CLINICAL STUDY REPORT

FINAL version

Tracking number: 1.3

Study Title: NON-INTERVENTIONAL CLINICALSTUDY TO ASSESS THEIMPACT OF THEAVONEX® TREATMENT ON QUALITY OF LIFE IN PATIENTS WITH CIS/CDMS

Start of Study Date:	12 December 2009
End of Study Date:	05 February 2016
Report Date:	07 February 2017
Study Sponsor:	

Biogen (Czech Republic) s.r.o.
Na Pankráci 1683/127
140 00 Praha 4, Czech Republic

and

Biogen Slovakia s.r.o.
Aupark Tower, Einsteinova 24
851 01 Bratislava, Slovak Republic

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

TABLE OF CONTENTS

List of Tables

List of Figures

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

AE	Adverse Event
AI	Ambulation Index
AIFP	Association of Innovative Pharmaceutical Industry
ARR	Annualised Relapse Rate
CDMS	Clinically Definite Multiple Sclerosis
CIS	Clinically Isolated Syndrome
CRF	Case Report Form
df	Degrees of Freedom
DMT	Disease Modifying Treatment
EC	Ethics Committee
EDSS	Kurtzke Expanded Disability Status Scale
EOS	End of Study
EU	European Union
FS	Functional Status
HRQOL	Health-Related Quality of Life
ICF	Informed Consent Form
MCS	Mental Component Summary
MS	Multiple Sclerosis
N	Count
N/A	Not Applicable
NARCOMS	North American Research Committee on Multiple Sclerosis database
NRS	Neurologic Rating Scale
PASAT	Paced Auditory Serial Addition Test
PCS	Physical Component Summary
QoL	Quality of Life
SAE	Severe Adverse Event
SD	Standard Deviation
SelfAdmin	Self-Administration
SF-36	36-Item Short Form Health Survey
SFS	Sum of the EDSS Functional Scores
SUKL	State Institute for Drug Control

VAS	Visual Analogue Scale

2. PROTOCOL SYNOPSIS

STUDY TITLE	Non-interventional Clinical Study to Assess Impact of Avonex® Treatment on Quality of Life in Patients with CIS/CDMS
PROTOCOL NUMBER/VERSION	LD140409/ Version 1.0_CZ – Amendment 1 from 6 Aug 2010 LD140409/ Version 1.0 from 01 Sep 2009
SPONSOR	BIOGEN IDEC
STUDY PHASE	Non-interventional clinical study
STUDY SITE(S)/COUNTRY(IES)	14 sites in the Czech Republic and 10 sites in Slovakia specialized in clinically isolated syndrome/clinically definite multiple sclerosis (CIS/CDMS) diagnosis, therapy and long-term follow-up observation
PLANNED STUDY PERIOD (FIRST ENROLMENT-LAST SUBJECT OUT)	6 years (12th December 2009 – 5th February 2016)
STUDY OBJECTIVES	Primary objectives: • To evaluate the impact of Avonex® treatment on quality of life in patients with CIS/CDMS assessed by the patient every 12 months (visual analogue scale of quality of life – VAS QoL and 36-item Short Form Health Survey - SF-36). Secondary objectives: • Quality of life assessed by the physician (VAS QoL every 12 months) • Assessment of disability progression evaluated by physician (Kurtzke Expanded Disability Status Scale – EDSS) and patient

	(EDSSpts) every 6 months and correlation between EDSS and EDSSpts. • Assessment of cognitive function changes every 12 months (Paced Auditory Serial Addition Test – PASAT). • Occurrence of relapses in the course of study. • Evaluation of weekly injection application by patients (VAS of self-administration – VAS SelfAdmin). • Impact of the disease on patient's employment. • Assess the development of CDMS in patients with CIS. • Switches in medication (product and rationale).
STUDY DESIGN AND PLAN	Prospective, observational, multicentre, non-interventional clinical study. Data to be evaluated: **a) <u>by physician:</u>** • Patient's date of birth, sex, employment, date of CIS/CDMS diagnosis • Adverse events (AE)/serious adverse event (SAE) reporting • VAS QoL (0, 12, 24 and 36 months) • EDSS functional score (0, 6, 12, 18, 24, 30 and 36 months) • Number of relapses (0, 6, 12, 18, 24, 30 and 36 months). • PASAT test (0, 12, 24 and 36 months) • Switches in medication (product and rationale) **b) <u>by patient:</u>** • VAS QoL, VAS SelfAdmin (0, 12, 24 and 36 months) • EDSSpts (0, 6, 12, 18, 24, 30 and 36 months) • SF-36 (0, 12, 24 and 36 months)
PLANNED NUMBER OF SUBJECTS	400 patients enrolled in the Czech Republic and 200 patients enrolled in Slovakia during 3 years

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION	**Inclusion criteria:** • Signed written informed consent • ≥ 18 years of age • Diagnosis of CIS or CDMS • Beginning of Avonex® medication according to medical guidelines (Summary of Product Characterization) no longer that 3 months prior enrolment • No other DMT for treatment of CIS/CDMS than Avonex® used before enrolment in the study • Recent relapse more than 30 days before the date of enrolment **Exclusion criteria:** • Legal incapability or limited legal capability • Medical or psychological condition which in the opinion of the investigator would not permit the patient to complete the study or sign meaningful informed consent • Pregnancy
STATISTICAL METHODS	In general, continuous variables like VAS QoL, VAS SelfAdmin, EDSS score etc. will be summarized with descriptive statistics (N, Mean, Median, Minimum, Maximum and Standard deviation - SD). Discrete variables like the number of relapses etc. will be presented with frequency distributions (N, %). EDSS functional scores evaluated by patient will be compared with the EDSS scores evaluated by physician using both correlation and linear regression analyses. Interim analyses are carried out during the study according to the Sponsor's requirements.

3. SUMMARY OF RESULTS AND CONCLUSIONS

Number of Subjects (Planned and Analysed):

The study projection was for 600 subjects to participate in the study; 604 subjects were screened, and data from all 559 subjects were analysed.

Criteria for Evaluation:

- VAS QoL assessed by patient
- SF-36 assessed by patient
- VAS QoL assessed by physician
- PASAT test of cognitive functions
- EDSS
- EDSS assessed by the patient (EDSSpts)
- number of relapses during last 6 months prior visit
- VAS SelfAdmin for evaluation of weekly injection application by patient
- information on subjects' employment
- CIS/CDMS diagnosis
- switch in medication (product and rationale)
- AE/SAE

Results:

- The improvement of quality of life was detected during the Avonex® treatment by VAS QoL and SF-36 questionnaires, the primary endpoints of the study. However, this improvement was only mild or negligible in most of SF-36 scores. No test of significance was made. Furthermore, the same result pattern was detected for separate analysis in population of patients who completed both questionnaires at all time points (pairwise cases) to eliminate the impact of prematurely withdrawn patients.
- The correlation between EDSS and EDSSpts is significant at the 0.01 level (2-tailed) with P-value < 0.001 in each visit. The correlation is low positive.
- During the study, the improving trend was detected for quality of life by VAS assessed by physician, cognitive function by PASAT RATE #1, decreasing occurrence of relapses and rate of employed patients [80.0% at baseline and 84.3% at end of study visit (EOS)].
- Endpoints with only slight improvement or variation around the same value include EDSS, EDSSpts and VAS to evaluate burden of weekly injection application for a patient.
- 180 patients discontinued Avonex® treatment during the study because of low efficacy (41.1%), problems with application (35.6%), patient request (12.8%), and pregnancy (10.6%).
- 173 events (AE 48.6%, SAE 51.4 %) were reported in 134 cases. The most frequent events were multiple sclerosis (MS) relapse (29.5%), followed with neurology difficulties (15.6%) and flu-like syndrome (8.7%).

Conclusion(s): The present study confirmed significant effect of Avonex® treatment on relapse

rate reduction and stabilization of patients' clinical status. The treatment had a positive effect on quality of life assessed both by a patient and a physician using VAS questionnaires and on cognitive functions. The other evaluated endpoints slightly improved or remained stable during the followed three years of treatment.

4. ETHICS

4.1. Ethics Committees

This study is non-interventional, and therefore falls outside the scope of the European Union (EU) Directive 2001/20/EC and the EU Directive 2005/28/EC.

As required by applicable local regulations, Act on pharmaceuticals No. 378/2007 in the Czech Republic as well as Health Care Act No. 576/2004 in Slovakia, all legal regulatory aspects were covered during the study conduct. This study adhered to all local regulatory requirements applicable to non-interventional studies.

Before initiating the study, the study protocol was submitted together with its associated documents (patient information and consent form) to the relevant ethic committee (EC) for their opinion, despite the fact that it is not required upon local requirements. A list of the ECs for the sites participating in the study is included in Appendix A.

The study protocol and applicable documentation was submitted to the database of non-interventional studies of the Czech Health Authority, State Institute for Drug Control (SÚKL), to The Association of Innovative Pharmaceutical Industry in the Czech Republic and Slovakia (AIFP) and to Health Insurance Companies in Slovakia.

Furthermore, the investigators were responsible for ensuring that the study was performed in accordance with the protocol, the Declaration of Helsinki and applicable regulatory requirements.

4.2. Patient Information and Consent

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

The first patient signed ICF on 12th December 2009, while the last patient first visit was held on 14th January 2013.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

5.1. Investigators

The study was performed as a multicentre study at 24 investigational sites in the Czech Republic (14) and Slovakia (10). Except site SK02, all sites had enrolled subjects. A Principal Investigator at each site was responsible for the conduct of the study at that site. Doc. MUDr. Pavel Štourač, Ph.D., prof. MUDr. Peter Turčáni, PhD., and doc. MUDr. Eleonóra Klímová, CSc. acted as the scientific coordinators for all sites in the Czech Republic resp. Slovakia. A list of all Investigators and their affiliations is provided in Appendix B. Investigators' curricula vitae are available upon request.

All investigators and the study staff were trained on protocol, case report form (CRF) completion, proper ICF obtaining, and pharmacovigilance reporting at study initiation visit. In case of any concern, training was repeated any time during the study.

5.2. Study Committees

No study committee was held in this study; therefore, this section is not applicable.

5.3. Vendors

A list of vendors and contractors that had responsibilities for study conduct, and data handling, analysis, and reporting are presented in Table 2.

Table 2: Vendors That Participated in Study

Vendor Name	Vendor Address	Responsibilities
Neox s.r.o.	V Jámě 1, 110 00 Praha 1, Czech Republic	monitoring, data management and statistical analyses, pharmacovigilance and medical writing
Transmedic Slovakia s.r.o.	Lazovná 68, 974 01 Banská Bystrica, Slovakia	pharmacovigilance

5.4. Milestones

Planned	Czech Republic	Slovakia
Study initiation	January 2010	September 2009
End of patient recruitment	January 2013	August 2012
Last observation	January 2016	August 2015
Data evaluation	February 2016	October 2015

Actual	Czech Republic	Slovakia
First patient in study	26 January 2010	12 December 2009
Last patient first visit	26 July 2012	14 January 2013
Last patient last visit	24 June 2015	5 February 2016
Close out visit	31 May 2016	27 April 2016
Data evaluation	May/June 2016	May/June 2016

6. STATISTICAL ANALYSIS PLAN

6.1. Analysis Populations

6.1.1. Effectiveness

The full analysis set to assess the effectiveness includes all eligible subjects, who must meet all inclusion and no exclusion criteria and must be treated by Avonex® within the study.

6.1.2. Safety

No safety population is defined for this study.

6.2. Statistical Methods for Study Endpoints

In general, continuous variables like VAS QoL, VAS SelfAdmin, EDSS score etc. were summarized with descriptive statistics (N, Mean, Median, Minimum, Maximum and SD). Discrete variables like number of relapses etc. were presented with frequency distributions (N, %).

Statistical analysis for correlation between EDSS assessed by physician and patient was done by a Pearson correlation coefficient. In the case that the data distribution shows to be significantly different from normal distribution, nonparametric versions of the tests, namely Spearman correlation coefficient, would be used. All testing will use two-sided tests with the criteria set at $\alpha = 0.05$.

All results (including p-values of tests) are presented in a descriptive manner in the form of graphs and tables.

6.3. Interim Analyses

Interim analyses were performed in January 2012, October 2013 and March 2016. The same endpoints were analysed as for final analyses. Results of interim analysis from October 2013 were published in the scientific medical journal (Štourač et al, 2014).

6.4. Determination of Sample Size

Assuming that the detected effect size would be similar to that observed in (Pittock SJ et al., 2004; Putzki et al., 2009; Twork S, et al, 2010), a sample size of 400 subjects in Czech Republic was determined to be included. The sample size is sufficient to detect at a significance level of 0.05 a mean difference of 0.02 from baseline in utility value assessed by the VAS, SF-36 and EQ-5D questionnaire, based on a standard deviation of 0.13 and a power of 80% with an estimated drop-out rate of 20%.

