (6.69%)	12 / 200 (6.00%)	22 / 338 (6.51%)	9 / 100 (9.00%)	20 / 277 (7.22%)
FU after 24 months	59 / 1114 (5.30%)	10 / 247 (4.05%)	8 / 197 (4.06%)	26 / 324 (8.02%)	3 / 92 (3.26%)	12 / 254 (4.72%)
Last Visit	170 / 1684 (10.10%)	39 / 391 (9.97%)	21 / 274 (7.66%)	58 / 479 (12.11%)	17 / 149 (11.41%)	35 / 391 (8.95%)

N = number of patients; % = percentage of patients, FU = follow-up
Source: Appendix, Table 8.1

The percentage of patients with new MS relapses since the previous visit ranged from 5.30% to 10.74% (ranging between 4.05% and 12.61% for Avonex, 4.06% and 10.42% for Betaferon, 6.51% and 12.21% for Copaxone, 3.26% and 12.40% for Extavia, and 4.72% and 10.41% for Rebif).

Of the patients with relapses, up to 10.17% had one relapse. Up to 11 patients (last visit) had two relapses and none had more than two relapses (Appendix, Table 8.3).

The Annual relapse (ARR) rate is given in Table 9-14. The ARR was assessed for the subgroup of patients documented for at least one year.

Table 9-14: Annual relapse rate (ARR) (N=1705)

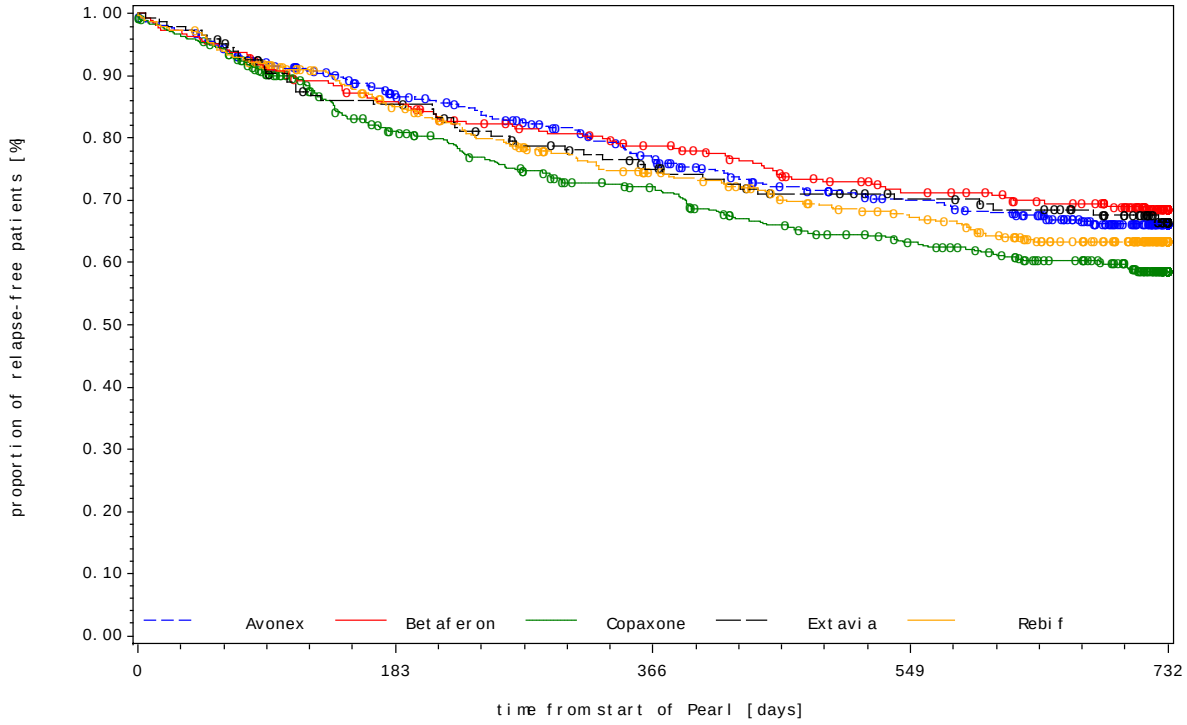
		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
n	1646	381	271	468	146	380
Missing value	59	14	4	23	5	13
Mean	0.39	0.38	0.33	0.44	0.41	0.39
SD	0.770	0.814	0.633	0.784	0.848	0.767
Median	0.0	0.0	0.0	0.0	0.0	0.0

n = number of patients; SD = standard deviation
Source: Appendix, Table 8.4

The mean ARR was 0.39 ± 0.770. For 586 patients with MS relapses after start of PEARL, the median time from baseline to first relapse was 215.5 days (Avonex: 244.0 days, Betaferon: 193.0 days, Copaxone: 213.5 days, Extavia: 210.0 days, Rebif: 220.5 days). The relapses were reported to be ongoing for 188 patients (32.08%) and to be more than 15 days for 144 patients (24.57%). Over the two years, 20.14% of the patients were hospitalized. Most of them were treated with steroids (87.37%).; (Appendix, Table 8.5).

A Kaplan-Meier Plot for new MS relapses for the different first-line DMTs is presented in Figure 9-1.

Figure 9-1: Kaplan Meier Plot for new MS relapses (N=1705)



Source: Appendix, Graph 8.7

The characterization of new MS relapses after start of PEARL is given in Table 9-15.

Table 9-15: Characterization of new MS relapses (N=586; patients with relapse after start of PEARL)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Intensity (EDSS Score)*						
Missing	16 (2.73%)	5 (3.91%)	1 (1.19%)	7 (3.63%)	1 (2.08%)	2 (1.50%)
≤1.5	49 (8.36%)	7 (5.47%)	12 (14.29%)	14 (7.25%)	3 (6.25%)	13 (9.77%)
>1.5 to ≤2.5	122 (20.82%)	25 (19.53%)	18 (21.43%)	38 (19.69%)	14 (29.17%)	27 (20.30%)
>2.5 to ≤3.5	160 (27.30%)	37 (28.91%)	23 (27.38%)	54 (27.98%)	11 (22.92%)	35 (26.32%)
>3.5 to ≤4.5	117 (19.97%)	29 (22.66%)	11 (13.10%)	38 (19.69%)	11 (22.92%)	28 (21.05%)
>4.5 to ≤5.5	51 (8.70%)	14 (10.94%)	9 (10.71%)	17 (8.81%)	1 (2.08%)	10 (7.52%)
>5.5 to ≤6.5	48 (8.19%)	8 (6.25%)	6 (7.14%)	18 (9.33%)	3 (6.25%)	13 (9.77%)
>6.5	23 (3.92%)	3 (2.34%)	4 (4.76%)	7 (3.63%)	4 (8.33%)	5 (3.76%)
Characterization of MS relapse (multiple response)						
Visual	134 (22.87%)	29 (22.66%)	17 (20.24%)	40 (20.73%)	14 (29.17%)	34 (25.56%)
Pyramidal	265 (45.22%)	62 (48.44%)	34 (40.48%)	85 (44.04%)	23 (47.92%)	61 (45.86%)
Sensory	371 (63.31%)	70 (54.69%)	51 (60.71%)	139 (72.02%)	26 (54.17%)	85 (63.91%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cerebral	73 (12.46%)	19 (14.84%)	11 (13.10%)	17 (8.81%)	4 (8.33%)	22 (16.54%)
Brain stem	80 (13.65%)	20 (15.63%)	13 (15.48%)	29 (15.03%)	6 (12.50%)	12 (9.02%)
Cerebellar	84 (14.33%)	20 (15.63%)	12 (14.29%)	18 (9.33%)	11 (22.92%)	23 (17.29%)
Intestinal tract and bladder	48 (8.19%)	10 (7.81%)	7 (8.33%)	18 (9.33%)	5 (10.42%)	8 (6.02%)
Outcome of MS relapse**						
Missing	11 (1.88%)	6 (4.69%)	1 (1.19%)	3 (1.55%)	0 (0.00%)	1 (0.75%)
Complete remission	157 (26.79%)	31 (24.22%)	23 (27.38%)	50 (25.91%)	14 (29.17%)	39 (29.32%)
Extensive remission	194 (33.11%)	42 (32.81%)	30 (35.71%)	63 (32.64%)	15 (31.25%)	44 (33.08%)
Partial remission	83 (14.16%)	17 (13.28%)	14 (16.67%)	26 (13.47%)	8 (16.67%)	18 (13.53%)
Light remission	22 (3.75%)	9 (7.03%)	1 (1.19%)	8 (4.15%)	0 (0.00%)	4 (3.01%)
No remission	5 (0.85%)	0 (0.00%)	0 (0.00%)	4 (2.07%)	0 (0.00%)	1 (0.75%)
Attack ongoing	114 (19.45%)	23 (17.97%)	15 (17.86%)	39 (20.21%)	11 (22.92%)	26 (19.55%)

N = number of patients; % = percentage of patients, EDSS = Expanded Disability Status Scale
* Worst case scenario: Patient was allocated based on the MS relapse with the highest intensity (EDSS score).
** Worst case scenario: Patient was allocated based on the MS relapse with the worst outcome.
Source: Appendix, Table 8.5

Overall, the intensity of the relapses was most frequently >2.5 to ≤3.5 points (27.30%), followed by >1.5 to ≤2.5 points (20.82%) and >3.5 to ≤4.5 points (19.97%) based on the EDSS score. A total of 63.31% of patients had sensory relapses, 45.22% of patients had pyramidal relapses and 22.87% of patients had visual relapses. All other types of relapses occurred in less than 15% of patients. The outcome of the relapse was extensive remission in 33.11% of the patients or complete remission in 26.79%. For about half of the patients, the MS relapses were reported to have no causality with therapy (55.80%).

An event based characterization of the new MS relapses is given in Appendix, Table 8.6.

9.4.2.2 Documentation of MRI

Table 9-16 provides a summary on the absolute and relative frequencies of patients with performed MRIs since the previous visit.

Table 9-16: Absolute and relative frequencies of patients with performed MRIs since the previous visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N / Patient FAS (%)	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
Baseline*						
MRI performed since last visit	1548 / 1705 (90.79%)	362 / 395 (91.65%)	250 / 275 (90.91%)	449 / 491 (91.45%)	129 / 151 (85.43%)	358 / 393 (91.09%)
MRI with contrast media	1370 / 1548 (88.50%)	326 / 362 (90.06%)	219 / 219 (87.60%)	396 / 449 (88.20%)	108 / 129(83.72%)	321 / 358 (89.66%)
FU after 3 months						
MRI performed since last visit	202 / 1656(12.20%)	46 / 385 (11.95%)	31 / 268 (11.57%)	59 / 469 (12.58%)	15 / 147 (10.20%)	51 / 387 (13.18%)
MRI with contrast media	179 / 202 (88.61%)	42 / 46 (91.30%)	29 / 31 (93.55%)	48 / 59 (81.36%)	13 / 15 (86.67%)	47 / 51 (92.16%)
FU after 6 months						
MRI performed since last visit	198 / 1564 (12.66%)	51 / 370 (13.78%)	31 / 259 (11.97%)	56 / 434 (12.90%)	19 / 136 (13.97%)	41 / 365 (11.23%)
MRI with contrast media	173 / 198 (87.37%)	44 / 51 (86.27%)	27 / 31 (87.10%)	48 / 56 (85.71%)	16 / 19 (84.21%)	38 / 41 (92.68%)
FU after 9 months						
MRI performed since last visit	190 / 1481 (12.83%)	34 / 343 (9.91%)	28 / 248 (11.29%)	57 / 418 (13.64%)	23 / 129 (17.83%)	48 / 343 (13.99%)
MRI with contrast media	169 / 190 (88.95%)	32 / 34 (94.12%)	25 / 28 (89.29%)	50 / 57 (87.72%)	15 / 23 (65.22%)	47 / 48 (97.92%)
FU after 12 months	1432 (100.00%)	333 (100.00%)	243 (100.00%)	402 (100.00%)	125 (100.00%)	329 (100.00%)
MRI performed since last visit	200 / 1432 (13.97%)	41 / 333 (12.31%)	30 / 243 (12.35%)	59 / 402 (14.68%)	21 / 125 (16.80%)	49 / 329 (14.89%)
MRI with contrast media	189 / 200 (94.50%)	39 / 41 (95.12%)	27 / 30 (90.00%)	54 / 59 (91.53%)	20 / 21 (95.24%)	49 / 49 (100.00%)
FU after 15 months	1340 (100.00%)	312 (100.00%)	223 (100.00%)	379 (100.00%)	115 (100.00%)	311 (100.00%)
MRI performed since last visit	166 / 1340 (12.39%)	39 / 312 (12.50%)	25 / 223 (11.21%)	49 / 379 (12.93%)	12 / 115 (10.43%)	41 / 311 (13.18%)
MRI with contrast media	149 / 166 (89.76%)	35 / 39 (89.74%)	22 / 25 (88.00%)	45 / 49 (91.84%)	12 / 12 (100.00%)	35 / 41 (85.37%)
FU after 18 months	1279 (100.00%)	299 (100.00%)	217 (100.00%)	358 (100.00%)	106 (100.00%)	299 (100.00%)
MRI performed since last visit	141 / 1279 (11.02%)	34 / 299 (11.37%)	26 / 217 (11.98%)	42 / 358 (11.73%)	8 / 106 (7.55%)	31 / 299 (10.37%)
MRI with contrast media	122 / 141 (86.52%)	30 / 34 (88.24%)	24 / 26 (92.31%)	35 / 42 (83.33%)	6 / 8 (75.00%)	27 / 31 (87.10%)
FU after 21 months	1184 (100.00%)	269 (100.00%)	200 (100.00%)	338 (100.00%)	100 (100.00%)	277 (100.00%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N / Patient FAS (%)	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**	**N / Patient FAS (%)**
MRI performed since last visit	139 / 1184 (11.74%)	36 / 269 (13.38%)	15 / 200 (7.50%)	40 / 338 (11.83%)	7 / 100 (7.00%)	41 / 277 (14.80%)
MRI with contrast media	124 / 139 (89.21%)	32 / 36 (88.89%)	13 / 15 (86.67%)	35 / 40 (87.50%)	6 / 7 (85.71%)	38 / 41 (92.68%)
FU after 24 months	1114 (100.00%)	247 (100.00%)	197 (100.00%)	324 (100.00%)	92 (100.00%)	254 (100.00%)
MRI performed since last visit	137 / 1114 (12.30%)	24 / 247 (9.72%)	27 / 197 (13.71%)	42 / 324 (12.96%)	12 / 92 (13.04%)	32 / 254 (12.60%)
MRI with contrast media	124 / 137 (90.51%)	21 / 24 (87.50%)	25 / 27 (92.59%)	38 / 42 (90.48%)	11 / 12 (91.67%)	29 / 32 (90.63%)
Last Visit	1684 (100.00%)	391 (100.00%)	274 (100.00%)	479 (100.00%)	149 (100.00%)	391 (100.00%)
MRI performed since last visit	261 / 1684 (15.50%)	53 / 391 (13.55%)	40 / 274 (14.60%)	78 / 479 (16.28%)	26 / 149 (17.45%)	64 / 391 (16.37%)
MRI with contrast media	241 / 261 (92.34%)	47 / 53 (88.68%)	38 / 40 (95.00%)	71 / 78 (91.03%)	24 / 26 (92.31%)	61 / 64 (95.31%)