7. STUDY SUBJECTS

7.1. Subject Accountability

7.1.1. Recruited patients

The international, multicentre study LD140409 was carried out in 2 countries: Czech Republic and Slovakia. From a total of 604 screened patients, 559 patients were enrolled to the study. Overview of screened patients in total and in each country separately, is provided in Table 3.

Table 3: Subjects Population - Screened Subjects

	Total	Czech Republic	Slovakia
Number of Screened patients	604	426	178
1) Number of Screen Failures	45	26	19
2) Number of Enrolled patients	559	400	159
2a) Number of Completed patients	331	245	86
2b) Number of Discontinued patients	228	155	73

The statistical analysis is based on data from all available CRF's from Czech Republic and Slovakia. The total count of analysed patients is 559.

Table 4: Subjects data availability

	Valid visits		Missing visits	
	N	%	N	%
Baseline (0 months)	559	100%	0	0%
6 months	521	93%	38	7%
12 months	483	86%	76	14%
18 months	424	76%	135	24%
24 months	370	66%	189	34%
30 months	327	58%	232	42%
36 months	308	55%	251	45%
End of Study	559	100%	0	0%

The first patient in the study (SK10-001) was enrolled in Slovakia on 12th December 2009 and the last patient (SK07-021) was enrolled in Slovakia on 14thJanuary 2013. The last visit in study was recorded on 5th February 2016 (SK08-013).

Table 5 and Figure 1 describe number of patients enrolled at each study site.

Table 5: Number of enrolled subjects per site

Site number	N	%
CZ01	103	18%
CZ02	18	3%
CZ03	25	4%
CZ04	19	3%
CZ05	8	1%
CZ06	14	3%
CZ07	35	6%
CZ08	38	7%
CZ09	18	3%
CZ10	49	9%
CZ11	37	7%
CZ12	16	3%
CZ13	10	2%
CZ14	10	2%
SK01	9	2%
SK02	0	0%
SK03	5	1%
SK04	7	1%
SK05	19	3%
SK06	45	8%
SK07	20	4%
SK08	11	2%
SK09	16	3%
SK10	27	5%
Total	559	100%

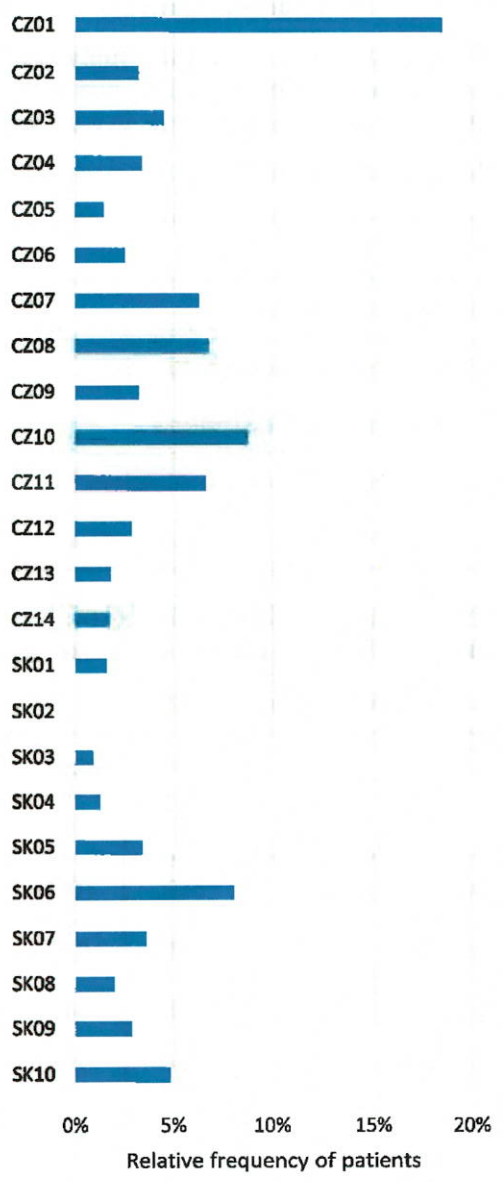


Figure 1: Bar chart of number of subjects per site

7.1.2. Withdrawals

In total, 228 subjects withdrew from the study. As summarized in Table 6 and Figure 2, the reasons for withdrawal and the reasons for treatment switch were multiple-choice question, when one or more answers could be selected.

Table 6: Reason for withdrawal and treatment switch

		N	Withdrawal (%)	Treatment switch (%)
1) IC withdrawal		53	21.1%	
2) Death of patient		1	0.4%	
3) Lost of contact		17	6.8%	
4) Treatment switch		180	71.7%	100.0%
	Low efficacy	74	29.5%	41.1%
	Problems with application	67	25.5%	35.6%
	Patient request	22	9.2%	12.8%
	Pregnancy	19	7.6%	10.6%

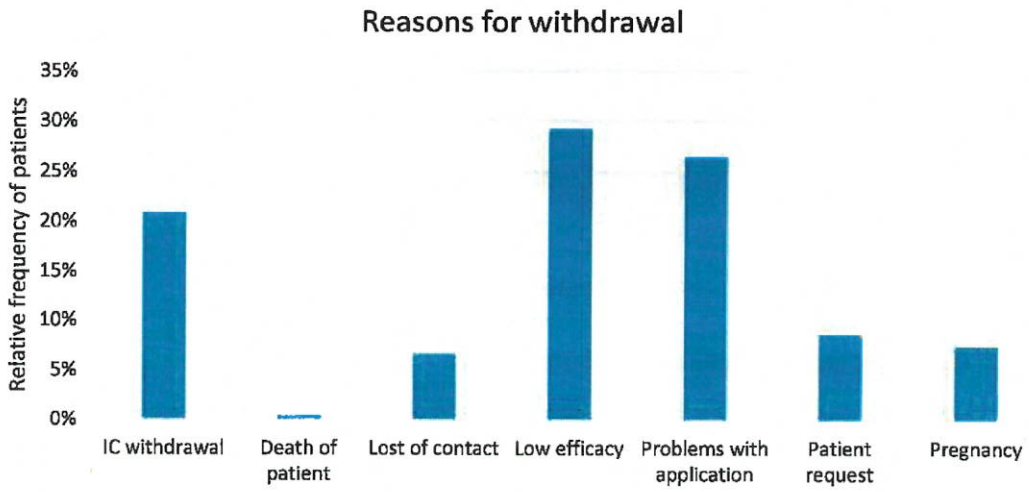


Figure 2: Bar chart of reasons for withdrawal

7.2. Demographics

All demographic and baseline characteristics are listed by subject.

Summary statistics is provided for demographic and baseline characteristics (sex, age, CDMS/CIS duration, and time from last MS attack) as described in the Table 7 and Table 8 and the following figures. Among patients with MS, female to male ratio was 2.3 in year 2000 (Alonso and Hernan 2008), what is in accordance with gender distribution in the study population (70.5% of females and 29.5% of males)

No statistical comparison of the treatment groups was performed.

Table 7: Gender distribution

	N	%
Male	165	29.5%
Female	394	70.5%
Total	**559**	**100.0%**

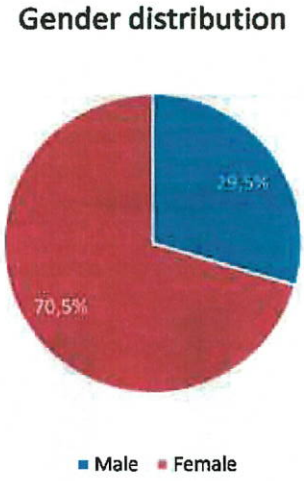


Figure 3: Pie chart of gender distribution (N = 559)

Table 8: Descriptive statistics of age and disease characteristics

	N	Mean	SD	Median	Minimum	Maximum
Age [years]	559	33.4	9.20	33	18	60
CIS/CDMS diagnosis before study [months]	559	20.3	39.33	6	0	334
CDMS diagnosis before study [months]	302	31.5	49.76	9	0	334
CIS diagnosis before study [months]	257	7.1	11.75	5	0	130
Last attack before study [months]	559	6.8	6.99	5	1	79

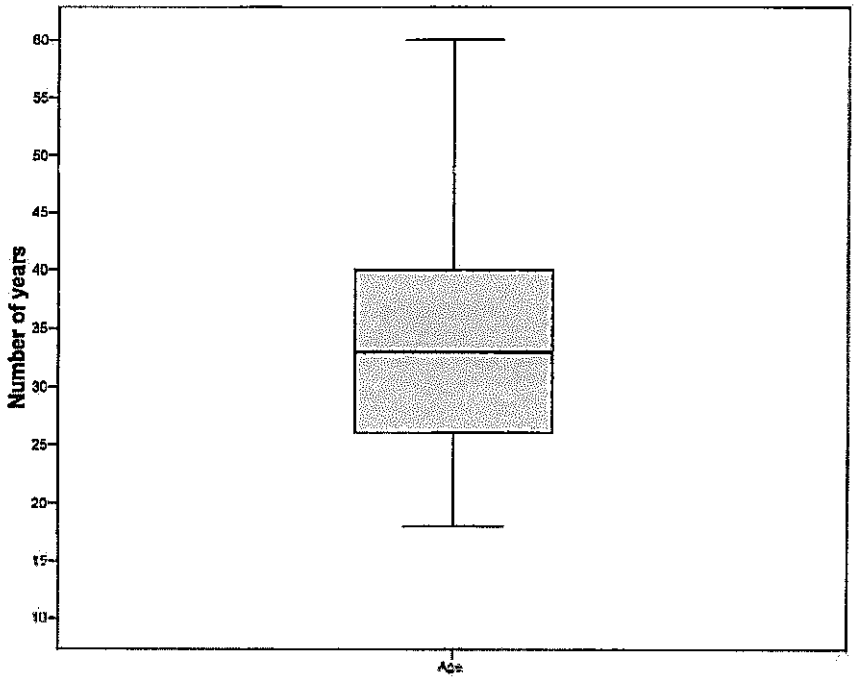
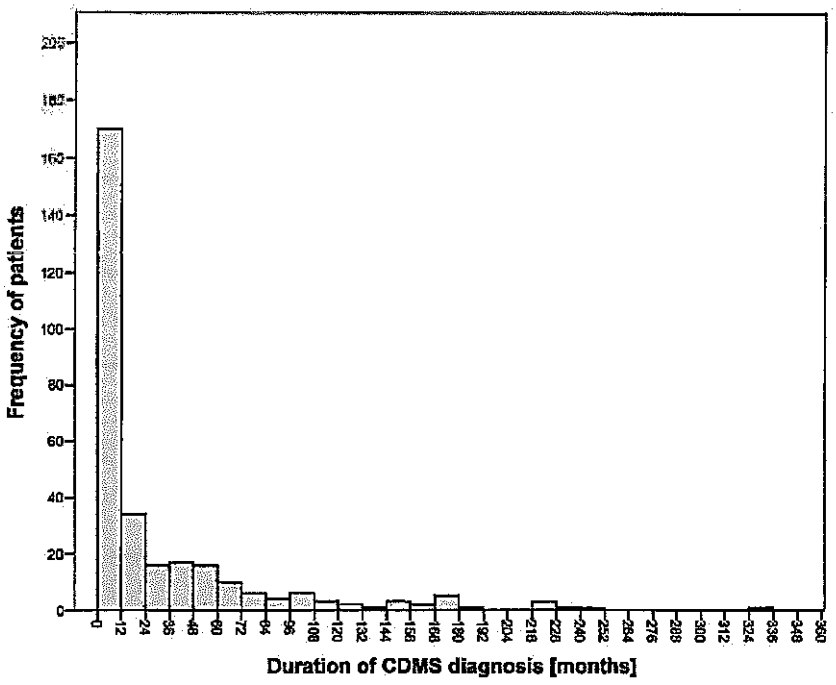


Figure 4: Boxplot of age (N = 559)

CDMS



CIS

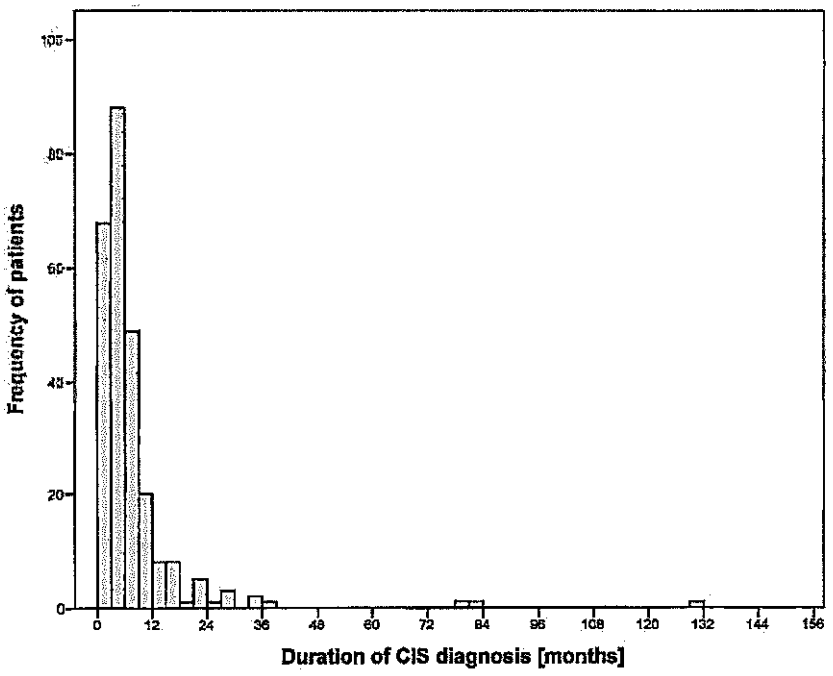


Figure 5: Histograms of CDMS (N = 302) and CIS (N = 257) duration in months at baseline

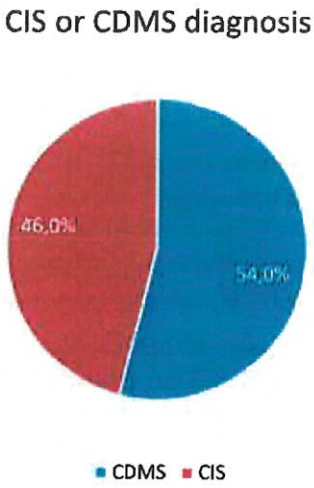


Figure 6: Pie chart of frequency of CDMS and CIS diagnosis at baseline (N = 559)

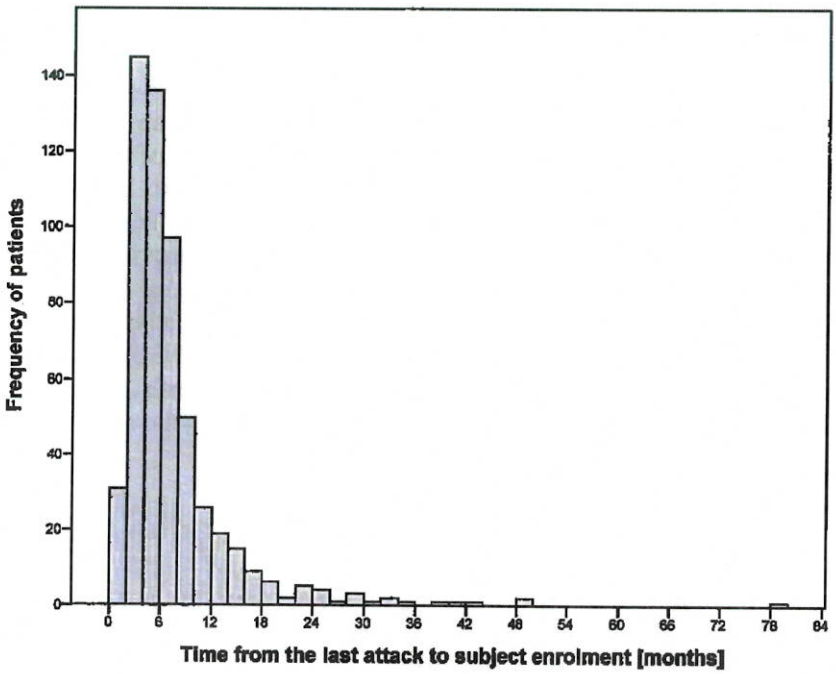


Figure 7: Histogram of time from the last attack to subject enrolment (in months)

8. STUDY RESULTS

8.1. Primary efficacy analysis

The primary objective of the study was to evaluate the impact of Avonex® treatment on quality of life in patients with CIS/CDMS. The questionnaires VAS QoL and SF-36 were selected as primary endpoints to assess patients' quality of life at baseline and then every year, i.e. month 12, 24, and 36. Statistical analysis of collected data was performed according to the protocol "Protocol Amendment 1 – LD140409 – AMETYST, version 1.0_CZ from 6th Aug 2010.

The VAS is extensively used in the assessment of health-related quality of life (HRQOL) (Shmueli, 2005). The VAS assesses influence of MS on everyday life in the scale from 0 (no influence at all) to 100 (a lot). The scale is administered by patient.

The SF-36 v2 Health Survey asks 36 questions to measure functional health and well-being from the patient's point of view. The SF-36 v2® provides scores for each of the eight health domains and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. The survey uses norm-based scoring with range from 0 (very low QoL) to 100 (very high QoL). The questionnaire is administered by patient.

8.1.1. Quality of life assessed by patient – VAS QoL

During the study, quality of life assessed by VAS QoL was improving. As described in the Table 10 and on Figure 8, the mean baseline value 29.1 gradually decreased to mean value 22.2 at month 36. Furthermore, the same analysis was performed for population of patients who completed VAS QoL at all time points (complete-case analysis) to eliminate impact of the prematurely withdrawn patients. Results are summarized in the Table 11 and on Figure 9 and Figure 10. As for the whole study population, VAS QoL mean score was improving (from 27.8 at baseline to 21.6 at month 36), although there are slight fluctuations at the other time points (23.5 at month 12 and 24.2 at month 24). However, median values exactly copy course of the whole population median curve (25 at baseline and 20 at month 12, 24 and 36). In addition, negative mean VAS QoL changes from baseline (-1.1 at month 12, -2.1 at month 24, and -5.4 at month 36 as shown in Table 12) confirm that VAS QoL was improving during the study.

Table 9: Number of collected VAS QoL assessed by patient

	yes		no	
	N	%	N	%
0 MONTHS	555	99.3%	4	0.7%
12 MONTHS	477	98.8%	6	1.2%
24 MONTHS	366	98.9%	4	1.1%
36 MONTHS	302	98.1%	6	1.9%

Table 10: Descriptive statistics of VAS QoL assessed by patient every 12 months – available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	555	29.1	22.99	25	0	95
12 MONTHS	477	26.0	22.12	20	0	100
24 MONTHS	366	24.9	20.89	20	0	100
36 MONTHS	302	22.2	19.48	20	0	100

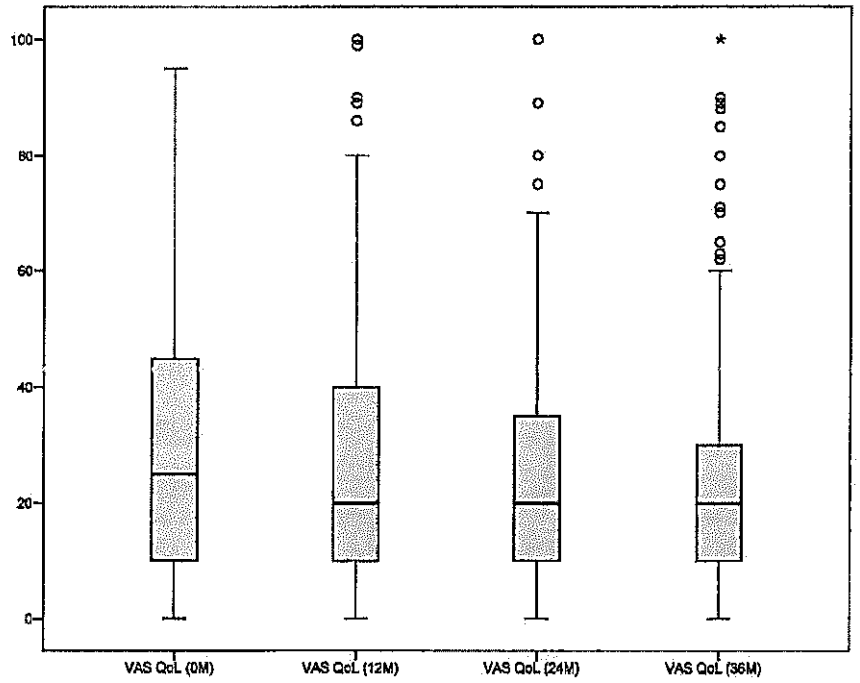


Figure 8: Boxplot of VAS QoL assessed by patient every 12 months – available-case analysis

Table 11: Descriptive statistics of VAS QoL assessed by patient every 12 months – complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	266	27.8	21.94	25	0	90
12 MONTHS	266	23.5	20.32	20	0	99
24 MONTHS	266	24.2	20.73	20	0	100
36 MONTHS	266	21.6	18.80	20	0	100

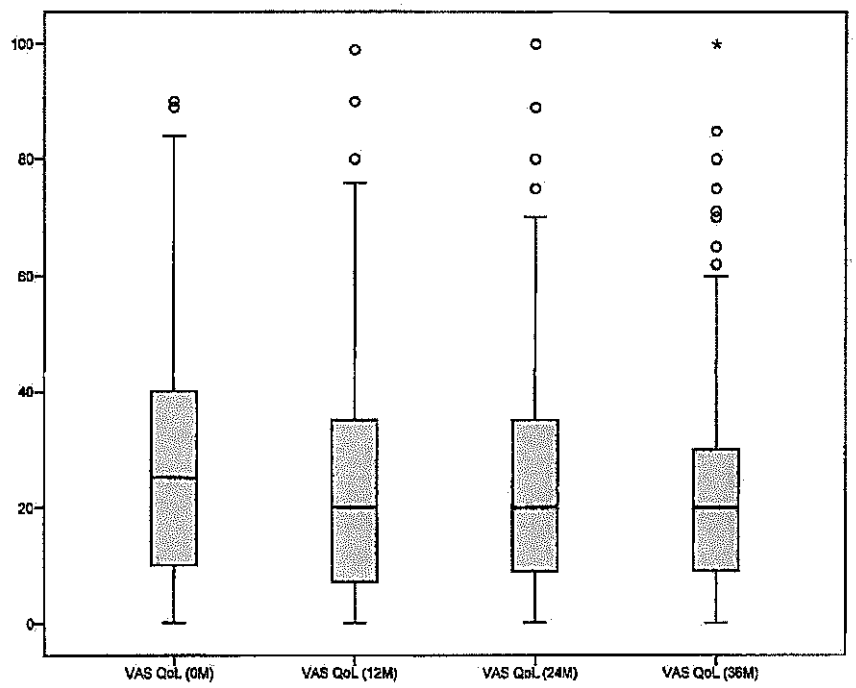


Figure 9: Boxplot of VAS QoL assessed by patient every 12 months – complete-case analysis (N = 266)

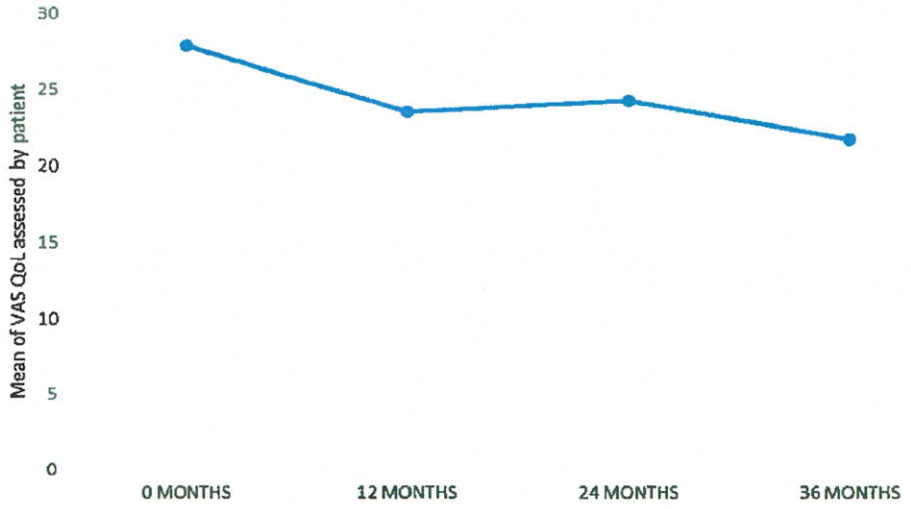


Figure 10: Line graph of mean of VAS QoL assessed by patient every 12 months (N = 266)

Table 12: Descriptive statistics of VAS QoL change from baseline assessed by patient every 12 months

	N	Mean	Standard Deviation	Median	Minimum	Maximum
12 - 0 MONTHS	474	-2.3	20.35	0	-89	100
24 - 0 MONTHS	364	-3.3	21.38	0	-85	92
36 - 0 MONTHS	299	-5.4	20.99	-4	-88	92

8.1.2. Quality of life assessed by patient – SF-36

As shown on the Figure 11, the lowest score was observed for Reported health transition, General health and Vitality. The highest scores were observed for Physical functioning, Bodily pain and Role limitation due to emontional problems.