N = number of patients; % = percentage of patients
* For baseline visit parameter analyses “last MRI known”.
Source: Appendix, Table 9.4.1

MRIs were reported for 11% to 14% of patients at each visit, meaning that a MRI was performed between the respective visit and the previous visit. At the last visit, 15.50% of patients have had an MRI since the previous visit (Appendix, Table 9.4.1). The median time since the last MRI ranged from 41.5 days at the 6 month FU to 55.0 days at the last visit (Appendix, Table 9.4.2).

The number of lesions in T2 weighted scan is summarized in Table 9-17.

Table 9-17: Number of lesions in T2 weighted scan (Patients with performed MRI)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Baseline						
n	1548 (100.00%)	362 (100.00%)	250 (100.00%)	449 (100.00%)	129 (100.00%)	358 (100.00%)
Missing	826 (53.36%)	192 (53.04%)	118 (47.20%)	240 (53.45%)	69 (53.49%)	207 (57.82%)
None	18 (1.16%)	7 (1.93%)	3 (1.20%)	1 (0.22%)	0 (0.00%)	7 (1.96%)
1 to ≤2	75 (4.84%)	19 (5.25%)	18 (7.20%)	19 (4.23%)	4 (3.10%)	15 (4.19%)
3 to ≤9	284 (18.35%)	64 (17.68%)	50 (20.00%)	83 (18.49%)	26 (20.16%)	61 (17.04%)
>9	304 (19.64%)	72 (19.89%)	52 (20.80%)	90 (20.04%)	29 (22.48%)	61 (17.04%)
Multiple	41 (2.65%)	8 (2.21%)	9 (3.60%)	16 (3.56%)	1 (0.78%)	7 (1.96%)
12 months FU						
n	200 (100.00%)	41 (100.00%)	30 (100.00%)	59 (100.00%)	21 (100.00%)	49 (100.00%)
Missing	130 (65.00%)	24 (58.54%)	21 (70.00%)	36 (61.02%)	13 (61.90%)	36 (73.47%)
None	1 (0.50%)	0 (0.00%)	0 (0.00%)	1 (1.69%)	0 (0.00%)	0 (0.00%)
1 to ≤2	5 (2.50%)	2 (4.88%)	0 (0.00%)	1 (1.69%)	0 (0.00%)	2 (4.08%)
3 to ≤9	25 (12.50%)	6 (14.63%)	1 (3.33%)	10 (16.95%)	4 (19.05%)	4 (8.16%)
>9	26 (13.00%)	4 (9.76%)	7 (23.33%)	7 (11.86%)	4 (19.05%)	4 (8.16%)
Multiple	13 (6.50%)	5 (12.20%)	1 (3.33%)	4 (6.78%)	0 (0.00%)	3 (6.12%)
24 months FU						
n	137 (100.00%)	24 (100.00%)	27 (100.00%)	42 (100.00%)	12 (100.00%)	32 (100.00%)
Missing	85 (62.04%)	20 (83.33%)	17 (62.96%)	21 (50.00%)	7 (58.33%)	20 (62.50%)
None	1 (0.73%)	0 (0.00%)	0 (0.00%)	1 (2.38%)	0 (0.00%)	0 (0.00%)
1 to ≤2	4 (2.92%)	0 (0.00%)	1 (3.70%)	1 (2.38%)	0 (0.00%)	2 (6.25%)
3 to ≤9	16 (11.68%)	0 (0.00%)	1 (3.70%)	7 (16.67%)	4 (33.33%)	4 (12.50%)
>9	13 (9.49%)	2 (8.33%)	2 (7.41%)	7 (16.67%)	0 (0.00%)	2 (6.25%)
Multiple	18 (13.14%)	2 (8.33%)	6 (22.22%)	5 (11.90%)	1 (8.33%)	4 (12.50%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Last visit						
n	261 (100.00%)	53 (100.00%)	40 (100.00%)	78 (100.00%)	26 (100.00%)	64 (100.00%)
Missing	166 (63.60%)	36 (67.92%)	26 (65.00%)	46 (58.97%)	16 (61.54%)	42 (65.63%)
None	2 (0.77%)	0 (0.00 %)	0 (0.00%)	1 (1.28%)	0 (0.00%)	1 (1.56%)
1 to ≤2	7 (2.68%)	1 (1.89%)	1 (2.50%)	1 (1.28%)	0 (0.00%)	4 (6.25%)
3 to ≤9	32 (12.26%)	5 (9.43%)	1 (2.50%)	11 (14.10%)	8 (30.77%)	7 (10.94%)
>9	28 (10.73%)	5 (9.43%)	4 (10.00%)	13 (16.67%)	0 (0.00%)	6 (9.38%)
Multiple	26 (9.96%)	6 (11.32%)	8 (20.00%)	6 (7.69%)	2 (7.69%)	4 (6.25%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 9.6.1

Data on the number of lesions was missing in the MRI reports: missing data at baseline 53.36%, 12 months FU: 65.00%, 24 months FU: 62.04% last visit: 63.60%. The proportion of patients with > 9 lesions over the course of the study was as follows: baseline: 19.64%, 12 months FU: 13.00%, 24 months FU: 9.49%, last visit: 10.73%. The proportion of patients with 3 to ≤9 lesions over the course of the study was as follows: baseline: 18.35%, 12 months FU: 12.50%, 24 months FU: 11.68%, last visit: 12.26%. Multiple lesions were reported for 13.14% at 24 months FU and 9.96%at last visit.

A shift table of lesions in T2 weighted scan at initial visit versus last visit is provided in Appendix, Table 9.6.2.

Number of patients with gadolinium enhancing lesions is presented in Table 9-18.

Table 9-18: Number of patients with gadolinium enhancing lesions (Patients with performed MRI with contrast media)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline						
n	1370 (100.00%)	326 (100.00%)	219 (100.00%)	396 (100.00%)	108 (100.00%)	321 (100.00%)
Missing	118 (8.61%)	29 (8.90%)	22 (10.05%)	35 (8.84%)	8 (7.41%)	24 (7.48%)
Yes	449 (32.77%)	113 (34.66%)	65 (29.68%)	139 (35.10%)	37 (34.26%)	95 (29.60%)
No	803 (58.61%)	184 (56.44%)	132 (60.27%)	222 (56.06%)	63 (58.33%)	202 (62.93%)
12 months FU						
n	189 (100.00%)	39 (100.00%)	27 (100.00%)	54 (100.00%)	20 (100.00%)	49 (100.00%)
Missing	12 (6.35%)	2 (5.13%)	1 (3.70%)	4 (7.41%)	2 (10.00%)	3 (6.12%)
Yes	35 (18.52%)	5 (12.82%)	7 (25.93%)	10 (18.52%)	3 (15.00%)	10 (20.41%)
No	142 (75.13%)	32 (82.05%)	19 (70.37%)	40 (74.07%)	15 (75.00%)	36 (73.47%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
24 months FU						
n	124 (100.00%)	21 (100.00%)	25 (100.00%)	38 (100.00%)	11 (100.00%)	29 (100.00%)
Missing	8 (6.45%)	0 (0.00%)	3 (12.00%)	2 (5.26%)	2 (18.18%)	1 (3.45%)
Yes	20 (16.13%)	4 (19.05%)	3 (12.00%)	6 (15.79%)	1 (9.09%)	6 (20.69%)
No	96 (77.42%)	17 (80.95%)	19 (76.00%)	30 (78.95%)	8 (72.73%)	22 (75.86%)
Last visit						
n	241 (100.00%)	47 (100.00%)	38 (100.00%)	71 (100.00%)	24 (100.00%)	61 (100.00%)
Missing	17 (7.05%)	0 (0.00%)	4 (10.53%)	3 (4.23%)	4 (16.67%)	6 (9.84%)
Yes	64 (26.56%)	14 (29.79%)	7 (18.42%)	23 (32.39%)	5 (20.83%)	15 (24.59%)
No	160 (66.39%)	33 (70.21%)	27 (71.05%)	45 (63.38%)	15 (62.50%)	40 (65.57%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 9.5

Gadolinium enhancing lesions were present in 449 out of 1370 patients with performed MRI with contrast media (32.77%) at baseline, in 35 out of 189 patients (18.52%) at the 12 months FU, in 20 out of 124 patients (16.13%) at the 24 months FU, and in 64 out of 241 patients (26.56%) at last visit.

9.4.2.3 Expanded Disability Status Scale (EDSS)

The EDSS is a method of quantifying disability in MS using a score from 0.0 (normal neurological exam) to 10.0 (death due to MS).

The EDSS score throughout the observation period is given in Table 9-19.