Table 13: Number of collected SF-36 assessed by patient

	yes		no	
	N	%	N	%
0 MONTHS	559	100.0%	0	0.0%
12 MONTHS	476	98.6%	7	1.4%
24 MONTHS	368	99.5%	2	1.1%
36 MONTHS	303	98.4%	5	1.6%

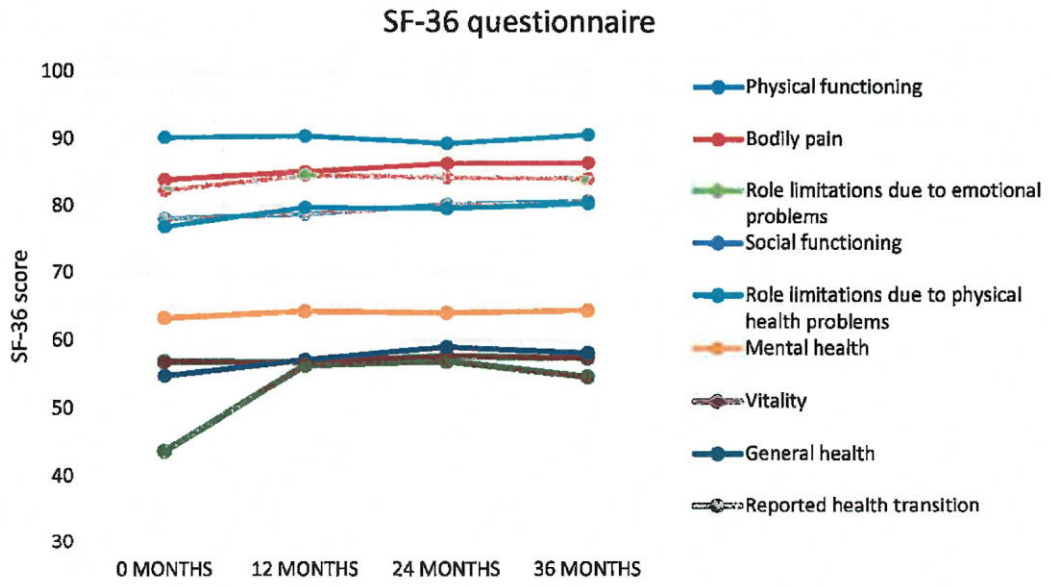


Figure 11: Line graph of mean of SF-36 scores assessed by the patient every 12 months – complete-case analysis (N = 223)

8.1.2.1 SF-36: Physical functioning

During the study, the average score for physical functioning was improving (87.48 at baseline to 90.03 at month 36); however median was the same for the whole study (95).

Table 14: SF-36 Physical functioning every 12 months

PF	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	551	87.48	16.629	95	10	100
12 MONTHS	468	87.59	16.842	95	10	100
24 MONTHS	365	87.89	17.950	95	5	100
36 MONTHS	299	90.03	14.893	95	15	100

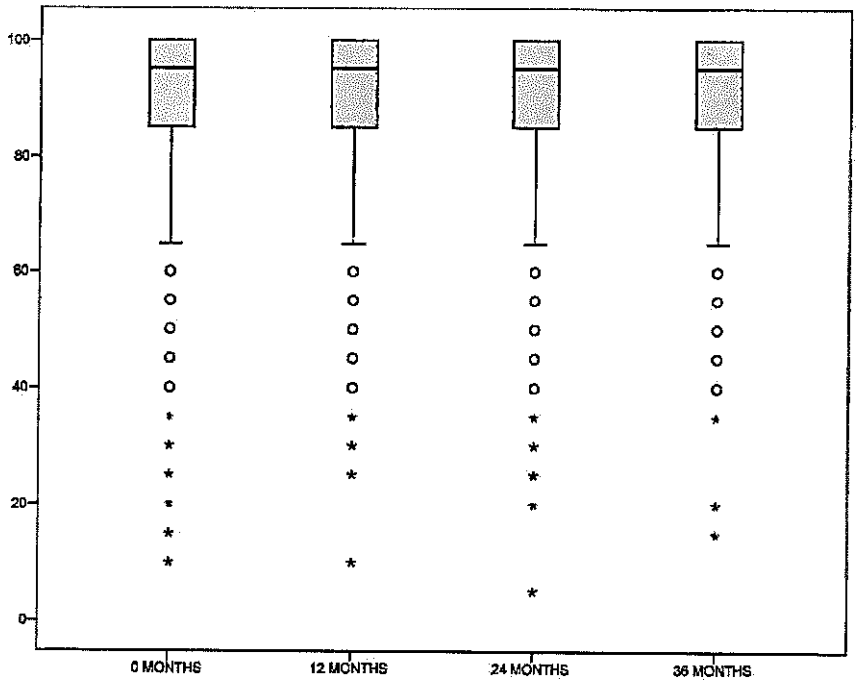


Figure 12: Boxplot of Physical functioning every 12 months

8.1.2.2 SF-36: Role limitations due to physical health problems

During the study, the average score for role limitations due to physical health problems was improving (74.97 at baseline to 79.38 at month 36); however median was the same for the whole study (81.25).

Table 15: Role limitations due to physical health problems every 12 months

RP	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	553	74.97	23.586	81	0	100
12 MONTHS	469	76.56	23.349	81	0	100
24 MONTHS	367	76.69	22.701	81	0	100
36 MONTHS	300	79.38	20.043	81	0	100

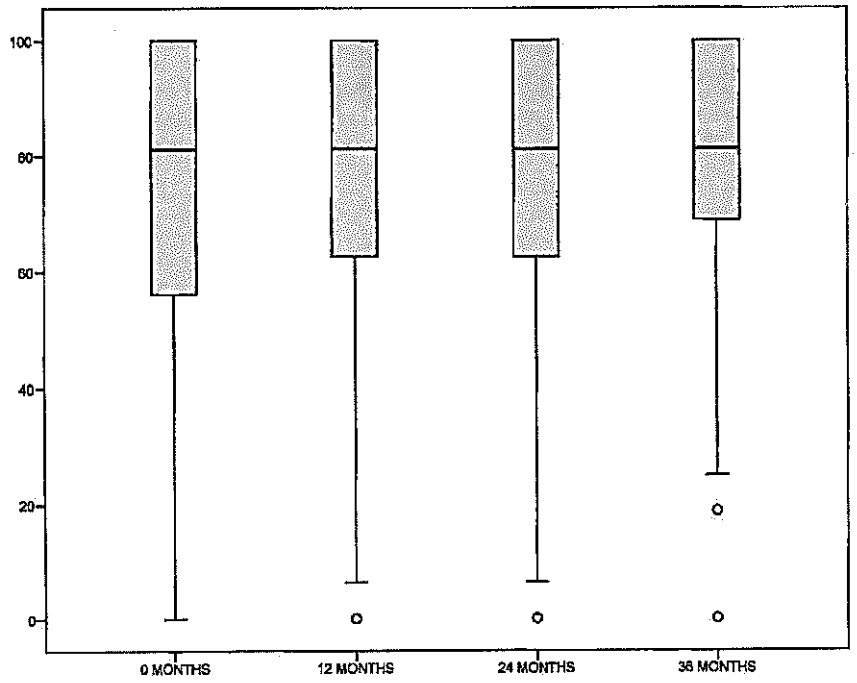


Figure 13: Boxplot of Role limitation due to physical health problems every 12 months

8.1.2.3 SF-36: Bodily pain

During the study, the average score for bodily pain was improving (82.23 at baseline to 85.72 at month 36), although there is a slight fluctuation at month 12 (82.14).

Table 16: Bodily pain every 12 months

BP	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	558	82.23	20.873	90	23	100
12 MONTHS	475	82.14	21.552	90	20	100
24 MONTHS	368	84.17	21.028	100	10	100
36 MONTHS	302	85.72	18.996	100	23	100

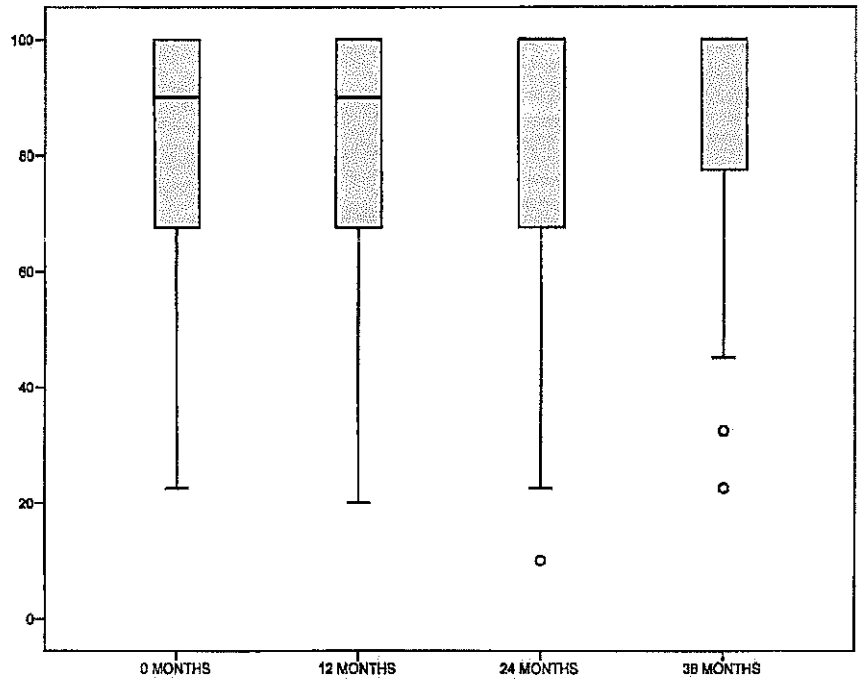


Figure 14: Boxplot of Bodily pain every 12 months

8.1.2.4 SF-36: General health

During the study, the average score for general health was gradually improving (53.77 at baseline to 57.92 at month 36). Although median was the same for months 24 and 36 (60.00), it also improved considerably during the study as the baseline value was 50.00.

Table 17: General health every 12 months

GH	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	549	53.77	18.851	50	0	100
12 MONTHS	473	54.60	19.185	55	0	100
24 MONTHS	365	57.00	18.876	60	10	100
36 MONTHS	301	57.92	17.562	60	10	100

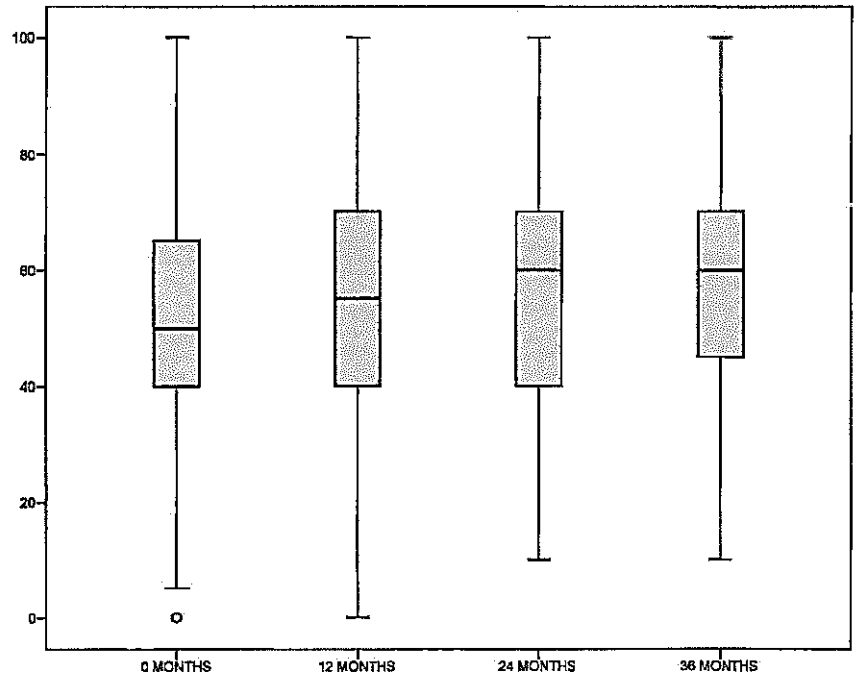


Figure 15: Boxplot of General health every 12 months

8.1.2.5 SF-36: Vitality

During the study, the average score for vitality was improving (55.35 at baseline to 57.81 at month 36), although there is a slight fluctuation at month 12 (55.02).