Table 9-19: EDSS Score (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
Baseline						
n	1672	387	274	478	147	386
Mean (SD)	2.3 (1.52)	2.3 (1.41)	2.2 (1.48)	2.4 (1.51)	2.3 (1.53)	2.2 (1.65)
Median	2.0	2.0	2.0	2.0	2.0	2.0
FU after 6 months						
n	1545	369	259	426	131	360
Mean (SD)	2.4 (1.54)	2.4 (1.45)	2.3 (1.53)	2.4 (1.51)	2.5 (1.52)	2.3 (1.66)
Median	2.0	2.0	2.0	2.0	2.0	2.0
FU after 6 months - Difference to Baseline						
n	1526	363	258	420	129	356
Mean (SD)	0.1 (0.73)	0.1 (0.62)	0.1 (0.76)	0.1 (0.82)	0.2 (0.70)	0.1 (0.73)
Median	0.0	0.0	0.0	0.0	0.0	0.0

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
FU after 12 months						
n	1412	329	242	395	121	325
Mean (SD)	2.4 (1.60)	2.4 (1.51)	2.5 (1.67)	2.5 (1.57)	2.7 (1.62)	2.3 (1.67)
Median	2.0	2.0	2.0	2.0	2.0	2.0
FU after 12 months - Difference to Baseline						
n	1394	323	241	389	119	322
Mean (SD)	0.2 (0.81)	0.2 (0.74)	0.3 (0.78)	0.2 (0.78)	0.4 (0.88)	0.2 (0.89)
Median	0.0	0.0	0.0	0.0	0.0	0.0
FU after 18 months						
n	1264	299	214	355	102	294
Mean (SD)	2.5 (1.62)	2.4 (1.55)	2.5 (1.62)	2.5 (1.57)	2.7 (1.62)	2.4 (1.75)
Median	2.0	2.0	2.0	2.0	2.8	2.0
FU after 18 months - Difference to Baseline						
n	1249	294	213	350	99	293
Mean (SD)	0.2 (0.89)	0.2 (0.79)	0.3 (0.71)	0.2 (0.86)	0.3 (0.90)	0.3 (1.10)
Median	0.0	0.0	0.0	0.0	0.0	0.0
FU after 24 months						
n	1101	244	195	321	91	250
Mean (SD)	2.5 (1.62)	2.5 (1.61)	2.5 (1.67)	2.5 (1.58)	2.6 (1.60)	2.4 (1.67)
Median	2.0	2.0	2.0	2.0	2.0	2.0
FU after 24 months - Difference to Baseline						
n	1087	242	194	314	89	248
Mean (SD)	0.2 (0.82)	0.2 (0.79)	0.3 (0.72)	0.2 (0.88)	0.3 (0.80)	0.3 (0.87)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Last visit						
n	1565	369	263	434	133	366
Mean (SD)	2.5 (1.64)	2.5 (1.58)	2.4 (1.62)	2.5 (1.62)	2.7 (1.66)	2.5 (1.73)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Last visit - Difference to Baseline						
n	1538	363	262	423	130	360
Mean (SD)	0.3 (0.87)	0.3 (0.83)	0.2 (0.78)	0.2 (0.91)	0.4 (0.94)	0.3 (0.92)
Median	0.0	0.0	0.0	0.0	0.0	0.0

EDSS = Expanded Disability Status Scale; FU: follow-up (visit); n = number of patients; SD = standard deviation
To avoid overly long text tables, only n, mean (SD) and median are presented here.
Source: Appendix, Table 9.3.1.1

The mean EDSS score was 2.3 ± 1.52 at baseline (Avonex: 2.3 ± 1.41, Betaferon: 2.2 ± 1.48, Copaxone: 2.4 ± 1.51, Extavia: 2.3 ± 1.53, Rebif: 2.2 ± 1.65; median 2.0) and 2.5 ± 1.64 at the last visit with possible EDSS assessment (Avonex: 2.5 ± 1.58, Betaferon: 2.4 ± 1.62,

Copaxone: 2.5 ± 1.62, Extavia: 2.7 ± 1.66, Rebif: 2.5 ± 1.73; median 2.0). The mean difference from baseline to the last visit with possible EDSS assessment was 0.3 ± 0.87(Avonex: 0.3 ± 0.83, Betaferon: 0.2 ± 0.78, Copaxone: 0.2 ± 0.91, Extavia: 0.4 ± 0.94, Rebif: 0.3 ± 0.92).

The proportion of patients by EDSS score were as follows: ≤1.5 (baseline: 38.36%, last visit: 30.57%), >1.5 to ≤2.5 (baseline: 24.93%, last visit 24.47%) and >2.5 to ≤3.5 (baseline: 17.65%, last visit: 18.36%). The proportion of patients receiving Extavia by EDSS score were: >1.5 to ≤2.5 (29.20%), ≤1.5 (22.63%) and >2.5 to ≤3.5 (20.44%) at last visit (Appendix, Table 9.3.2.1).

A shift table of total EDSS from baseline to last visit is provided in Appendix, Table 9.3.4.

9.4.2.4 Clinical Global Impression (CGI)

The CGI severity is rated on a 7-point scale using a range of responses from “normal, not at all ill” to “extremely ill”.

The proportions of patients who were reported to be “mildly ill” were: baseline 31.44% and last visit 30.23%. The proportions of patients reported to be “moderately ill” were: baseline25.34% and last visit 28.80% (Appendix, Table 9.1.1).

The CGI improvement is rated on a 7-point scale using a range of responses from “very much improved” to “very much worse”. The CGI improvement at last visit is presented in Table 9-20.

Table 9-20: CGI improvement scale at last visit (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	1684 (100.00%)	391 (100.00%)	274 (100.00%)	479 (100.00%)	149 (100.00%)	391 (100.00%)
Missing	30 (1.78%)	6 (1.53%)	8 (2.92%)	9 (1.88%)	5 (3.36%)	2 (0.51%)
Cannot be evaluated	2 (0.12%)	0 (0.00%)	1 (0.36%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Very much improved	2 (0.12%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.67%)	1 (0.26%)
Much improved	25 (1.48%)	5 (1.28%)	5 (1.82%)	9 (1.88%)	2 (1.34%)	4 (1.02%)
Minimally improved	72 (4.28%)	21 (5.37%)	14 (5.11%)	10 (2.09%)	10 (6.71%)	17 (4.35%)
No change	1300 (77.20%)	302 (77.24%)	214 (78.10%)	372 (77.66%)	105 (70.47%)	307 (78.52%)
Minimally worse	233 (13.84%)	50 (12.79%)	30 (10.95%)	71 (14.82%)	23 (15.44%)	59 (15.09%)
Much worse	18 (1.07%)	7 (1.79%)	2 (0.73%)	6 (1.25%)	2 (1.34%)	1 (0.26%)
Very much worse	2 (0.12%)	0 (0.00%)	0 (0.00%)	2 (0.42%)	0 (0.00%)	0 (0.00%)

N = number of patients; % = percentage of patients; CGI = Clinical global impression
Source: Appendix, Table 9.2.1

Overall, 77.20% showed “no change” of CGI at last visit. A total of 13.84% of patients were “minimally worse” and 4.28% of patients “minimally improved”.

9.4.2.5 Assessment of effectiveness

The assessment of effectiveness by physicians and patients is presented in Table 9-21.

Table 9-21: Assessment of effectiveness at last visit (FU after 24 months or discontinuation visit) (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Physician's assessment						
n	1458 (100.00%)	328 (100.00%)	249 (100.00%)	420 (100.00%)	128 (100.00%)	333 (100.00%)
Missing	54 (3.70%)	10 (3.05%)	10 (4.02%)	13 (3.10%)	8 (6.25%)	13 (3.90%)
Very good	506 (34.71%)	99 (30.18%)	95 (38.15%)	149 (35.48%)	43 (33.59%)	120 (36.04%)
Good	667 (45.75%)	163 (49.70%)	117 (46.99%)	187 (44.52%)	58 (45.31%)	142 (42.64%)
Satisfactory	108 (7.41%)	27 (8.23%)	10 (4.02%)	34 (8.10%)	9 (7.03%)	28 (8.41%)
Insufficient	123 (8.44%)	29 (8.84%)	17 (6.83%)	37 (8.81%)	10 (7.81%)	30 (9.01%)

		Type of First-line disease modifying therapy at Baseline				
	Overall	Avonex	Betaferon	Copaxone	Extavia	Rebif
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Patient's assessment						
n	1458 (100.00%)	328 (100.00%)	249 (100.00%)	420 (100.00%)	128 (100.00%)	333 (100.00%)
Missing	81 (5.56%)	14 (4.27%)	15 (6.02%)	24 (5.71%)	9 (7.03%)	19 (5.71%)
Very good	427 (29.29%)	82 (25.00%)	75 (30.12%)	129 (30.71%)	43 (33.59%)	98 (29.43%)
Good	653 (44.79%)	158 (48.17%)	118 (47.39%)	180 (42.86%)	56 (43.75%)	141 (42.34%)
Satisfactory	156 (10.70%)	39 (11.89%)	20 (8.03%)	46 (10.95%)	7 (5.47%)	44 (13.21%)
Insufficient	141 (9.67%)	35 (10.67%)	21 (8.43%)	41 (9.76%)	13 (10.16%)	31 (9.31%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 9.7.1 and Table 9.8.1

Physicians rated the effectiveness at last visit (FU after 24 months or discontinuation visit) as “good” (overall: 45.75%, Avonex: 49.70%, Betaferon: 46.99%, Copaxone: 44.52%, Extavia: 45.31%, Rebif: 42.64%) or “very good” (overall: 34.71%, Avonex: 30.18%, Betaferon: 38.15%, Copaxone: 35.48%, Extavia: 33.59%, Rebif: 36.04%). At the 24 month FU the overall ratings were 48.83% (good) and 41.65% (very good), while at the discontinuation visit, effectiveness was rated as “good” (35.76%) or “insufficient” (28.78%) (Appendix, Table 9.7.1).

Patient’s assessment of effectiveness at last visit (24 month FU or discontinuation visit) was “good” (overall: 44.79%, Avonex: 48.17%, Betaferon: 47.39%, Copaxone: 42.86%, Extavia: 43.75%, Rebif: 42.34%) or “very good” (overall: 29.29%, Avonex: 25.00%, Betaferon: 30.12%, Copaxone: 30.71%, Extavia: 33.59%, Rebif: 29.43%). The percentages at the 24 month FU were 50.27% (good) and 35.64% (very good), while at the discontinuation visit, effectiveness was rated as “insufficient” (33.43%) or “good” (27.03%) (Appendix, Table 9.8.1).

9.4.3 Patient reported effectiveness results

The patient questionnaires were collected at certain predefined visits. For calculation of the last visit, data were used from the last visit with filled out questionnaires.

9.4.3.1 Treatment satisfaction - TSQM-9 questionnaire

This abbreviated 9-item questionnaire measured the patient’s satisfaction with the treatment. on 7-point- or 5-point scales with 1 being the most negative answer. The TSQM-9 score is the sum of all single TSQM-9 question ranging between 7 (low satisfaction) and 59 (high satisfaction). The TSQM-9 questionnaire was provided at start of observation and subsequently every 3 months and was filled out at any visit by 1699 out of 1705 patients in total. For the majority of patients the TSQM-9 questionnaires were available at all FU visits (Appendix, Table Sub 6.0).

An overview on the results of the TSQM-9 questionnaire is given in Table 9-22.

Table 9-22: Overview TSQM-9 questionnaire (N=1699)

	Baseline					12 months FU				
	n	Missing value	Mean	SD	Median	n	Missing value	Mean	SD	Median
Satisfaction with prevention or treatment [1]	1667	22	5.6	1.34	6.0	1369	22	5.5	1.28	6.0
Satisfaction with symptoms relief [1]	1624	65	5.3	1.46	5.0	1360	31	5.3	1.30	5.0
Satisfaction with time to start working [1]	1548	141	5.2	1.41	5.0	1321	70	5.3	1.25	5.0
Difficulty to use [2]	1671	18	5.1	1.37	5.0	1374	17	5.2	1.37	5.0
Difficulty to plan when to use [2]	1679	10	5.8	1.13	6.0	1372	19	5.7	1.12	6.0
Convenience to take the medication [3]	1675	14	5.3	1.29	5.0	1373	18	5.3	1.28	5.0
Confidence that medication is a good thing [4]	1676	13	4.2	0.81	4.0	1372	19	4.2	0.84	4.0
Good things about medication outweigh bad things [5]	1668	21	4.0	0.88	4.0	1371	20	4.0	0.84	4.0
Overall satisfaction with medication [1]	1677	12	5.6	1.12	6.0	1373	18	5.5	1.11	6.0
	24 months FU					Last visit				
	n	Missing value	Mean	SD	Median	n	Missing value	Mean	SD	Median
Satisfaction with prevention or treatment [1]	1080	15	5.6	1.21	6.0	1616	52	5.4	1.35	6.0
Satisfaction with symptoms relief [1]	1073	22	5.4	1.24	6.0	1604	64	5.2	1.37	5.0
Satisfaction with time to start working [1]	1048	47	5.4	1.17	5.0	1557	111	5.2	1.30	5.0
Difficulty to use [2]	1079	16	5.3	1.30	5.0	1619	49	5.3	1.34	5.0
Difficulty to plan when to use [2]	1081	14	5.7	1.10	6.0	1619	49	5.6	1.15	6.0
Convenience to take the medication [3]	1081	14	5.3	1.24	5.0	1621	47	5.3	1.28	5.0
Confidence that medication is a good thing [4]	1079	16	4.1	0.83	4.0	1620	48	4.0	0.93	4.0
Good things about medication outweigh bad things [5]	1082	13	4.0	0.83	4.0	1621	47	3.9	0.93	4.0
Overall satisfaction with medication [1]	1081	14	5.5	1.10	6.0	1618	50	5.3	1.25	5.0

n = number of patients; SD = standard deviation
[1] 7-point-scale from 1: extremely dissatisfied to 7: extremely satisfied
[2] 7-point-scale from 1: extremely difficult to 7: extremely simple
[3] 7-point-scale from 1: extremely difficult and inconvenient to 7: extremely simple and convenient
[4] 5-point-scale from 1: not at all confident to 5: very confident
[5] 5-point-scale from 1: not at all certain to 5: very certain.
Source: Appendix, Table Practice 6.1.1, 6.2.1, 6.3.1, 6.4.1, 6.5.1, 6.6.1, 6.7.1, 6.8.1, 6.9.1

Overall, patients were satisfied with:

- the ability of the medication to prevent or treat the condition (baseline: extremely satisfied 31.20%, satisfied 26.05%, very satisfied 25.10%; last visit: very satisfied 30.82%, satisfied 25.72%, extremely satisfied 20.62%; Appendix, Table Sub 6.1.2),
- the symptoms relief (baseline: satisfied 25.81%, extremely satisfied 24.22%, very satisfied 22.20%; last visit: very satisfied 27.58%, satisfied 26.44%, extremely satisfied 16.97%; Appendix, Table Sub 6.2.2),
- the time it took the MS medication to start working (baseline: satisfied 29.66%, extremely satisfied 20.54%, very satisfied 18.83%; last visit: satisfied 31.06%, very satisfied 25.36%; Appendix, Table Sub 6.3.2), and
- the medication overall (baseline: satisfied 30.37%, very satisfied 27.29%, extremely satisfied 24.75%); last visit: satisfied 29.02%, very satisfied 29.44%; Appendix, Table Sub 6.9.2).

At baseline, patients documented that the MS medication was somewhat difficult (27.29%) or simple to use (24.33%) overall and for most of the first-line DMT groups. Rebif was rated as extremely simple to use (29.92%) or simple (25.58%). At the last visit, the difficulty to use the MS medication was rated as simple (25.18%) and very simple (24.34%; Appendix, Table Sub 6.4.2).

Overall, patients rated the difficulty planning to use the MS medication each time as simple (baseline: extremely simple 33.98%, simple 28.18%, very simple 23.74%; last visit: simple 28.78%, extremely simple 26.26%, very simple 25.72%; Appendix, Table Sub 6.5.2).

Overall, the convenience to take the medication as instructed was assessed as simple and convenient (baseline: simple and convenient 26.41%, extremely simple and convenient 23.62%, somewhat difficult and inconvenient 23.15%; last visit: simple and convenient 26.62%, very simple and convenient 23.56%, somewhat difficult and inconvenient 22.36%). At baseline, patients receiving Betaferon (30.74%) or Extavia (31.76%) rated the convenience as simple and convenient and patients receiving Rebif as extremely simple and convenient (32.99%). At the last visit, patients receiving Avonex or Extavia rated the convenience as simple and convenient (Avonex: 26.92%, Extavia: 29.45%) or somewhat difficult and inconvenient (Avonex: 25.64%, Extavia: 25.34%), patients receiving Betaferon (32.35%) or Copaxone (28.18%) as simple and convenient, and patients receiving Rebif very simple and convenient (27.58%) and extremely simple and convenient (24.48%; Appendix, Table Sub 6.6.2).

Patients were confident (baseline: 39.73%, last visit: 42.03%) or very confident (baseline: 41.74%, last visit: 31.95%) that taking the medication was a good thing (Appendix, Table Sub 6.7.2).

Patients at baseline and last visit were certain (baseline: 43.04%, last visit: 46.40%) or very certain (baseline: 31.62%, last visit: 25.90%) that the good things about the medication outweighed the bad things (Appendix, Table Sub 6.8.2).

At baseline, the mean TSQM-9 score was 46.3 ± 7.47 (median 46.0) and at last visit the mean TSQM-9 score was 45.2 ± 8.34 (median 46.0; Appendix, Table Sub 6.10.1). The mean difference from last visit to baseline was -1.1 ± 7.38 (Appendix, Table Sub 6.10.2).

9.4.3.2 Neurological Disability - UK NDS questionnaire

The UK NDS questionnaire, assessing different fields of neurological disability, was filled out at start of observation and every 12 months. The questionnaire assesses neurological functions in 13 areas. Questions were presented as yes/no questions. Depending on the answers several sub-questions were posed. Each/question or sub-question was attributed a score of 1 or 0, from which the overall 13 subscores were calculated. For all subscores scales were used ranging from 0 (normal status) to 5 (total loss of function), with the exception of the cognition subscale ranging from 0 to 3. A total score was calculated from the individual subscores ranging from 0 to 63.

At any visit, the UK NDS questionnaire was filled out by 1696 out of 1705 patients (Appendix, Table Sub 1.0).

The UK NDS questionnaire scores at baseline and last visit are summarized in Table 9-23.

Table 9-23: Overview UK NDS questionnaire (N=1696)

	Baseline					Last visit				
UK NDS Score	**n**	**Missing value**	**Mean**	**SD**	**Median**	**n**	**Missing value**	**Mean**	**SD**	**Median**
Cognition score	1663	26	0.7	0.91	0.0	1401	19	0.6	0.87	0.0
Mood score	1616	73	1.1	1.31	1.0	1328	92	0.8	1.17	0.0
Visus score	1569	30	0.3	0.57	0.0	1406	14	0.2	0.56	0.0
Communication score	1661	28	0.5	0.95	0.0	1391	29	0.4	0.86	0.0
Swallowing score	1661	28	0.1	0.38	0.0	1403	17	0.1	0.34	0.0
Arm score*	1442	247	0.5	0.90	0.0	1240	180	0.4	0.85	0.0
Leg score	1669	20	0.6	0.87	0.0	1397	23	0.6	0.91	0.0
Bladder score	1638	51	0.7	1.29	0.0	1378	42	0.6	1.24	0.0
Bowel score	1605	84	0.3	1.02	0.0	1356	64	0.3	0.92	0.0
Fatigue score	1643	46	1.9	1.40	2.0	1359	61	1.5	1.36	1.0
Sex score	1648	41	0.7	1.46	0.0	1391	29	0.6	1.35	0.0
Pain score	1639	50	0.7	1.22	0.0	1357	63	0.6	1.07	0.0
Other problems score	1606	83	0.8	1.21	0.0	1348	72	0.5	1.04	0.0
Total score	1150	539	8.1	7.30	6.0	963	457	6.2	6.65	4.0

n = number of patients; SD = standard deviation
*For calculation of the arm score, all of several pre-defined questions had to be answered. For the other scores a consecutive calculation was used. Therefore, the number of patients with calculated arm score was lower than for the other sub-scores, due to missing values in some of the respective questions.
Cognition sub-score ranges from 0 to 3, all other sub-scores range from 0 (normal status) to 5 (total loss of function).
Total score sums all sub-scores and ranges from 0 to 63.
Source: Appendix, Table Sub 1.1

The mean total score was 8.1 ± 7.30 (median 6.0) at baseline and 6.2 ± 6.65 (median 4.0) at last visit (Appendix, Table Sub 1.1). Individual mean sub-scores ranged from 0.1 ± 0.38 (swallowing score) to 1.9 ± 1.40 (fatigue score) at baseline and from 0.1 ± 0.34 (swallowing score) to 1.5 ± 1.36 (fatigue score) at last visit. The median mood score at baseline was 1.0, the median fatigue score was 2.0 at baseline and 1.0 at last visit. All other median sub-scores were 0.0.

Overall, the mean difference from last visit to baseline for the total score was -1.2 ± 4.95. The mean difference from last visit to baseline for swallowing score was 0.0 ± 0.35 and for fatigue score: -0.3 ± 1.31 (Appendix, Table Sub 1.2).

9.4.3.3 HrQoL - EQ-5D questionnaire

The EQ-5D is a HrQoL assessment covering the areas mobility, self-care, usual activities, pain / discomfort and anxiety / depression and was to be recorded at start of observation and every 6 months. The EQ-5D questionnaire consists of 2 parts - the EQ-5D descriptive system and the EQ-5D visual analogue scale (VAS). All 5 areas assessed by the EQ-5D have 3 levels: no problems, some problems, extreme problems. The EQ-5D VAS records the patient´s self-rated health on a scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state).

The EQ-5D questionnaire was filled out by 1697 out of 1705 patients at any visit. For the vast majority of patients EQ-5D questionnaires were available at all FU visits at which data were collected (Appendix, Table Sub 2.0).

At baseline, patients reported to have no problems in walking around (68.68%), with self-care (95.68%), or with performing usual activities (64.95%). About half of the patients had no pain or discomfort (49.85%), the other half had moderate pain or discomfort (46.54%). The state of health compared to 12 months ago had remained roughly the same for 66,55%. For Extavia, the percentage of patients with moderate pain or discomfort was 52.03% and the percentage of patients with no pain or discomfort was 42.57%. About half of the patients were not anxious or depressed (54.94%), while to other half was moderately anxious or depressed (41.86%; Appendix, Table Sub 2.1).

The mean current health state on the VAS ranging from 0 (worst) to 100 (best imaginable health state) was 71.5 ± 18.63 (median 75.0) at baseline. The state of health in patients with Betaferon therapy at baseline was 73.2 ± 18.35 (median 80.0) and 68.9 ± 19.28 (median 70.0) for patients with Extavia and 69.8 ± 18.64 (median 70.0).

At the last visit, about half of the patients had no pain or discomfort (53.99%) and the other half had moderate pain or discomfort (42.84%). Two-third of patients were not anxious or depressed (60.01%) and the state of health compared to 12 months ago had remained roughly the same for 71.17%. At the last visit, the mean current health state on the VAS was 71.0 ± 18.72 (median 74.0) and 71.5 ± 18.63 (median 75.0) at baseline.

9.4.3.4 HrQoL - PRIMUS questionnaire

The PRIMUS is a questionnaire assessing QoL and activity in MS patients. The PRIMUS QoL questionnaire consisted of 45 questions, which could be answered with “true” (score 1) or “not true” (score 0). The questions were presented in a way that a “true” answer indicated

an effect of the disease on the patient´s QoL. A sum score across all questions was calculated if all questions were answered.

The PRIMUS activity questionnaire consisted of 19 questions regarding daily activities with the answers “could be done by oneself without difficulties” (score 0), “could be done by oneself with difficulties” (score 1) and “could not be done by oneself” (score 2). A sum score across all questions was calculated if all questions were answered.

PRIMUS activity and QoL questionnaires were recorded at start of observation and every 6 months.

The PRIMUS questionnaire was filled out at any visit by 1697 out of 1705 patients in total. For the vast majority of patients the PRIMUS activity and QoL questionnaires were available at all FU visits at which data were collected (Appendix, Table Sub 3.0 and Sub 4.0).

The mean PRIMUS QoL Score was 8.4 ± 8.76 (median 5.0) at baseline and 7.4 ± 8.92 (median 4.0) at the last visit (Appendix, Table Sub 3.1.1). The mean difference from last visit to baseline was -0.9 ± 6.22 (median 0.0; Appendix, Table Sub 3.1.2).

The mean PRIMUS activity score was 4.2 ± 5.16 (median 3.0) at baseline and 4.5 ± 5.77 (median 3.0) at the last visit with possible PRIMUS QoL assessment (Appendix, Table Sub 4.1.1). The mean difference from last visit to baseline was 0.4 ± 3.25 (median 0.0; Appendix, Table Sub 4.1.2).

9.4.3.5 Patient compliance - Compliance questionnaire

The patient questionnaire regarding compliance was to be filled out at start of observation and subsequently every 3 months.

The compliance questionnaire was provided every 3 months and was filled out at any visit by 1699 patients in total. For the majority of patients the compliance questionnaires were available at all FU visits (Appendix, Table Sub 5.0).

At baseline, 83.71% of patients stated that they did not occasionally forget to take the MS medication. At the last visit, the proportion of patients was 81.22%. The medication was used always at the same time by 79.80% of the patients (Appendix, Table Sub 5.1).

The majority of patients regularly took the MS medication. Only few had occasional abstinence, when feeling good (3.61%) or when feeling bad (5.81%).

A total of 11.73% of patients reported the existence of typical situations for non-use of MS medication. The mean number of days without medication in the last two weeks was 0.4 ± 1.23 days.

The mean number of days without medication in the last two weeks was 0.4 ± 1.23 before baseline and 1.6 ± 3.24 before the last visit.

9.4.4 Practice questionnaire

A total of 167 practice questionnaires were documented. MS patients amounted to a mean of 17.5 ± 21.31% of patients (median 10.0%) in their practice (Appendix, Table Practice 1).

On average, the physicians saw 157.6 ± 155.60 MS patients (median 100.0 MS patients) per quarter (Appendix, Table Practice 2). The mean percentage of MS patients receiving first-line DMTs was 64.3 ± 21.08% (median 70.0%; Appendix, Table Practice 3).

Staff, available at the study sites for the treatment of MS, included doctor's assistant (91.62%), nurse/ MS nurse (62.87%) and neuropsychologist/ psychologist (23.35%; multiple response; Appendix, Table Practice 4).

The physicians cooperated with physiotherapists (95.21%), other specialists (87.43%), general practitioners (83.83%), and occupational therapists/ ergotherapists (82.63%; multiple response; Appendix, Table Practice 5).