Table 18: Vitality every 12 months

EF	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	555	55.35	15.486	55	10	90
12 MONTHS	470	55.02	15.835	55	10	90
24 MONTHS	366	56.27	15.051	55	10	90
36 MONTHS	299	57.81	14.147	60	15	90

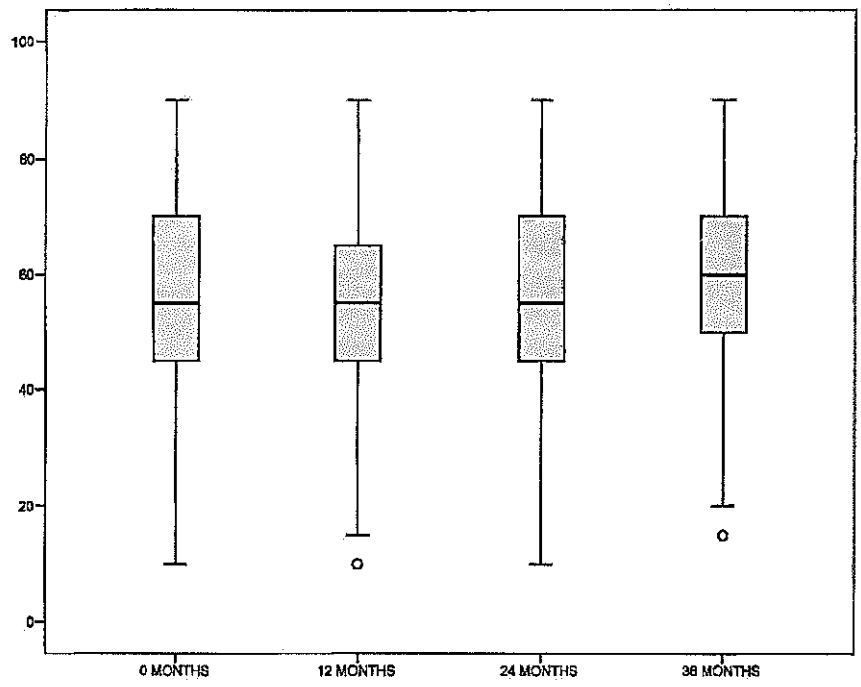


Figure 16: Boxplot of Vitality every 12 months

8.1.2.6 SF-36: Social functioning

During the study, the average score for social functioning was improving (75.78 at baseline to 79.86 at month 36), although there is a fluctuation at month 12 (74.95).

Table 19: Social functioning every 12 months

SF	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	547	75.78	22.607	75	13	100
12 MONTHS	469	74.95	22.660	75	0	100
24 MONTHS	367	77.72	22.846	88	0	100
36 MONTHS	301	79.86	20.685	88	13	100

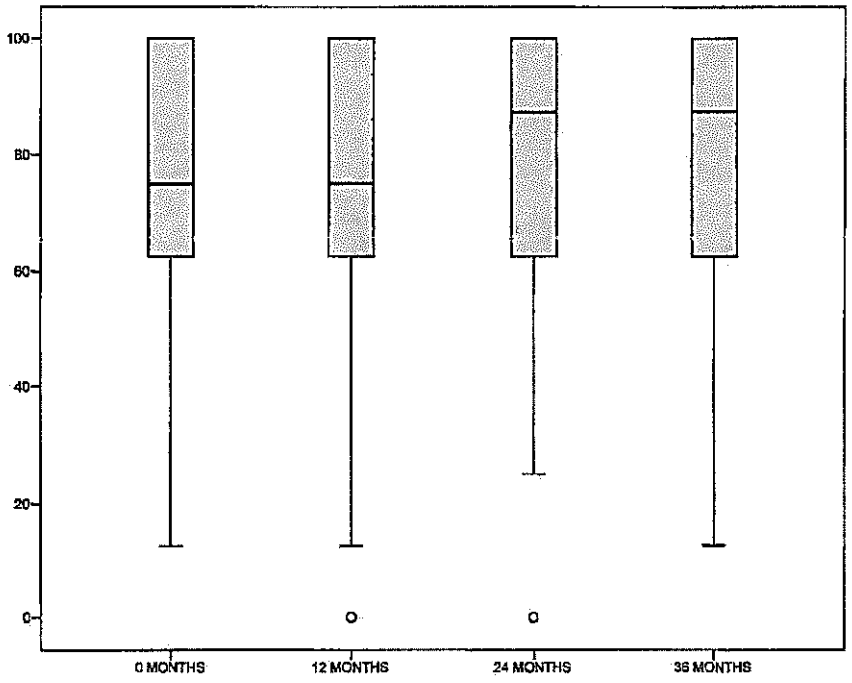


Figure 17: Boxplot of Social functioning every 12 months

8.1.2.7 SF-36: Role limitations due to emotional problems

During the study, the average score for role limitations due to emotional problems was varying as described in Table 20. Median value remained the same (91.67) at all time points except month 24 (83.33).

Table 20: Role limitations due to emotional problems every 12 months

RE	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	554	82.33	20.865	92	0	100
12 MONTHS	473	82.19	20.756	92	0	100
24 MONTHS	368	81.61	20.543	83	0	100
36 MONTHS	300	83.22	19.071	92	0	100

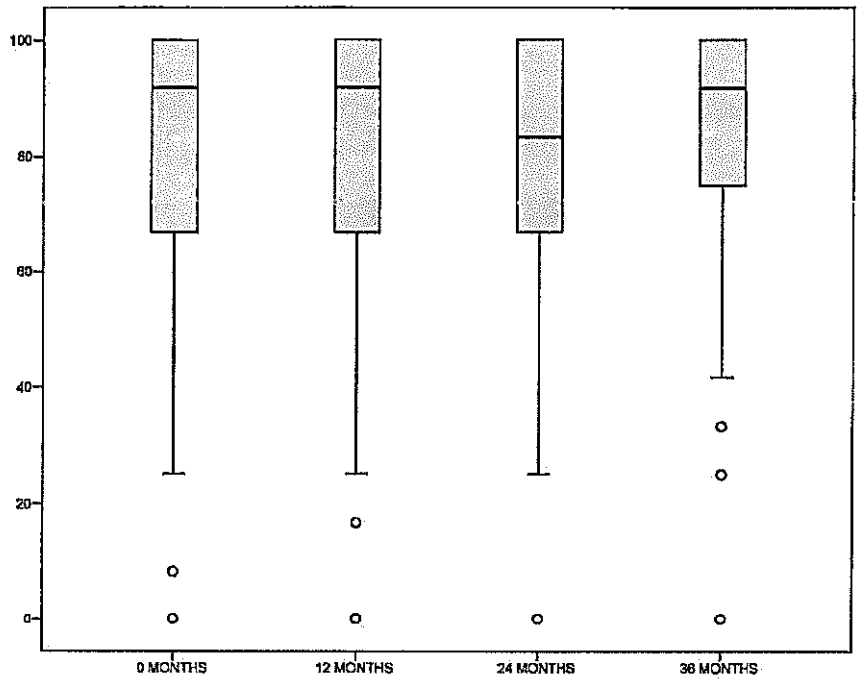


Figure 18: Boxplot of Role limitation due to emotional problems every 12 months

8.1.2.8 SF-36: Mental health

During the study, the average score for mental health was improving (62.33 at baseline to 64.27 at month 36), although median values remained the same from baseline to month 24 (64.00). At month 36, median increased to 66.00.

Table 21: Mental health every 12 months

EW	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	549	62.33	13.818	64	20	88
12 MONTHS	473	62.70	13.614	64	8	88
24 MONTHS	364	63.11	12.954	64	16	88
36 MONTHS	300	64.27	12.823	66	16	88

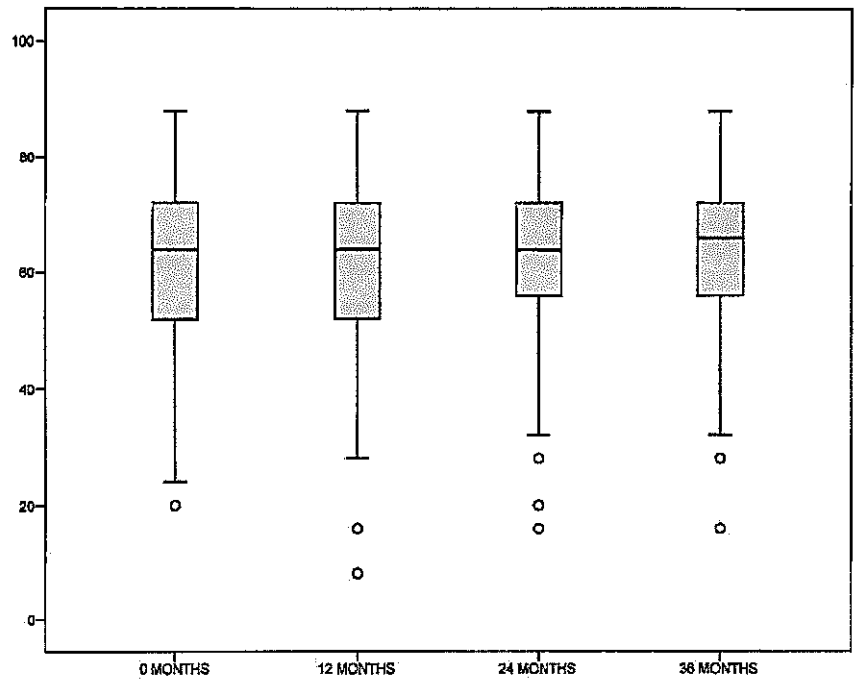


Figure 19: Boxplot of Mental health every 12 months

8.1.2.9 SF-36: Reported health transition

Subjects had to evaluate the change in their health status over one previous year. Most of the subjects assessed their health status about the same as one year ago during the whole study.

As summarized in Table 22, there were clear trends for answers "much better now than year ago", and "somewhat better now than year ago", that were reported with decreasing frequencies during the study. On the opposite, the frequency of answer "about the same as one year ago" was the only one that obviously increased in time. Frequency of answer "somewhat worse now than one year ago" increased after baseline from 10% to 19% at month 12 and 24 with a very slight drop to 18% at month 36. At last, frequency of answer "much worse now than year ago" increased after baseline from 4% to 10% at month 12 followed by decrease at month 24 (8%) and further decrease to 5% at month 36.

Table 22: SF-36 Reported health transition every 12 months

	Much better now than one year ago		Somewhat better now than one year ago		About the same as one year ago		Somewhat worse now than one year ago		Much worse now than one year ago	
	N	%	N	%	N	%	N	%	N	%
0M	29	5%	190	34%	258	47%	55	10%	22	4%
12M	8	2%	87	18%	242	51%	92	19%	46	10%
24M	3	1%	38	10%	230	63%	69	19%	28	8%
36M	2	1%	27	9%	204	67%	54	18%	16	5%

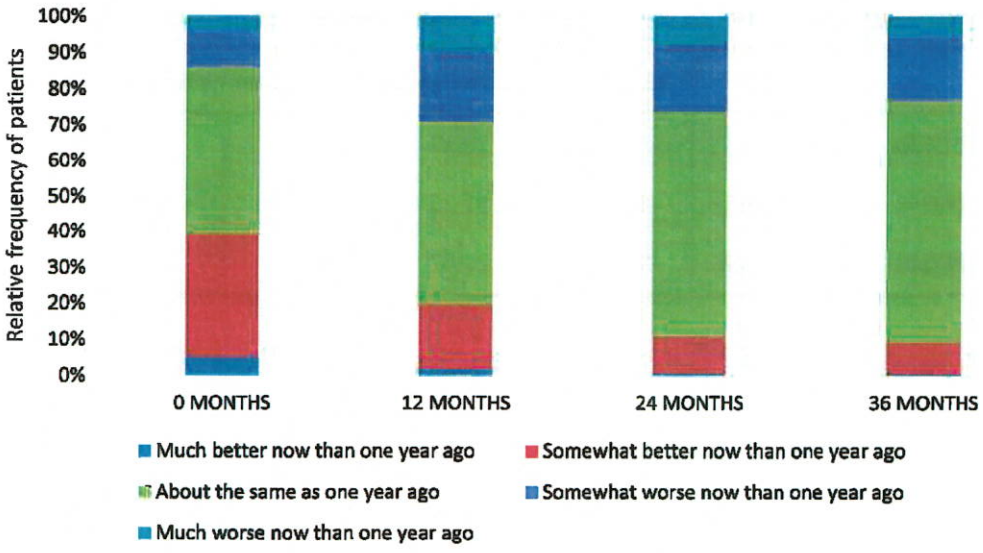


Figure 20: Bar chart of SF-36 Reported health transition every 12 months

8.2. Secondary efficacy analysis

8.2.1. Quality of life assessed by physician – VAS QoL

The VAS assesses influence of MS on everyday life in scale from 0 (no influence at all) to 100 (a lot). The scale was assessed by physician.

Table 23: Number of collected VAS QoL assessed by the physician

	yes		no	
	N	%	N	%
0 MONTHS	555	99.3%	4	0.7%
12 MONTHS	477	98.8%	6	1.2%
24 MONTHS	368	99.5%	2	0.5%
36 MONTHS	302	98.1%	6	1.9%

During the study, quality of life assessed by VAS QoL was improving. The mean baseline value 29.4 gradually decreased to mean value 23.3 at month 36 (Table 25). It corresponds with mean changes from baseline -2.9 at month 12, -4.7 at month 24, and -5.4 at month 36 (Table 24). Furthermore, the separate analysis was performed for population of patients for whom VAS QoL was completed at all time points (complete-case analysis) to eliminate impact of prematurely withdrawn patients. Even though median was the same for the whole study (20)), VAS QoL mean score improved during the study with the following values (28.7 at baseline, 23.4 at month 12 and 22.9 at month 30 and 36) as described in the Table 26 and on Figure 22 and Figure 23.