The median time, physicians spent for diagnosis of MS patients was 45.0 min, the median time for therapy initiation was 30.0 min, the median time spent for FU examinations was 20.0 min and the median time spent for advice was 20.0 min (Appendix, Table Practice 6).

For study nurses, the median time spent for diagnosis of MS patients was 30.0 min, the median time for therapy initiation was 35.0 min, the median time spent for FU examinations was 15.0 min and the median time spent for advice was 15.0 min (Appendix, Table Practice 7).

The decision for prescription of first-line DMT was made by the physician (100.0%), the patient (95.21%), by family/partner/friend of the patient (41.92%), and the nurse/ doctor's assistant (18.56%; multiple response; Appendix, Table Practice 8).

For the physicians, the most important topics about MS therapy in dialogue with the patients included side effects (90.42%), effectiveness regarding relapse rates (85.03%), effectiveness regarding disease progression (79.04%), and the possibility of self-application (64.07%; multiple response; Appendix, Table Practice 9).

The physicians documented that on average 81.8 ± 13.48% of patients (median 85.0%) displayed perfect compliance with therapy (Appendix, Table Practice 10).

Influence factors on patients' therapy compliance were assessed on a scale ranging from 1 (slight influence) to 5 (strong influence). The influence factors on patients' therapy compliance are presented in Table 9-24.

Table 9-24: Influence factors on patients' therapy compliance – Overview (N=167)

	n	Missing value	Mean	SD	Median
Cutaneous side effects	165	2	3.6	0.87	4.0
Difficulties with application	165	2	3.6	0.97	4.0
Fatigue	164	3	3.0	1.10	3.0
Influenza-like symptoms	163	4	3.6	0.98	4.0
Frequency of injections	165	2	3.0	1.04	3.0
Holidays	165	2	1.9	0.90	2.0
Lifestyle (business trips, leisure activities)	165	2	2.5	0.96	2.0
Occurrence of new relapses	165	2	4.0	1.07	4.0
Pain at injection	165	2	3.9	0.84	4.0
Services of pharmaceutical company	164	3	2.7	0.95	3.0
Personal motivation of patient	165	2	4.6	0.66	5.0

n = number of patients; SD = standard deviation
Note: scale from 1: slight influence to 5: strong influence
Source: Appendix, Table Practice 11.1

The factor with the highest influence on patient's compliance was personal motivation of the patient (mean 4.6 ± 0.66; median 5.0), followed by occurrence of new relapses (mean 4.0 ± 1.07; median 4.0), pain at injection (mean 3.9 ± 0.84; median 4.0), cutaneous side effects (mean 3.6 ± 0.87; median 4.0), difficulties with application (mean 3.6 ± 0.97; median 4.0), and influenza-like symptoms (mean 3.6 ± 0.98; median 4.0).

Physicians considered the following parameters to influence the patient's compliance:

- occurrence of new relapses (5: 35.33%, 4: 39.52%)
- personal motivation of patient (5: 65.27%, 4: 26.35%)
- pain at injection (5: 20.36%, 4: 52.69%)
- cutaneous side effects (5: 11.98%, 4: 50.30%%),
- difficulties with application (5: 13.17%, 4: 46.11%),
- fatigue (4: 29.34%, 3: 32.93%) and
- influenza-like symptoms (5: 16.17%, 4: 43.71%, 3: 23.35%)

Factors with slight influence on the patient's compliance were lifestyle (1: 10.18%, 2: 44.91%) and holidays (2: 39.52%, 1: 40.12%) (Appendix, Table Practice 11.2.

On average, physicians were satisfied with the treatment situation of MS patients assessed on a scale rating from 1 = very dissatisfied to 5 = very satisfied (mean 3.4 ± 0.73; median 3.0), the therapy options for MS patients (mean 3.2 ± 0.72; median 3.0), the care for MS patients (mean 3.4 ± 0.84; median 3.0), and the cooperation with other professional groups for MS (mean 3.3 ± 0.87; median 3.0; Appendix, Table Practice 12.1).

The satisfaction with specific treatment situations for MS patients in categories is provided in Appendix, Table Practice 12.2.

9.5 Other analyses

9.5.1 Subgroup analysis by therapy switch

9.5.1.1 EDSS

For patients with therapy switch, the EDSS score at the last visit with possible EDSS assessment was 2.8 ± 1.61 and 2.5 ± 1.64 for patients without therapy switch (Appendix, Table 9.3.1.2). The mean difference in EDSS score from last visit to baseline was 0.2 ± 0.84 for patients without and 0.4 ± 1.03 for patients with therapy switch (median 0.0 for both groups; Appendix, Table 9.3.3.2).

The proportions by EDSS category at last visit were: ≤1.5 (32.36% and 21.46%), >1.5 to ≤2.5 (24.23% and 25.67%) and >2.5 to ≤3.5 (17.38% and 23.37%) in patients without therapy switch and in patients with therapy switch, respectively (Appendix, Table 9.3.2.2).

9.5.1.2 CGI

The proportion of patients in the CGI categories were: mildly ill up to 33.33% and 33.63% and moderately ill up to 37.75% and 28.09% in patients with treatment switch and patients without treatment switch, respectively. (Appendix, Table 9.1.2).

The CGI improvement scale at last visit by therapy switch is presented in Table 9-25.

Table 9-25: CGI improvement scale at last visit by therapy switch (N=1705)

	Therapy switch during documentation		
	Overall	No	Yes
	N (%)	N (%)	N (%)
Patients (FAS)	1684 (100.00%)	1405 (100.00%)	279 (100.00%)
Missing	30 (1.78%)	22 (1.57%)	8 (2.87%)
Cannot be evaluated	2 (0.12%)	2 (0.14%)	0 (0.00%)
Very much improved	2 (0.12%)	2 (0.14%)	0 (0.00%)
Much improved	25 (1.48%)	19 (1.35%)	6 (2.15%)
Minimally improved	72 (4.28%)	56 (3.99%)	16 (5.73%)
No change	1300 (77.20%)	1144 (81.42%)	156 (55.91%)
Minimally worse	233 (13.84%)	153 (10.89%)	80 (28.67%)
Much worse	18 (1.07%)	7 (0.50%)	11 (3.94%)
Very much worse	2 (0.12%)	0 (0.00%)	2 (0.72%)

N = number of patients; % = percentage of patients; CGI = Clinical global impression
Source: Appendix, Table 9.2.2

CGI improvement scale showed no change in 81.42% patients without therapy switch and in 55.91% patients with therapy switch. About one third (28.67%) of patients with therapy switch and 10.89% of patients without therapy switch had a “minimally worse” CGI at last visit.

9.5.1.3 Assessment of effectiveness

Physicians rated the effectiveness at the last visit as very good (38.16% and 18.00%) and good (48.59% and 32.00%) for patients without therapy switch and patients with therapy switch, respectively. For about a third of patients (29.20%) with therapy switch physicians rated the effectiveness at the last visit as “insufficient”, while 4.14% of patients without therapy switch had a rating of “insufficient” (Appendix, Table 9.7.2).

Patients without a treatment switch rated the effectiveness as very good (32.62%) or good (48.43%). A total of 35.20% of patients with therapy switch rated the effectiveness at the last visit as “insufficient” (Appendix, Table 9.8.2).

9.6 Adverse events and adverse reactions

9.6.1 Explanation of definitions

The terms AEs and SAEs as used in Section 2.5 describe AEs regardless of their relationship to study drug. For the purpose of the statistical analysis, events were further distinguished according to their relationship to study drug. Using a conservative approach, all events with missing causality assessments or causality assessments of “not assessable” were classified as adverse drug reactions (causality suspected).

Based on this, the following categories were used:

- nsAE (no caus.): non-serious AE, causality with regard to study drug: none or improbable
- nsADR: non-serious adverse drug reaction, causality with regard to study drug: certain, probable, possible, not assessable, missing
- SAE (no caus.): serious AE, causality with regard to study drug: none or improbable
- SADR: serious adverse drug reaction, causality with regard to study drug: certain, probable, possible, not assessable, missing

AEs were summarized using the MedDRA coding system. Incidence rates for specific events were calculated as the number of specific events reported divided by the number of patients at risk, where the number of specific events was defined as the number of patients reporting the specific event and the number at risk was defined as all patients included in the safety analysis. For multiple occurrences of a specific event within one patient, the event was counted only once for patient based analyses.

In this study, AEs were to be documented from baseline examination to end of observation and, in case of premature discontinuation of the first-line DMT, up to 60 days after last administration. Beyond that, AEs were only documented in case of (possible) relation to the first-line DMT.

9.6.2 Overall results

During this study, a total of 1165 AEs were documented in 506 of 1705 patients (29.68%) (Appendix, Tables 10.3 and 10.6).

Table 9-26 provides a summary of the AEs based on patients and on events.

Table 9-26: Incidences of adverse events – patient-based and event-based (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Patients	**1705 (100.00%)**	**395 (100.00%)**	**275 (100.00%)**	**491 (100.00%)**	**151 (100.00%)**	**393 (100.00%)**
Any AEs	506 (29.68%)	107 (27.09%)	88 (32.00%)	158 (32.18%)	45 (29.80%)	108 (27.48%)
nsAE	300 (17.60%)	63 (15.95%)	53 (19.27%)	95 (19.35%)	24 (15.89%)	65 (16.54%)
SAE	70 (4.11%)	13 (3.29%)	13 (4.73%)	23 (4.68%)	7 (4.64%)	14 (3.56%)
nsADR	240 (14.08%)	55 (13.92%)	42 (15.27%)	68 (13.85%)	22 (14.57%)	53 (13.49%)
SADR	31 (1.82%)	7 (1.77%)	5 (1.82%)	10 (2.04%)	6 (3.97%)	3 (0.76%)
Events	**1165 (100.00%)**	**232 (100.00%)**	**196 (100.00%)**	**384 (100.00%)**	**123 (100.00%)**	**230 (100.00%)**
nsAE	573 (49.18%)	113 (48.71%)	106 (54.08%)	190 (49.48%)	43 (34.96%)	121 (52.61%)
SAE	106 (9.10%)	16 (6.90%)	18 (9.18%)	34 (8.85%)	20 (16.26%)	18 (7.83%)
nsADR	442 (37.94%)	96 (41.38%)	65 (33.16%)	144 (37.50%)	49 (39.84%)	88 (38.26%)
SADR	44 (3.78%)	7 (3.02%)	7 (3.57%)	16 (4.17%)	11 (8.94%)	3 (1.30%)

N = number of AEs/patients; % = percentage of AEs/patients
Source: Appendix, Table 10.3 and Table 10.6

In 300 patients (overall: 17.60%; Avonex: 15.95%, Betaferon: 19.27%, Copaxone: 19.35%, Extavia: 15.89%, Rebif: 16.54%), a nsAE (no caus.) was reported. An nsADR was documented in 240 patients (overall: 14.08%; Avonex: 13.92%, Betaferon: 15.27%, Copaxone: 13.85%, Extavia: 14.57%, Rebif: 13.49%). A total of 70 patients (overall: 4.11%; Avonex: 3.29%, Betaferon: 4.73%, Copaxone: 4.68%, Extavia: 4.64%, Rebif: 3.56%) had an SAE and for 31 patients (overall: 1.82%; Avonex: 1.77%, Betaferon: 1.82%, Copaxone: 2.04%, Extavia: 3.97%, Rebif: 0.76%) at least one event met the criteria for a SADR.

The AE incidences per patient year are given in Table 9-27.

Table 9-27: Adverse event incidences per patient year (N=1705)

	All	**nsAE**	**SAE**	**nsADR**	**SADR**
Total	0.17370	0.10299	0.02403	0.08239	0.01064
Avonex	0.15966	0.09401	0.01940	0.08207	0.01045
Betaferon	0.17721	0.10673	0.02618	0.08458	0.01007
Copaxone	0.19092	0.11480	0.02779	0.08217	0.01208
Extavia	0.17655	0.09416	0.02746	0.08631	0.02354
Rebif	0.16269	0.09791	0.02109	0.07984	0.00452

Note: Multiple events with the same PT are only counted once per patient.
Source: Appendix, Table 10.10

The AE incidence per patient year was 0.17370 overall, 0.10299 for nsAEs, 0.02403 for SAEs, 0.08239 for nsADRs, and 0.01064 for SADRs. Overall, Copaxone had the highest incidence rate of AEs per patient year (0.19092) compared to the IFN-beta products (Avonex: 0.15966, Betaferon: 0.17721, Extavia: 0.17655, Rebif: 0.16269). In the Extavia group, The

incidence of SADRs by treatment were: Avonex: 0.01045, Betaferon: 0.01007, Copaxone 0.01208, Extavia 0.02354 and Rebif 0.00452.

Several patients had combinations of AEs, i.e. multiple events, which were classified differently (e.g. a patient could have both an nsAE [no caus.] and an SADR [caus.] or an nsAE and an nsADR). Combinations of events were documented for 121 patients; a summary of these is given in the Appendix, Table 10.4. The most common combination was nsAE / nsADR, occurring in 68 out of 1705 patients (3.99%).

A summary of the number of AEs per patient is given in Table 9-28.

Table 9-28: Number of adverse events per patient (N=1705)

		Type of First-line disease modifying therapy at Baseline				
	Overall	**Avonex**	**Betaferon**	**Copaxone**	**Extavia**	**Rebif**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Patients (FAS)	1705 (100.00%)	395 (100.00%)	275 (100.00%)	491 (100.00%)	151 (100.00%)	393 (100.00%)
Patients without AEs	1199 (70.32%)	288 (72.91%)	187 (68.00%)	333 (67.82%)	106 (70.20%)	285 (72.52%)
1 AE	261 (15.31%)	57 (14.43%)	44 (16.00%)	75 (15.27%)	24 (15.89%)	61 (15.52%)
2 AEs	102 (5.98%)	24 (6.08%)	20 (7.27%)	33 (6.72%)	5 (3.31%)	20 (5.09%)
3 AEs	53 (3.11%)	9 (2.28%)	10 (3.64%)	16 (3.26%)	5 (3.31%)	13 (3.31%)
4 AEs	29 (1.70%)	4 (1.01%)	5 (1.82%)	14 (2.85%)	3 (1.99%)	3 (0.76%)
5 AEs	18 (1.06%)	7 (1.77%)	2 (0.73%)	5 (1.02%)	1 (0.66%)	3 (0.76%)
6 AEs	14 (0.82%)	2 (0.51%)	4 (1.45%)	5 (1.02%)	3 (1.99%)	0 (0.00%)
7 AEs	11 (0.65%)	2 (0.51%)	1 (0.36%)	4 (0.81%)	1 (0.66%)	3 (0.76%)
8 AEs	6 (0.35%)	0 (0.00%)	0 (0.00%)	2 (0.41%)	0 (0.00%)	4 (1.02%)
9 AEs	4 (0.23%)	0 (0.00%)	0 (0.00%)	2 (0.41%)	2 (1.32%)	0 (0.00%)
10 AEs	3 (0.18%)	0 (0.00%)	1 (0.36%)	1 (0.20%)	0 (0.00%)	1 (0.25%)
11 AEs	2 (0.12%)	1 (0.25%)	1 (0.36%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
12 AEs	2 (0.12%)	1 (0.25%)	0 (0.00%)	1 (0.20%)	0 (0.00%)	0 (0.00%)
14 AEs	1 (0.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.66%)	0 (0.00%)

N = number of patients; % = percentage of patients
Source: Appendix, Table 10.5

Most frequently, patients had only one AE (15.31%).

A total of 50 patients had recurring events. These are listed in Appendix, Table 10.8.

As laid out in the Statistical Analysis Plan, recurring events were counted only once and the patients were excluded from the patient number at risk for subsequent analysis. Therefore, the number of AEs in the following analyses is 1084 when counted overall (see Table 9-29).

All AEs were coded according to MedDRA and the respective SOCs and PTs are presented in Table 9-29.

Table 9-29: Classified adverse events – MedDRA SOCs and PTs (cutoff: PT >1%) - patient based (multiple responses possible) and event based (N=1705)

	Patients		Events	
	N	%	N	%
Total patients/ events	1705	100.00	1084	100.00
Patients without AEs	1199	70.32		
Patients with AEs	506	29.68		
Nervous system disorders	131	7.68	154	14.21
Headache	28	1.64	28	2.58
Multiple sclerosis relapse	25	1.47	25	2.31
Migraine	13	0.76	13	1.20
Dizziness	11	0.65	11	1.01
Infections and infestations	123	7.21	162	14.94
Nasopharyngitis	42	2.46	42	3.87
General disorders and administration site conditions	108	6.33	139	12.82
Fatigue	25	1.47	25	2.31
Influenza like illness	18	1.06	18	1.66
Chills	14	0.82	14	1.29
Pain	11	0.65	11	1.01
Psychiatric disorders	101	5.92	129	11.90
Depression	42	2.46	42	3.87
Sleep disorder	26	1.52	26	2.40
Suicidal ideation	11	0.65	11	1.01
Musculoskeletal and connective tissue disorders	62	3.64	83	7.66
Pain in extremity	17	1.00	17	1.57
Back pain	12	0.70	12	1.11
Injury, poisoning and procedural complications	63	3.70	76	7.01
Maternal exposure during pregnancy	28	1.64	28	2.58
Skin and subcutaneous tissue disorders	52	3.05	59	5.44
Erythema	11	0.65	11	1.01
Gastrointestinal disorders	46	2.70	54	4.98
Vascular disorders	38	2.23	43	3.97
Hypertension	14	0.82	14	1.29
Reproductive system and breast disorders	19	1.11	22	2.03
Surgical and medical procedures	20	1.17	21	1.94

	Patients		Events	
	N	%	N	%
Metabolism and nutrition disorders	16	0.94	17	1.57
Vitamin D deficiency	11	0.65	11	1.01
Cardiac disorders	14	0.82	20	1.85
Investigations	14	0.82	16	1.48
Renal and urinary disorders	13	0.76	15	1.38
Respiratory, thoracic and mediastinal disorders	12	0.70	14	1.29
Eye disorders	12	0.70	12	1.11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	0.65	11	1.01
Ear and labyrinth disorders	9	0.53	10	0.92
Immune system disorders	9	0.53	9	0.83
Blood and lymphatic system disorders	6	0.35	6	0.55
Endocrine disorders	6	0.35	6	0.55
Hepatobiliary disorders	4	0.23	4	0.37
Pregnancy, puerperium and perinatal conditions	2	0.12	2	0.18

N = number of patients/events; % = percentage of patients/ events; Sequence of system organ classes is by decreasing frequency overall;
Source: Appendix, Table 10.7, Table 10.9.1

Regardless of seriousness or relationship, patients experienced AEs most frequently in the SOCs nervous system disorders (overall: 7.68%, Avonex: 6.58%, Betaferon: 9.82%, Copaxone: 7.54%, Extavia: 9.27%, Rebif: 6.87%), infections and infestations (overall: 7.21%, Avonex: 5.57%, Betaferon: 8.00%, Copaxone: 8.55%, Extavia: 5.96%, Rebif: 7.12%), and general disorders and administration site conditions (overall: 6.33%, Avonex: 7.09%, Betaferon: 7.27%, Copaxone: 6.11%, Extavia: 6.62%, Rebif: 5.09%) (Appendix, Table 10.7).

At the PT level, the most frequently reported events were nasopharyngitis (overall: 2.46%, Avonex: 1.77%, Betaferon: 2.91%, Copaxone: 3.05%, Extavia: 1.32%, Rebif: 2.54%) and depression (overall: 2.46%, Avonex: 2.53%, Betaferon: 3.27%, Copaxone: 3.05%, Extavia: 1.99%, Rebif: 1.27%), followed by headache (overall: 1.64%, Avonex: 1.27%, Betaferon: 2.91%, Copaxone: 0.81%, Extavia: 2.65%, Rebif: 1.78%), maternal exposure during pregnancy (overall: 1.64%, Avonex: 1.52%, Betaferon: 1.09%, Copaxone: 2.04%, Extavia: 2.65%, Rebif: 1.27%), and sleep disorder (overall: 1.52%, Avonex: 2.03%, Betaferon: 1.45%, Copaxone: 1.22%, Extavia: 0.66%, Rebif: 1.78%) (Appendix, Table 10.7).

9.6.3 Detailed Analyses

An event-based summary of the AE categories is given in Table 9-30.

Table 9-30: AEs by MedDRA SOC – event based, by type of AE (N=1705)

	All		nsAE		nsADR		SAE		SADR	
	N	%	N	%	N	%	N	%	N	%
Total number of AEs	1098	100.00	542	100.00	408	100.00	105	100.00	43	100.00
Infections and infestations	163	14.85	117	21.59	34	8.33	8	7.62	4	9.30
Nervous system disorders	159	14.48	89	16.42	49	12.01	8	7.62	13	30.23
General disorders and administration site conditions	142	12.93	24	4.43	111	27.21	6	5.71	1	2.33
Psychiatric disorders	131	11.93	75	13.84	44	10.78	9	8.57	3	6.98
Musculoskeletal and connective tissue disorders	83	7.56	43	7.93	36	8.82	4	3.81	0	0
Injury, poisoning and procedural complications	76	6.92	55	10.15	5	1.23	16	15.24	0	0
Skin and subcutaneous tissue disorders	61	5.56	7	1.29	47	11.52	5	4.76	2	4.65
Gastrointestinal disorders	54	4.92	30	5.54	12	2.94	9	8.57	3	6.98
Vascular disorders	43	3.92	20	3.69	21	5.15	2	1.90	0	0
Reproductive system and breast disorders	22	2.00	12	2.21	3	0.74	7	6.67	0	0
Surgical and medical procedures	21	1.91	9	1.66	3	0.74	8	7.62	1	2.33
Cardiac disorders	20	1.82	5	0.92	2	0.49	4	3.81	9	20.93
Metabolism and nutrition disorders	17	1.55	11	2.03	6	1.47	0	0	0	0
Renal and urinary disorders	16	1.46	6	1.11	7	1.72	3	2.86	0	0
Investigations	16	1.46	2	0.37	11	2.70	3	2.86	0	0
Respiratory, thoracic and mediastinal disorders	14	1.28	7	1.29	6	1.47	1	0.95	0	0
Eye disorders	12	1.09	10	1.85	1	0.25	1	0.95	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	1.00	0	0	1	0.25	7	6.67	3	6.98
Ear and labyrinth disorders	10	0.91	7	1.29	3	0.74	0	0	0	0
Immune system disorders	9	0.82	4	0.74	2	0.49	1	0.95	2	4.65
Blood and lymphatic system disorders	6	0.55	1	0.18	3	0.74	2	1.90	0	0
Endocrine disorders	6	0.55	5	0.92	0	0	1	0.95	0	0
Hepatobiliary disorders	4	0.36	1	0.18	1	0.25	0	0	2	4.65
Pregnancy, puerperium and perinatal conditions	2	0.18	2	0.37	0	0	0	0	0	0

N = number of events; % = percentage of events; SOC is by decreasing frequency overall;
Source: Appendix, Table 10.9.2

Overall, AEs were most frequently reported in the SOC infections and infestations (14.85%), followed by nervous system disorders (14.48%), general disorders and administration site

conditions (12.93%) and psychiatric disorders (11.93%). NsAEs were most frequently reported in the SOC infections and infestations (21.59%), followed by nervous system disorders (16.42%), while nsADRs were most frequently documented in the SOC general disorders and administration site conditions (27.21%). SAEs were most frequently found in the SOC injury, poisoning and procedural complications (15.24%) and SADRs in the SOC nervous system disorders (30.23%), followed by cardiac disorders (20.93%).

For three patients the Neoplasms benign, malignant and unspecified (PT breast cancer) was documented as SADR. The respective first-line DMT groups were Avonex, Copaxone and Extavia (Appendix, Table 10.9.2).

At the PT level, the most frequently reported AEs were nasopharyngitis and depression (3.92% each) overall, nasopharyngitis (7.01%), followed by depression and maternal exposure during pregnancy (4.61% each) for nsAEs, and influenza like illness (4.17%) followed by fatigue and depression (3.92% each) for nsADRs. SAEs occurred mainly in one or two cases with the exception of suicidal ideation in four patients (3.81%) and fall and myocardial infarction in three patients each (2.86%). SADRs were all single cases with the exception of breast cancer in three (6.98%) and dizziness in two patients (4.65%; Appendix, Table 10.9.2).

For Avonex and Extavia AEs were most often in the SOCs general disorders and administration site conditions (Avonex: 15.89%, Extavia: 14.88%), followed by psychiatric disorders (Avonex: 14.49%, Extavia: 10.74%) and nervous system disorders (Avonex: 14.49%, Extavia: 12.40%). The Betaferon group experienced AEs most often in the SOCs nervous system disorders (18.38%), infections and infestations (18.38%) and general disorders and administration site conditions (14.59%), the Copaxone group in the SOCs infections and infestations (15.54%), nervous system disorders (13.56%) and psychiatric disorders (10.17%) and the Rebif treated patients in the SOCS infections and infestations (15.63%), nervous system disorders (13.84%), general disorders and administration site conditions and psychiatric disorders (13.39% each; Appendix, Table 10.9.2).

Table 9-31 provides a detailed overview of the information the physician provided on causality, duration, intensity, and outcome of the AEs. Concerning causality, all events with missing causality assessments or causality assessments of “not assessable” were classified as nsADRs using a conservative approach.