Table 24: Descriptive statistics of VAS QoL change from baseline assessed by physician every 12 months

	N	Mean	Standard Deviation	Median	Minimum	Maximum
12 - 0 MONTHS	473	-2.9	20.37	0	-77	71
24 - 0 MONTHS	365	-4.7	21.26	0	-81	81
36 - 0 MONTHS	299	-5.4	20.67	-1	-82	50

Table 25: VAS QoL assessed by the physician every 12 months – available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	555	29.4	22.46	24	0	96
12 MONTHS	477	26.1	19.17	20	0	91
24 MONTHS	368	24.0	17.30	20	0	95
36 MONTHS	302	23.3	17.71	20	0	94

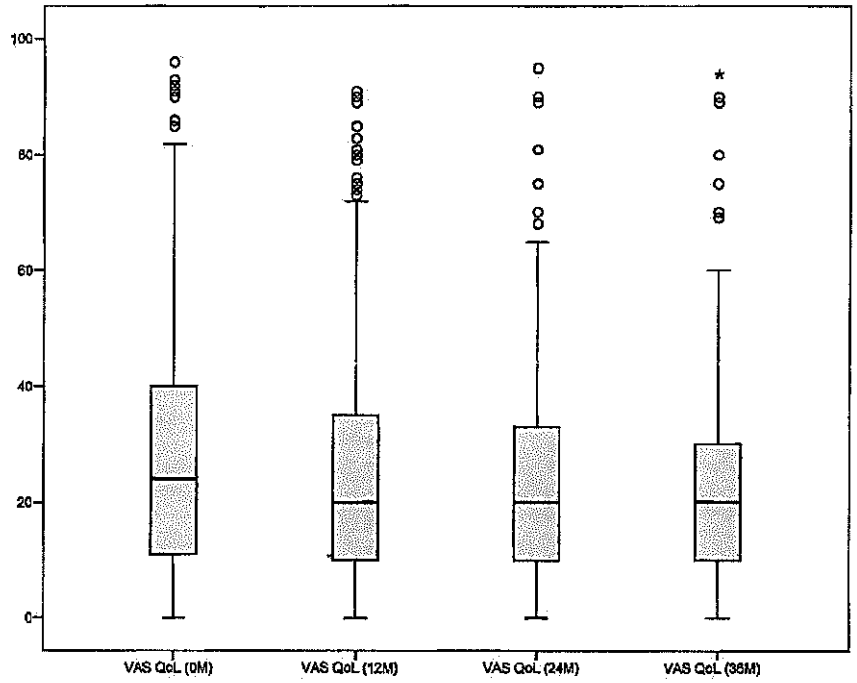


Figure 21: Boxplot of VAS QoL assessed by the physician every 12 months – available-case analysis

Table 26: Descriptive statistics of VAS QoL assessed by physician every 12 months – complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	266	28.7	21.92	20	0	96
12 MONTHS	266	23.4	17.43	20	0	90
24 MONTHS	266	22.9	16.47	20	0	95
36 MONTHS	266	22.9	17.05	20	0	94

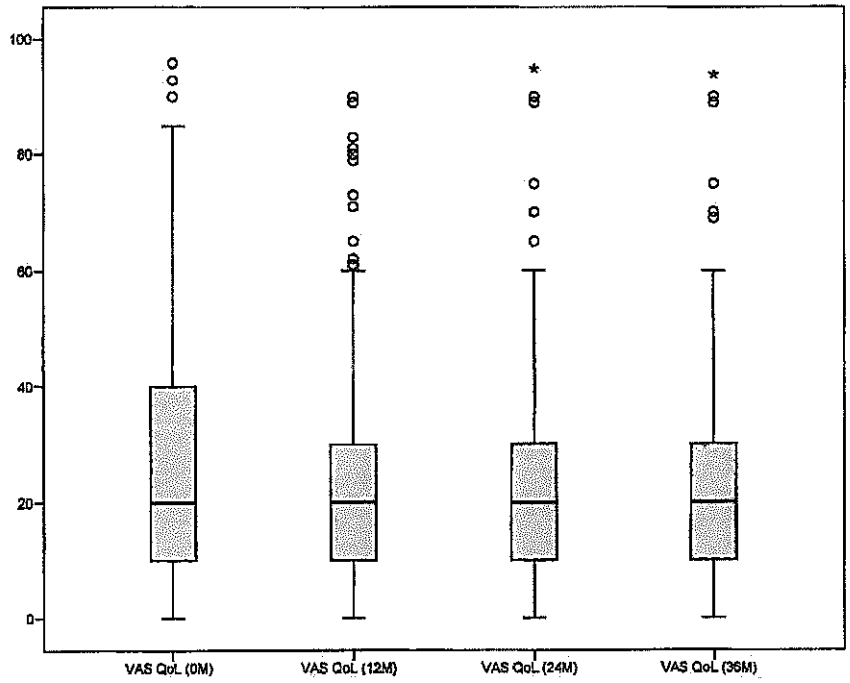


Figure 22: Boxplot of VAS QoL assessed by the physician every 12 months – complete-case analysis (N = 266)

Figure 23: Line graph of mean of VAS QoL assessed by the physician every 12 months (N = 266)

8.2.2. Assessment of disability progression evaluated by physician – EDSS

The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = normal neurologic exam; to (5) = ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS. In addition, it also provides eight subscale measurements called Functional System (FS) scores. These subscale categories are listed below. The levels of function within each category refer to the eight functional systems affected by MS.

EDSS was assessed every 6 months. During the study, the score was varying around the same value as described in the Table 28. The median value remained the same for the whole study (1.5). Exactly the same trends resulted from the separate analysis of complete-case analysis population (Table 29 and Figure 25 and Figure 26).

Table 27: Number of collected EDSS assessed by physician every 6 months

	yes		no	
	N	%	N	%
0 MONTHS	559	100.0%	0	0.0%
6 MONTHS	520	99.8%	1	0.2%
12 MONTHS	478	99.0%	5	1.0%
18 MONTHS	419	98.8%	5	1.2%
24 MONTHS	368	99.5%	2	0.5%
30 MONTHS	320	97.9%	7	2.1%
36 MONTHS	303	98.4%	5	1.6%

Table 28: EDSS assessed by physician every 6 months – available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	559	1.72	0.779	1.5	0.0	4.5
6 MONTHS	520	1.71	0.863	1.5	0.0	5.5
12 MONTHS	478	1.70	0.911	1.5	0.0	5.5
18 MONTHS	419	1.63	0.844	1.5	0.0	4.5
24 MONTHS	368	1.68	0.837	1.5	0.0	4.5
30 MONTHS	320	1.68	0.792	1.5	0.0	4.5
36 MONTHS	303	1.69	0.784	1.5	0.0	4.5

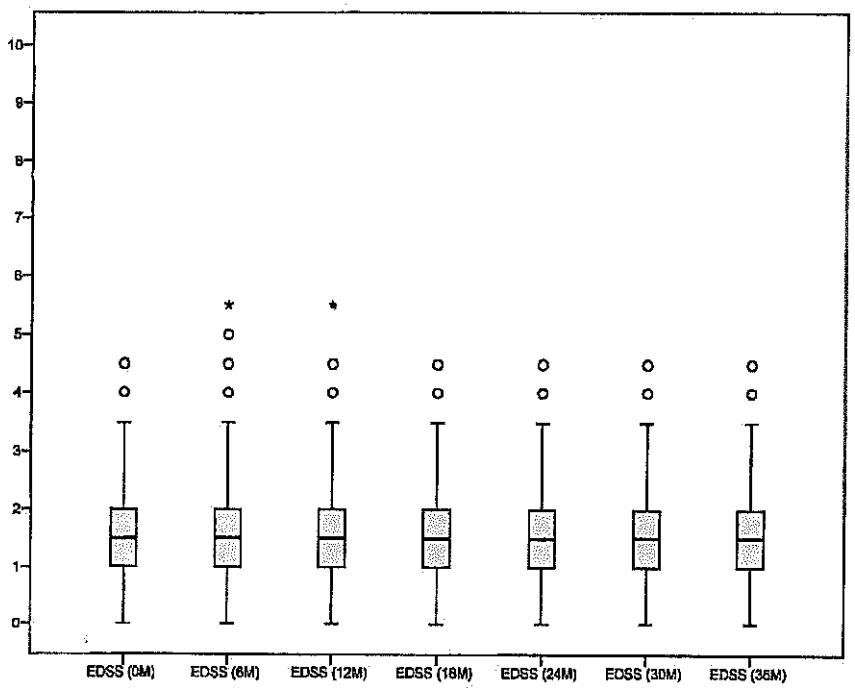


Figure 24: Boxplot of EDSS assessed by physician every 6 months – available-case analysis

Table 29: EDSS assessed by physician every 6 months – complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	250	1.66	0.713	1.5	0.0	4.5
6 MONTHS	250	1.59	0.707	1.5	0.0	4.5
12 MONTHS	250	1.56	0.765	1.5	0.0	4.5
18 MONTHS	250	1.58	0.754	1.5	0.0	4.5
24 MONTHS	250	1.59	0.741	1.5	0.0	4.5
30 MONTHS	250	1.63	0.762	1.5	0.0	4.5
36 MONTHS	250	1.69	0.805	1.5	0.0	4.5

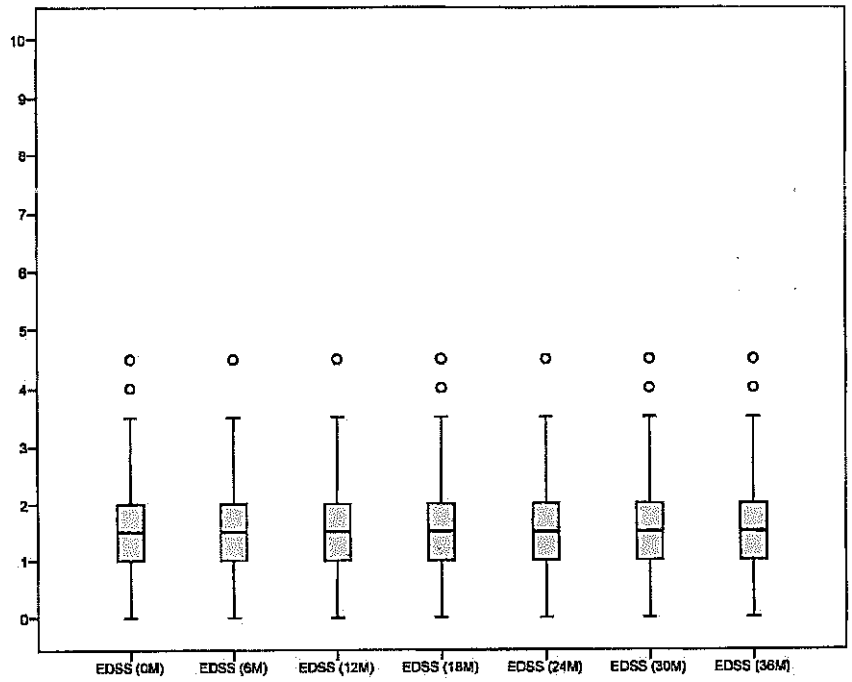


Figure 25: Boxplot of EDSS assessed by physician every 6 months – complete-case analysis (N = 250)

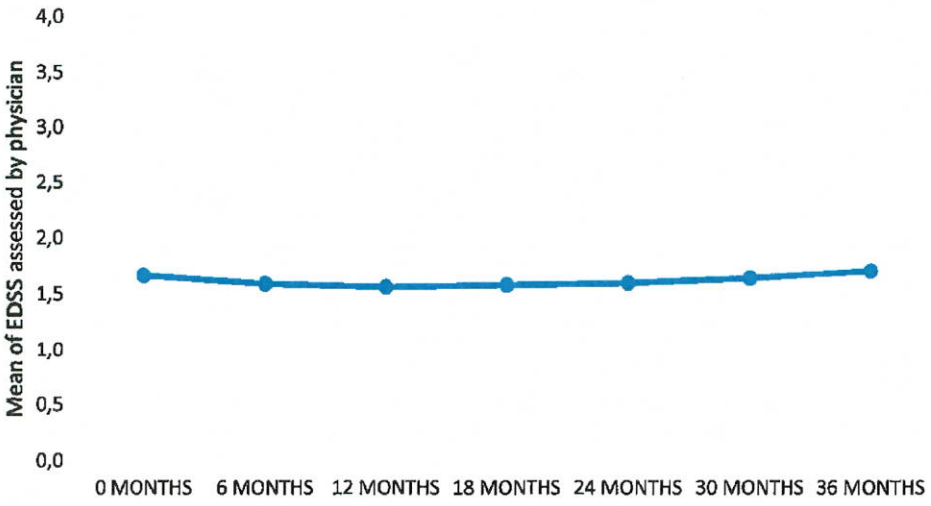


Figure 26: Line graph of mean of EDSS assessed by physician every 6 months (N = 250)

8.2.3. Assessment of cognitive function changes by physician – PASAT

The PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. The test score is the total number of correct sums given (out of 60 possible) in each trial. Following tables present percent of correct answers (0 is the worst and 100 is the best score).

During the study, PASAT test version A was used at visit Month 0 – baseline and visit Month 24, and version B was used at month 12 and month 36. Furthermore, two rates of stimuli presentation could be used during PASAT test. Rate #1 refers to presentation of a single digit every 3 seconds, while rate #2 corresponds to 2 seconds' interval. After PASAT RATE #1 completion, patient was offer to voluntarily perform PASAT RATE #2.

Table 30: Number of collected PASAT assessed by the physician

	yes		no	
	N	%	N	%
0 MONTHS	508	90.9%	51	9.1%
12 MONTHS	404	83.6%	79	16.4%
24 MONTHS	299	80.8%	71	19.2%
36 MONTHS	228	74.0%	80	26.0%

The evaluated cognitive function was improving during the study. The mean baseline value of PASAT RATE #1 81.2 gradually increased to mean value 87.2 at month 36 (Table 31). Even better improvement was recorded for complete-case analysis population, when 80.0 at baseline increased to 87.8 at month 36 (Table 32). As the PASAT RATE #2 was optional, it was often refused by a patient to perform it (Table 33 for the whole study population and Table 34 for complete-case analysis only).

Table 31: PASAT RATE #1 assessed by the physician every 12 months – available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	508	81.2	17.67	87	0	100
12 MONTHS	404	84.0	15.36	88	0	100
24 MONTHS	299	86.0	14.72	90	23	100
36 MONTHS	228	87.2	14.58	92	8	100

Table 32: PASAT RATE #1 assessed by the physician every 12 months – complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	190	80.0	18.63	85	0	100
12 MONTHS	190	83.1	15.48	87	23	100
24 MONTHS	190	85.8	15.01	90	23	100
36 MONTHS	190	87.8	13.87	93	30	100

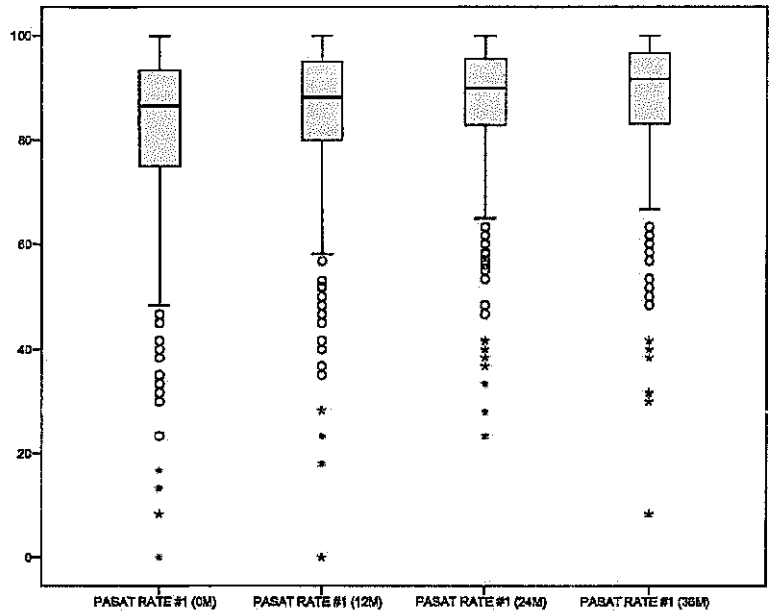


Figure 27: Boxplot of PASAT RATE #1 assessed by physician every 12 months – available-case analysis

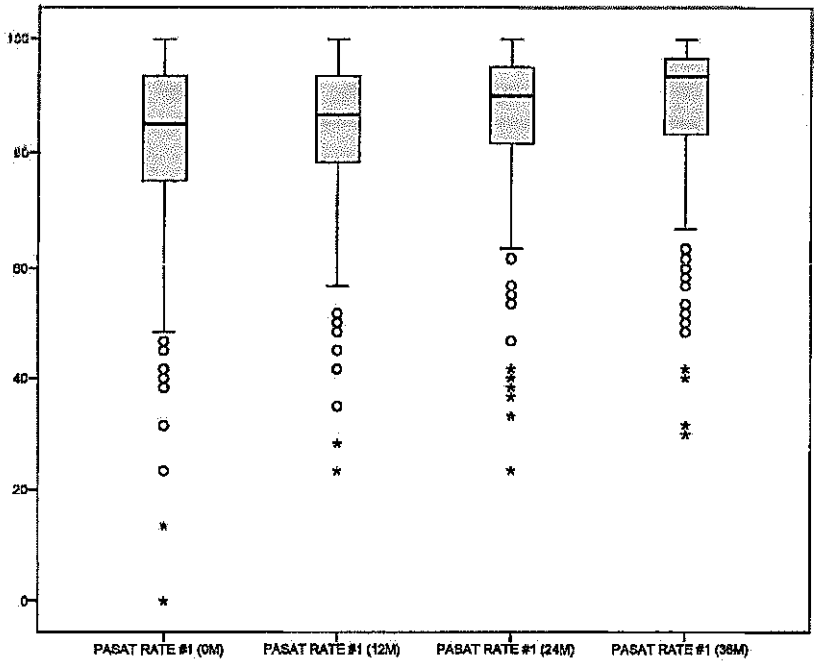


Figure 28: Boxplot of PASAT RATE #1 assessed by physician every 12 months – complete-case analysis (N = 190)

Table 33: PASAT RATE #2 assessed by the physician every 12 months – available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	132	75.1	20.56	81	0	100
12 MONTHS	38	72.8	21.53	82	8	98
24 MONTHS	14	65.5	26.75	68	17	100
36 MONTHS	0	-	-	-	-	-

Table 34: PASAT RATE #2 assessed by the physician every 12 months – complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	8	77.7	13.74	82	50	92
12 MONTHS	8	76.7	14.17	83	50	92
24 MONTHS	8	76.3	14.95	79	50	95
36 MONTHS	0	-	-	-	-	-

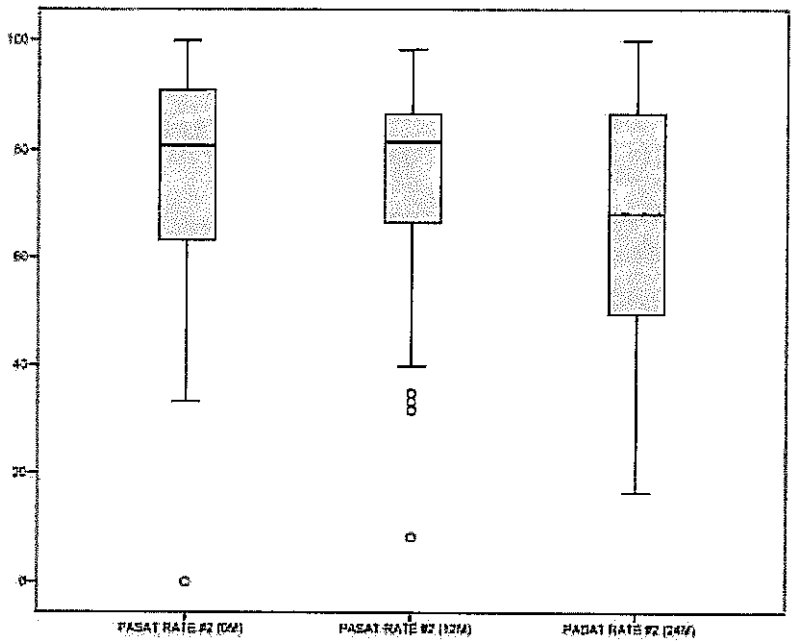


Figure 29: Boxplot of PASAT RATE #2 assessed by physician every 12 months – available-case analysis

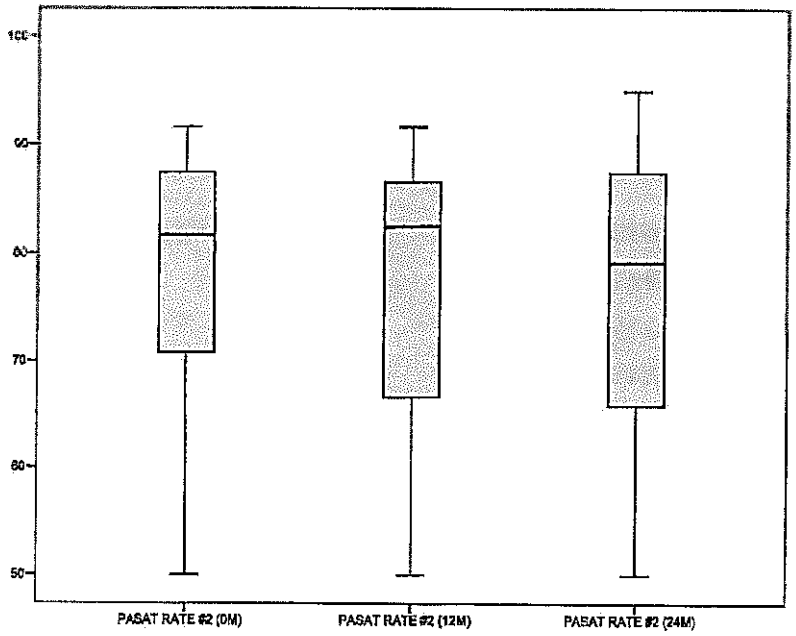


Figure 30: Boxplot of PASAT RATE #2 assessed by physician every 12 months – complete-case analysis (N = 8)

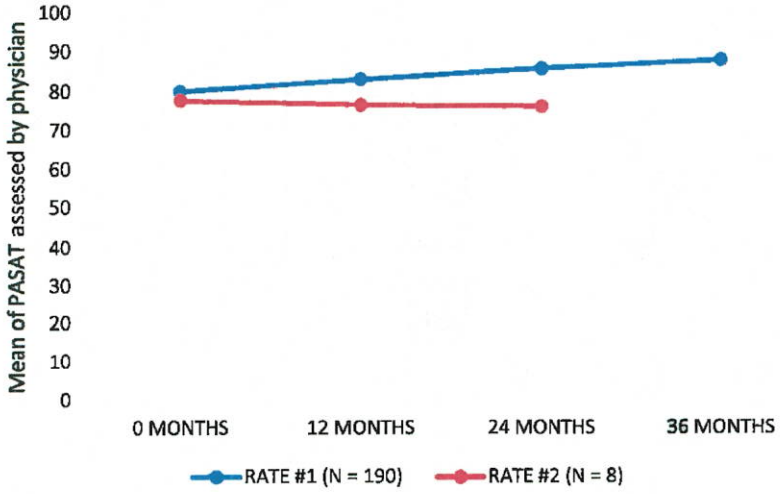


Figure 31: Line graph of mean of PASAT assessed by physician every 12 months (N = 8)

8.2.4. Correlation of quality of life assessment performed by patient and physician

The correlation is dependence between two random (numerical) variables. Correlation refers to the extent to which two variables have a linear relationship with each other. There are several correlation coefficients measuring the degree of correlation. Pearson correlation coefficient is sensitive only to a linear relationship between two variables. Other correlation coefficients, i.e. Spearman correlation coefficient, have been developed to be more robust than the Pearson correlation – that is more sensitive to nonlinear relationships.

The EDSS score assessed by physician is measured by standard Kurtzke scale. The EDSSpts assessed by patient is measured using battery of questions set by Goodin (Goodin, 1998). To compare both outcomes, question 1 from the EDSSpts questionnaire was used and following relation is applied:

1. answer is in accordance with EDSS score 0.0,
2. answer is in accordance with EDSS score 4.0,
3. answer is in accordance with EDSS score 4.5,
4. answer is in accordance with EDSS score 5.0,
5. answer is in accordance with EDSS score 5.5,
6. answer is in accordance with EDSS score 6.0,
7. answer is in accordance with EDSS score 6.5,
8. answer is in accordance with EDSS score 7.0,
9. answer is in accordance with EDSS score 7.5, and
10. answer is in accordance with EDSS score 8.0.

The correlation between EDSS assessed by physician and patient is attempted in next part of analysis.