Table 9-31: Classification of adverse events (N=1705)

		All	nsAE	SAE	nsADR	SADR
		N (%)	N (%)	N (%)	N (%)	N (%)
	Total	1165 (100.00%)	573 (100.00%)	106 (100.00%)	442 (100.00%)	44 (100.00%)
Duration	Missing	139 (11.93%)	30 (5.24%)	16 (15.09%)	81 (18.33%)	12 (27.27%)
	1-7 days	299 (25.67%)	137 (23.91%)	39 (36.79%)	111 (25.11%)	12 (27.27%)
	8-14 days	128 (10.99%)	72 (12.57%)	11 (10.38%)	43 (9.73%)	2 (4.55%)
	15-21 days	44 (3.78%)	31 (5.41%)	2 (1.89%)	11 (2.49%)	0 (0.00%)
	>21 days	105 (9.01%)	53 (9.25%)	12 (11.32%)	38 (8.60%)	2 (4.55%)
	Ongoing	450 (38.63%)	250 (43.63%)	26 (24.53%)	158 (35.75%)	16 (36.36%)
Intensity	Missing	91 (7.81%)	10 (1.75%)	25 (23.58%)	44 (9.95%)	12 (27.27%)
	Mild	395 (33.91%)	223 (38.92%)	10 (9.43%)	157 (35.52%)	5 (11.36%)
	Moderate	506 (43.43%)	281 (49.04%)	29 (27.36%)	190 (42.99%)	6 (13.64%)
	Severe	173 (14.85%)	59 (10.30%)	42 (39.62%)	51 (11.54%)	21 (47.73%)
Causality	Certain	167 (14.33%)	0 (0.00%)	0 (0.00%)	155 (35.07%)	12 (27.27%)
	Probable	79 (6.78%)	0 (0.00%)	0 (0.00%)	78 (17.65%)	1 (2.27%)
	Possible	99 (8.50%)	0 (0.00%)	0 (0.00%)	88 (19.91%)	11 (25.00%)
	Improbable	246 (21.12%)	219 (38.22%)	27 (25.47%)	0 (0.00%)	0 (0.00%)
	None	433 (37.17%)	353 (61.61%)	79 (74.53%)	1 (0.23%)	0 (0.00%)
	Not assessable	105 (9.01%)	0 (0.00%)	0 (0.00%)	86 (19.46%)	19 (43.18%)
	Not reported	36 (3.09%)	1 (0.17%)	0 (0.00%)	34 (7.69%)	1 (2.27%)
Outcome	Recovered	626 (53.73%)	309 (53.93%)	61 (57.55%)	239 (54.07%)	17 (38.64%)
	Not yet recovered	413 (35.45%)	235 (41.01%)	16 (15.09%)	150 (33.94%)	12 (27.27%)
	Fatal	3 (0.26%)	0 (0.00%)	2 (1.89%)	0 (0.00%)	1 (2.27%)
	Life-threatening	12 (1.03%)	0 (0.00%)	2 (1.89%)	0 (0.00%)	10 (22.73%)
	Hospitalization	106 (9.10%)	3 (0.52%)	72 (67.92%)	0 (0.00%)	31 (70.45%)
	Disability/incapacity	12 (1.03%)	0 (0.00%)	10 (9.43%)	0 (0.00%)	2 (4.55%)
	Medical significant event (by Novartis med. expert)	31 (2.66%)	0 (0.00%)	19 (17.92%)	0 (0.00%)	12 (27.27%)
	Unknown	42 (3.61%)	20 (3.49%)	1 (0.94%)	18 (4.07%)	3 (6.82%)
	Not assessed by physician	50 (4.29%)	9 (1.57%)	2 (1.89%)	36 (8.14%)	3 (6.82%)

N = number of events; % = percentage of events
Note: One non-serious event with stated causality by physician 'none' was converted to an ADR by Novartis Pharmacovigilance.
Note: One pregnancy with no reported causality by physician is classified as not drug related.
Note: Three hospitalizations were planned in advance and do not result in a SAE.
Source: Appendix, Table 10.11

The majority of AEs were of mild (33.91%) or moderate (43.43%) intensity. The causality was most frequently none (37.17%) or improbable (21.12%) and the outcome recovered

(53.73%) and not yet resolved (35.45%). For SAEs (67.92%) and SADRs (70.45%) the outcome was most frequently documented as hospitalization.

9.6.4 Serious adverse events and serious adverse drug reactions

During this study 106 SAEs in 70 patients and 44 SADRs in 31 patients were reported (Table 9-26).

All patients with documented SAEs or SADRs are presented in Table 9-32.

Table 9-32: SAEs and SADRs by MedDRA SOC – patient based (N=1705)

	SAE		SADR	
	N	%	N	%
Patients (Full Analysis Set)	70	100.00	31	100.00
Nervous system disorders	7	10.00	12	38.71
Infections and infestations	7	10.00	4	12.90
General disorders and administration site conditions	4	5.71	1	3.23
Psychiatric disorders	8	11.43	3	9.68
Musculoskeletal and connective tissue disorders	3	4.29	0	0
Injury, poisoning and procedural complications	14	20.00	0	0
Skin and subcutaneous tissue disorders	2	2.86	2	6.45
Gastrointestinal disorders	8	11.43	3	9.68
Vascular disorders	2	2.86	0	0
Reproductive system and breast disorders	7	10.00	0	0
Surgical and medical procedures	8	11.43	1	3.23
Cardiac disorders	4	5.71	3	9.68
Investigations	3	4.29	0	0
Renal and urinary disorders	2	2.86	0	0
Respiratory, thoracic and mediastinal disorders	1	1.43	0	0
Eye disorders	1	1.43	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	10.00	3	9.68
Immune system disorders	1	1.43	2	6.45
Blood and lymphatic system disorders	2	2.86	0	0
Endocrine disorders	1	1.43	0	0
Hepatobiliary disorders	0	0	2	6.45

N = number of events; % = percentage of events
Source: Appendix, Table 10.7

Patients had SAEs most frequently in the SOC injury, poisoning and procedural complications (20.00%), followed by psychiatric disorders, gastrointestinal disorders, surgical and medical procedures (11.43% each). SADRs occurred most frequently in the SOC nervous system disorders (38.71%), followed by infections and infestations (12.90%).

Two patients died during this study. The causality was not assessable in one case (death; Avonex) and assessed as "improbable" in the other case (pancreatitis and pancreatic carcinoma; Betaferon). A detailed listing these fatal events is given in Table 9-33.

Table 9-33: Listing of fatal events

Pat. / Age / Sex	Therapy at Baseline	MedDRA PT	Duration	Intensity	Causality
1382 / 51 years / Female	Avonex	Death	Missing	Severe	Not assessable
1522 / 45 years / Male	Betaferon	Pancreatitis	8-14 days	Severe	Improbable
		Pancreatic carcinoma	>21 days	Severe	Improbable

Source: Appendix, Table 10.12.3

9.6.5 Vital signs

The mean systolic blood pressure was 125.4 ± 14.09 mmHg at baseline and 125.4 ± 13.46 mmHg at last visit. The mean difference in systolic blood pressure was -0.6 ± 14.16 mmHg at the 12 months FU, -0.3 ± 14.76 mmHg at the 24 months FU, and -0.1 ±14.44 mmHg at the last visit. The mean diastolic blood pressure was 79.5 ± 9.50 mmHg at baseline and 79.4 ± 9.31 mmHg at the last visit. The mean difference in diastolic blood pressure was -0.3 ± 10.37 mmHg at the 12 months FU, -0.2 ± 10.56 mmHg at the 24 months FU, and -0.2 ±10.54 mmHg at the last visit (Appendix, Table 10.1.1, Table 10.1.2).

The mean heart rate was 73.6 ± 9.41 bpm at baseline and 73.8 ± 9.42 bpm at the last visit. The mean difference in heart rate was 0.3 ± 10.24 bpm at the 12 months FU, -0.0 ± 11.13 bpm at the 24 months FU, and 0.2 ±11.10 bpm at the last visit (Appendix, Table 10.2.1, Table 10.2.2).

10 Discussion

10.1 Key results

10.1.1 Patient characteristics

The descriptive statistical analysis was based on the documentation of 1705 patients. IFN-beta (Avonex: 23.17%; Rebif: 23.05%; Betaferon: 16.13%, Extavia: 8.86%) was more frequently prescribed than Copaxone (28.80%).

The majority of patients were female (72.55%), 27.27% were male (missing data: 0.18%). The overall mean age was 42.5 ± 10.34 years (mean ± SD). The diagnosis as per ICD 10 was G35.10 (MS with primarily relapsing-remitting course: without acute exacerbation or progression) for the majority of patients overall (65.75%). Further diagnoses reported in more than 5% of patients were G35.1 (MS with primarily relapsing-remitting course; overall 10.67%), G35.9 (MS: not specified; 9.15%), G35.11 (MS with primarily relapsing-remitting course: with acute exacerbation or progression; 7.57%) and G35.0 (First manifestation of MS; 5.34%). All other ICD 10 diagnoses were reported in less than 5% of patients.

For 53.36% of the patients with MRI, data on the number of lesions were missing at baseline. The proportion of patients with 3 to ≤9 T2 lesions was 18.35% and 19.64% with >9 T2 lesions. Gadolinium-enhancing lesions were reported for 32.77% of patients.

The mean relapse rate in the last 12 months before start of PEARL was 0.52 ± 0.863. The intensity of the last MS relapse before start of PEARL based on the EDSS score was >1.5 to ≤2.5 points in 26.99%, >2.5 to ≤3.5 in 23.74% and ≤1.5 points in 20.49% cases. The majority, i.e. 59.67% of patients had sensory relapses, 36.91% had pyramidal relapses and 20.49% had visual relapses. All other types occurred in less than 15% of patients.

The median time since start of first-line DMT was 2.6 years. The median observation period was 728.0 days.

About 20% of the patients (Avonex: 20.51%, Betaferon: 18.91%, Copaxone: 19.55%, Extavia: 23.84%, Rebif: 20.10%) prematurely discontinued the study. A switch of therapy during the observation period was reported for 279 (16.36%) patients. The proportion of patients who terminated the therapy or for whom data on therapy switches were missing were as follows: Avonex 33.82%, Betaferon 22.45% Copaxone 28.57%, Extavia 37.93, Rebif 29.23%.

10.1.2 Results on pharmacoeconomic data – resource utilization

Pharmacoeconomic parameters were based on the analysis of the patient resource questionnaire.

About two-third of the patients were employed (baseline: 60.45%, last visit: 57.58%) with two-third of these patients being full-time employed (baseline: 59.75%, last visit: 59.83%). At baseline, 21.74% of patients reported that they were on sick leave due to MS within the three past months. At the last visit 13.32% of patients documented a sick leave due to MS in the last 3 months (baseline: mean duration 21.1 ± 26.01 days, median 10.0 days; last visit: mean duration 13.8 ± 17.19 days, median 9.5 days). A reduction of working hours due to MS was reported by 6.37% of patients at baseline and 2.90% at 24 month FU.

In the past 3 months before baseline, 86.20% of patients consulted a physician or other health care professional due to MS. MS-related hospitalization was reported for 4.74% of patients and 2.01% had to stay in a rehabilitation clinic. None of the patients had to stay in a nursing home. Ambulatory treatments in the hospital were documented for 3.08% of patients.

In the last 12 months before baseline, examinations due to MS were performed in 77.26% of patients. These were mainly blood examinations (56.78%) and MRTs (54.88%). At the 24 month FU, the percentage of patients with blood examinations in the past twelve months was 44.86% and 37.31% with MRT.

Manual injection was used by 87.39% of the patients at baseline and 29.42% at last visit, and an autoinjector was used by 67.44% of the patients at baseline and 67.53% at last visit. About 10% of the patients needed assistance with manual injection, e.g. provided by the partner or family.

A training on MS treatment was attended by 24.45% of patients in the past 3 months before baseline and 15.46% of patients in the past 3 months before last visit.

In the past 3 months before baseline, 34.99% of patients had purchased over-the-counter medications because of MS (mean expenses 43.0 ± 68.40 Euro). In the past 3 months before

the last visit, the proportion of patients who had purchased over-the-counter medications because of MS was 31.10% (mean expenses 40.1 ± 58.15 Euro). Consumables due to MS were purchased by 10.60% of the patients in the past 3 months before baseline (mean expenses 29.4 ± 35.40 Euro) and by13.12% of the patients in the past 3 months before the last visit (mean expenses 32.6 ± 38.14 Euro).

MS-related expenses for equipment and devices in the past 12 months before baseline were documented by 8.11% of patients, thereof 57.66% were for walking aids and 34.31% for changes to the house. The expenses amounted to a mean of 3998.2 ± 8567.8 Euro and a median of 200.0 Euro. At 12 months and 24 months, expenses for equipment and devices were reported by about 5% of the patients, e.g. for walking aids and for use of a wheel chair.

Patients received assistance from family or friends (18.00% and 16.96%), from household help (4.50% and 5.45%), professionals (1.07% and 0.78%) and personal assistants (0.36% and 0.12%) in the past 3 months before baseline and before the last visit, respectively. For 1.18% and 1.08% of patients a mean work reduction of family members in the past 3 months before baseline and before the last visit, respectively, was reported. The proportion of patients who received benefits from long term care insurances was 2.31% and 2.10% in the past 3 months before baseline and before the last visit,

10.1.3 Results on clinical effectiveness

The overall mean ARR was 0.39 ± 0.770 assessed over the two year study period (Avonex: 0.38 ± 0.814; Betaferon: 0.33 ± 0.633; Copaxone: 0.44 ± 0.784; Extavia: 0.41 ± 0.848; Rebif: 0.39 ± 0.767). For the 586 patients with MS relapses after start of PEARL, the median time from baseline to first relapse was 215.5 days (Avonex: 244.0, Betaferon: 193.0, Copaxone: 213.5, Extavia: 210.0, Rebif: 220.5). Over the two years, 20.14% of the patients were hospitalized. Most of them were treated with steroids (87.37%).

MRIs were reported for 11% to 14% of patients at each visit, meaning that a MRI was performed between the respective visit and the previous visit. At the last visit, 15.50% of patients have had an MRI reported since the previous visit. Data on the number of lesions was missing in the MRI reports (missing data at baseline: 53.36%, 12 months FU: 65.00%, 24 months FU: 62.04%). The proportion of patients with > 9 lesions over the course of the study was as follows: baseline: 19.64%, 12 months FU: 13.00%, 24 months FU: 9.49%. The proportion of patients with 3 to ≤9 lesions over the course of the study was as follows: baseline: 18.35%, 12 months FU: 12.50%, 24 months FU: 11.68%. Gadolinium enhancing lesions were present in 449 out of 1370 patients with MRI performed (32.77%) at baseline, in 35 out of 189 patients (18.52%) at the 12 months FU and in 20 out of 124 patients (16.13%) at the 24 months FU.

The EDSS is a method of quantifying disability in MS using a score from 0.0 (normal neurological exam) to 10.0 (death due to MS). The mean EDSS score was 2.3 ± 1.52 at baseline (Avonex: 2.3 ± 1.41, Betaferon: 2.2 ± 1.48, Copaxone: 2.4 ± 1.51, Extavia: 2.3 ± 1.53, Rebif: 2.2 ± 1.65) and 2.5 ± 1.64 at the last visit with possible EDSS assessment (Avonex: 2.5 ± 1.58, Betaferon: 2.4 ± 1.62, Copaxone: 2.5 ± 1.62, Extavia: 2.7 ± 1.66, Rebif: 2.5 ± 1.73). The mean difference from baseline to the last visit with possible EDSS assessment was 0.3 ± 0.87 (Avonex: 0.3 ± 0.83, Betaferon: 0.2 ± 0.78, Copaxone: 0.2 ± 0.91, Extavia: 0.4 ± 0.94, Rebif: 0.3 ± 0.92.

The CGI severity is rated on a 7-point scale using a range of responses from “normal, not at all ill” to “extremely ill”. The proportions of patients who reported to be “mildly ill” were: baseline 31.44% and last visit 30.23%. The proportions of patients reported to be “moderately ill” were: baseline 25.34% and last visit 28.80%. Overall, 77.20% showed “no change” of CGI (CGI improvement scale rated on a 7-point scale using a range of responses from “very much improved” to “very much worse”) at last visit. A total of 13.84% of patients were “minimally worse” and 4.28% of patients “minimally improved”.

Most frequently, physicians and patients rated the effectiveness at last visit (FU after 24 months or discontinuation visit) as “good” (physicians: 45.75%, patients: 44.79%) or “very good” (physicians: 34.71%, patients: 29.29%).

10.1.4 Results on patient reported effectiveness

The TSQM-9 questionnaire measured the patients’ satisfaction with the treatment on 7-point- or 5-point scales with 1 being the most negative answer. The TSQM-9 score is the sum of all single TSQM-9 questions ranging between 7 (low satisfaction) and 59 (high satisfaction). At baseline, the mean TSQM-9 score was 46.3 ± 7.47 and at last visit the mean TSQM-9 score was 45.2 ± 8.34. The mean difference from last visit to baseline was -1.1 ± 7.38.

The UK NDS questionnaire assessed neurological functions in 13 areas. For all subscores scales were used ranging from 0 (normal status) to 5 (total loss of function), with the exception of the cognition subscale ranging from 0 to 3. A total score was calculated from the individual subscores ranging from 0 to 63.

The mean total score was 8.1 ± 7.30 at baseline and 6.2 ± 6.65 at last visit. Individual mean sub-scores ranged from 0.1 ± 0.38 (swallowing score) to 1.9 ± 1.40 (fatigue score) at baseline and from 0.1 ± 0.34 (swallowing score) to 1.5 ± 1.36 (fatigue score) at last visit. Overall, the difference from last visit to baseline for the total score was -1.2 ± 4.95.

The EQ-5D questionnaire measured HrQoL covering the areas mobility, self-care, usual activities, pain / discomfort and anxiety / depression using a 3-point scale (no problems, some problems, extreme problems) for the descriptive system and a VAS ranging from 100 (best imaginable health state) to 0 (worst imaginable health state). The state of health compared to 12 months ago stayed ‘roughly the same’ for 66.55% at baseline and 71.17% at the last visit. At the last visit, the mean current health state on the VAS was 71.0 ± 18.7 compared to baseline 71.5 ± 18.6.

The PRIMUS is a questionnaire assessing QoL impairment (sum score ranging from 0 [no effect of the disease on QoL] to 45 [strong effect of the disease on QoL]) and activity impairment (sum score ranging from 0 [activity “could be done by oneself without difficulties”] to 38 [activity “could not be done by oneself”]) in MS patients. The mean PRIMUS QoL score was 8.4 ± 8.76 at baseline and, 7.4 ± 8.92 at the last visit. The mean PRIMUS activity score was 4.2 ± 5.16 at baseline and 4.5 ± 5.7 at the last visit.

On the compliance questionnaire, 83.71% of patients stated at baseline that they did not occasionally forget to take the MS medication. At the last visit, the proportion of patients was 81.22%. The mean number of days without medication in the last two weeks was 0.4 ± 1.23 before baseline and 1.6 ± 3.24 before the last visit.

10.1.5 Results on the practice questionnaire

A total of 167 practice questionnaires were documented. MS patients amounted to a mean of 17.5 ± 21.31% of patients in the physicians' practices. On average, the physicians saw 158 MS patients per quarter. The mean percentage of MS patients receiving first-line DMT was 64.3 ± 21.08%.

Staff, available at the study sites for the treatment of MS, included doctor's assistant (91.62%), nurse/MS nurse (62.87%) and neuropsychologist/ psychologist (23.35%; multiple response). The physicians cooperated with physiotherapists (95.21%), other specialists (87.43%), general practitioners (83.83%), and occupational therapists/ergotherapists (82.63%).

Physicians spent their time on: diagnosis (median 45.0 min), therapy initiation (median 30.0 min), and advice (median 20.0 min). Nurses spent their time for: therapy initiation (median 35.0 min), diagnosis (median 30.0 min), and FU examinations and advice (median 15.0 min each). The decision for prescription of first-line DMT was made by the physician (100.0%) and the patient (95.21%).

The physicians documented that on average 81.8 ± 13.48% of patients displayed perfect compliance with therapy. The factor that had the highest influence on patient's compliance was personal motivation of the patient, followed by occurrence of new relapses, pain at injection, cutaneous side effects, difficulties with application, and influenza-like symptoms.

On average, physicians were satisfied with the treatment situation of MS patients assessed on a scale rating from 1 = very dissatisfied to 5 = very satisfied (mean 3.4 ± 0.73), the therapy options for MS patients (mean 3.2 ± 0.72), the care for MS patients (mean 3.4 ± 0.84), and the cooperation with other professional groups for MS (mean 3.3 ± 0.87).

10.1.6 Results on safety

During this study, 1165 AEs were documented in 506 of 1705 patients (29.68%). In 300 patients (overall 17.60%; Avonex: 15.95%, Betaferon: 19.27%, Copaxone: 19.35%, Extavia: 15.89%, Rebif: 16.54%), a nsAE (no causality) was reported. An nsADR was documented in 240 patients (overall 14.08%; Avonex: 13.92%, Betaferon: 15.27%, Copaxone: 13.85%, Extavia: 14.57%, Rebif: 13.49%). A total of 70 patients (overall 4.11%; Avonex: 3.29%, Betaferon: 4.73%, Copaxone: 4.68%, Extavia: 4.64%, Rebif: 3.56%) had an SAE and for 31 patients (overall 1.82%; Avonex: 1.77%, Betaferon: 1.82%, Copaxone: 2.04%, Extavia: 3.97%, Rebif: 0.76%) at least one event met the criteria for a SADR. Two patients died during this study. The causality was not assessable in one fatal case (Avonex) and assessed as "improbable" in the other fatal case (pancreatitis and pancreatic carcinoma; Betaferon). The AE incidence per patient year was 0.17370 overall, 0.10299 for nsAEs, 0.02403 for SAEs, 0.08239 for nsADRs, and 0.01064 for SADRs.

Regardless of seriousness or relationship, patients experienced AEs most frequently in the system organ classes nervous system disorders (overall: 7.68%, Avonex: 6.58%, Betaferon: 9.82%, Copaxone: 7.54%, Extavia: 9.27%, Rebif: 6.87%), infections and infestations (overall: 7.21%, Avonex: 5.57%, Betaferon: 8.00%, Copaxone: 8.55%, Extavia: 5.96%, Rebif: 7.12%), and general disorders and administration site conditions (overall: 6.33%, Avonex: 7.09%, Betaferon: 7.27%, Copaxone: 6.11%, Extavia: 6.62%, Rebif: 5.09%).

At the PT level, the most frequently reported events were nasopharyngitis (overall: 2.46%, Avonex: 1.77%, Betaferon: 2.91%, Copaxone: 3.05%, Extavia: 1.32%, Rebif: 2.54%) and depression (overall: 2.46%, Avonex: 2.53%, Betaferon: 3.27%, Copaxone: 3.05%, Extavia: 1.99%, Rebif: 1.27%), followed by headache (overall: 1.64%, Avonex: 1.27%, Betaferon: 2.91%, Copaxone: 0.81%, Extavia: 2.65%, Rebif: 1.78%), maternal exposure during pregnancy (overall: 1.64%, Avonex: 1.52%, Betaferon: 1.09%, Copaxone: 2.04%, Extavia: 2.65%, Rebif: 1.27%), and sleep disorder (overall: 1.52%, Avonex: 2.03%, Betaferon: 1.45%, Copaxone: 1.22%, Extavia: 0.66%, Rebif: 1.78%)

10.2 Limitations

This study was a non-interventional study with the limitations associated with all observational studies, including the lack of blinding and randomization, the heterogeneity of the patient population, and a high amount of missing or inconsistent data.

As the treating physician decides on the prescription of the respective medication and inclusion of the patient in the NIS, this may influence the patients' decisions and course of treatment, thereby introducing bias.

Patients that discontinue the documentation during the observation period may create an outcome bias.

To minimize bias, patients had to be enrolled in a consecutive order in each study center and centers had to be enrolled differentiatedly by region. In order to account for the effect of premature withdrawals, the data for all patients at the last completed visit were summarized in the form of a final FU (last visit).

Furthermore, the use of this specific, non-validated version of the UK NDS questionnaire may limit the informative value of the analysis.

10.3 Interpretation

The PEARL study quantifies resource utilization and health status of RRMS-patients on first-line DMTs (i.e. IFN-beta or glatiramer acetate) in Germany over a two-year time period with a focus on routine outpatient practice.

10.4 Generalizability

As this study was performed under daily practice conditions a broad range of patients was included. Patients of both sexes were enrolled. The age varied widely including also teenagers and elderly, although the majority of patients were between 20 years and 70 years. The EDSS score ranged from 0.0 (Normal Neurological Exam) to 8.5 (Essentially restricted to bed much of day, some effective use of arms, retains some self-care functions) with the majority of patients between 1.5 (No disability, minimal signs on 2 of 7 functional systems) and 4.5 (Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance, relatively severe disability, able to walk without aid 300 meters). Overall, this NIS included a broad range of patients with primarily mild to moderate RRMS in a real-life situation.

11 References

References are available upon request.

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12 Other information

Not applicable.