8.2.4.1 Correlation between EDSS and EDSSpts

To choose appropriate method for analysis of correlation between EDSS and EDSSpts, test of normal distribution of both EDSS and EDSSpts had to be performed as Pearson correlation coefficient is stated for normally distributed variables, while Spearman correlation coefficient is used for other cases. Tests of normality, namely Kolmogorov-Smirnov test and Shapiro-Wilk test, are used for the data distribution analysis. As shown in Table 35 and Table 36, values of both EDSS and EDSSpts are not normally distributed (P-value < 0.001). All testing uses two-sided tests with the significance level $\alpha = 0.05$.

Table 35: Tests of normality – EDSS assessed by physician

	Kolmogorov-Smirnov[a]			Shapiro-Wilk			Distribution of EDSS
	Statistic	df	P-value	Statistic	df	P-value	
EDSS (0M)	0.185	559	< 0.001	0.927	559	< 0.001	*Distribution is not normal.*
EDSS (6M)	0.190	520	< 0.001	0.916	520	< 0.001	*Distribution is not normal.*
EDSS (12M)	0.198	478	< 0.001	0.908	478	< 0.001	*Distribution is not normal.*
EDSS (18M)	0.203	419	< 0.001	0.916	419	< 0.001	*Distribution is not normal.*
EDSS (24M)	0.198	368	< 0.001	0.911	368	< 0.001	*Distribution is not normal.*
EDSS (30M)	0.204	320	< 0.001	0.904	320	< 0.001	*Distribution is not normal.*
EDSS (36M)	0.197	303	< 0.001	0.908	303	< 0.001	*Distribution is not normal.*

a. Lilliefors Significance Correction

Table 36: Tests of normality – EDSS assessed by patient

	Kolmogorov-Smirnov[a]			Shapiro-Wilk			Distribution of EDSSpts
	Statistic	df	P-value	Statistic	df	P-value	
EDSSpts (0M)	0.499	553	< 0.001	0.487	553	< 0.001	*Distribution is not normal.*
EDSSpts (6M)	0.490	519	< 0.001	0.518	519	< 0.001	*Distribution is not normal.*
EDSSpts (12M)	0.495	476	< 0.001	0.503	476	< 0.001	*Distribution is not normal.*
EDSSpts (18M)	0.504	418	< 0.001	0.473	418	< 0.001	*Distribution is not normal.*
EDSSpts (24M)	0.497	366	< 0.001	0.496	366	< 0.001	*Distribution is not normal.*
EDSSpts (30M)	0.515	320	< 0.001	0.429	320	< 0.001	*Distribution is not normal.*
EDSSpts (36M)	0.520	300	< 0.001	0.406	300	< 0.001	*Distribution is not normal.*

a. Lilliefors Significance Correction

The correlation coefficient is a measure of the linear correlation between two variables X and Y, giving a value between +1 and −1 inclusive, where 1 is total positive correlation, 0 is no correlation, and −1 is total negative correlation. It is used as a measure of the degree of linear dependence between two variables.

Results of the correlation analysis using Spearman correlation coefficient are summarized in Table 37. The correlation between EDSS and EDSSpts is significant at the 0.01 level (2-tailed) with P-value < 0.001 in each visit. The correlation is low positive.

Table 37: Correlation between EDSS and EDSSpts

	EDSS vs. EDSSpts (0M)	EDSS vs. EDSSpts (6M)	EDSS vs. EDSSpts (12M)	EDSS vs. EDSSpts (18M)	EDSS vs. EDSSpts (24M)	EDSS vs. EDSSpts (30M)	EDSS vs. EDSSpts (36M)
Spearman correlation coefficient	0.456	0.539	0.472	0.474	0.479	0.443	0.410
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

8.2.4.2 EDSS (patient-reported)

The EDSSpts is a questionnaire to assess neurological impairment in multiple sclerosis. It consists of 5 scales – EDSS (Expanded Disability Status Scale), NRS (Neurologic Rating Scale), AI (Ambulation Index), SFS (Sum of the EDSS Functional Scores), and FS (Functional Status). Every question is analysed separately.

Table 38: Number of collected EDSSpts assessed by patient every 6 months

	yes		no	
	N	%	N	%
0 MONTHS	559	100.0%	0	0.0%
6 MONTHS	519	99.6%	2	0.4%
12 MONTHS	478	99.0%	5	1.0%
18 MONTHS	419	98.8%	5	1.2%
24 MONTHS	368	99.5%	2	0.5%
30 MONTHS	320	97.9%	7	2.1%
36 MONTHS	303	98.4%	5	1.6%

As the summary of EDSSpts analysis, it can be stated that frequency of answers describing different levels of examined health problems varied around the same value for the most of the questions.

For some questions, the following trend could be seen: answers that there is no problem with the examined health issue slightly increased during the study, while the first level of difficulty with the examined health problem was slightly decreasing. Evaluation of the other more serious levels of examined health problems was complicated due to their low frequency. This result pattern applies for questions: no. 1 Ability to walk, no. 2 Functional abilities, no. 7 Double vision, no 10 Balance, no 11 Spasticity (stiffness) and/or spasms in the right arm and in the right leg, no 12 Cognitive (thinking) ability, no 13 Mood since getting MS and no. 16 Vertigo or dizziness.

For question no. 6, Corrected visual acuity of the right and the left eye, slight increase in the first year of study followed by no change in the other time points was detected for normal acuity. The opposite trend, the decrease in the first year and then no change, could be seen for mildly impaired acuity.

Following tables and figures show results of answers analysis performed for each question separately.

8.2.4.2.1 EDSSpts question no. 1

Table 39: Question no. 1 – Which of the following best describes your ability to walk?

	Walk without problem (0.0)		Walk without aid 500 m (4.0)		Walk without aid 300 m (4.5)		Walk without aid 200 m (5.0)		Walk without aid 100 m (5.5)		Aid required to walk 100 m (6.0)		Aid required to walk 20 m (6.5)		Aid required to walk 8 m (7.0)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0M	456	83%	75	14%	12	2%	3	1%	3	1%	3	1%	1	0%	0	0%
6M	417	80%	75	15%	16	3%	4	1%	2	0%	3	1%	1	0%	1	0%
12M	388	82%	63	13%	13	3%	3	1%	4	1%	3	1%	1	0%	1	0%
18M	349	84%	50	12%	11	3%	4	1%	0	0%	2	1%	1	0%	1	0%
24M	300	82%	48	13%	7	2%	5	1%	3	1%	1	0%	1	0%	1	0%
30M	276	86%	32	10%	4	1%	3	1%	3	1%	1	0%	1	0%	0	0%
36M	262	87%	30	10%	5	2%	2	1%	0	0%	1	0%	0	0%	0	0%

8.2.4.2.2 EDSSpts question no. 2

Table 40: Question no. 2 – When you move about, what percentage of the time you do so:

		Walk without aid (%)		Use a cane, a single crutch, or hold onto another person (%)		Use a walker or other bilateral support (%)		Use a wheel chair (%)	
	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0M	526	98.30	9.82	1.55	9.54	0.00	0.00	0.00	0.00
6M	490	97.44	12.53	2.08	11.77	0.00	0.00	0.00	0.00
12M	458	97.66	11.30	2.03	10.77	0.00	0.00	0.24	4.90
18M	405	97.72	11.30	2.17	11.86	0.00	0.00	0.00	0.00
24M	358	97.25	12.19	2.47	12.31	0.00	0.00	0.00	0.00
30M	314	97.94	11.02	1.67	10.58	0.00	0.00	0.00	0.00
36M	297	98.85	7.91	1.15	8.26	0.00	0.00	0.00	0.00

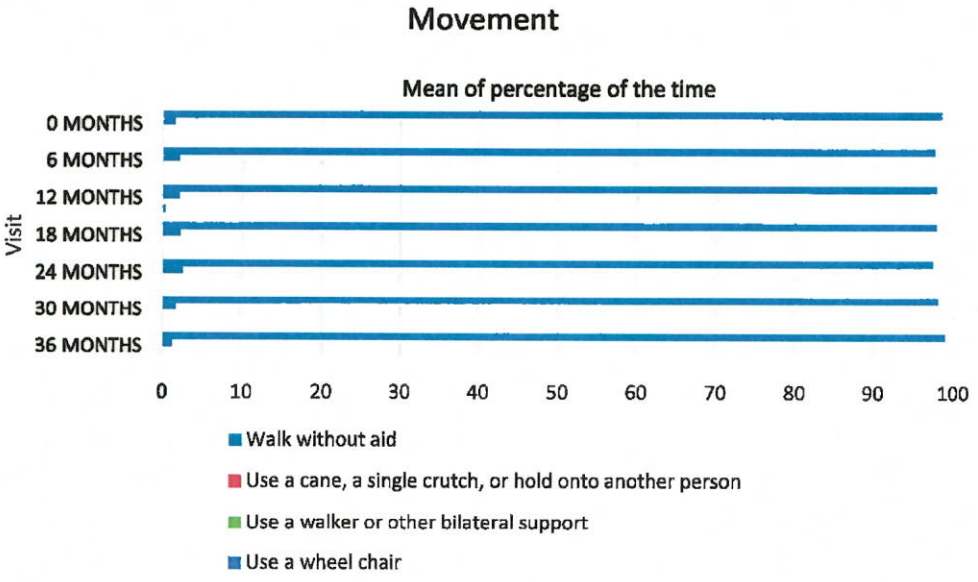


Figure 32: Bar chart of question no. 2 – When you move about, what percentage of the time you do so:

8.2.4.2.3 EDSSpts question no. 3

Table 41: Question no. 3 – Which of the following best describes your functional abilities?

Functional abilities										
	without limitation		limitations but can carry most of usual activities		only half of my usual daily activities		severely limited		require assistance with even basic self-care activities	
	N	%	N	%	N	%	N	%	N	%
0M	389	70.2%	144	26.0%	18	3.2%	3	0.5%	0	0.0%
6M	362	70.6%	133	25.9%	14	2.7%	4	0.8%	0	0.0%
12M	334	70.6%	123	26.0%	14	3.0%	2	0.4%	0	0.0%
18M	304	73.1%	100	24.0%	11	2.6%	1	0.2%	0	0.0%
24M	271	74.7%	82	22.6%	8	2.2%	2	0.6%	0	0.0%
30M	253	79.6%	57	17.9%	7	2.2%	1	0.3%	0	0.0%
36M	231	76.7%	67	22.3%	3	1.0%	0	0.0%	0	0.0%

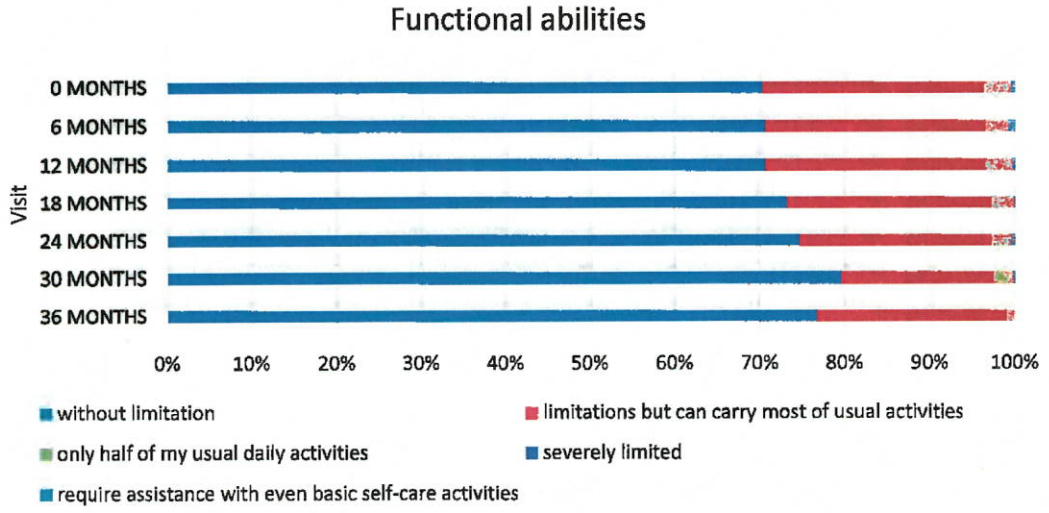


Figure 33: Bar chart of question no. 3 – Which of the following best describes your functional abilities?

8.2.4.2.4 EDSSpts question no. 4

Table 42: Question no. 4 – Which of the following best describes your strength (power) in the right arm?

Strength (power) in the right arm								
	normal		mildly weak		moderately weak		severely weak	
	N	%	N	%	N	%	N	%
0M	458	83.1%	77	14.0%	16	2.9%	0	0.0%
6M	428	82.8%	76	14.7%	13	2.5%	0	0.0%
12M	404	84.7%	58	12.2%	14	2.9%	1	0.2%
18M	359	86.1%	45	10.8%	13	3.1%	0	0.0%
24M	305	83.3%	53	14.5%	8	2.2%	0	0.0%
30M	278	86.9%	36	11.3%	6	1.9%	0	0.0%
36M	259	85.8%	39	12.9%	4	1.3%	0	0.0%

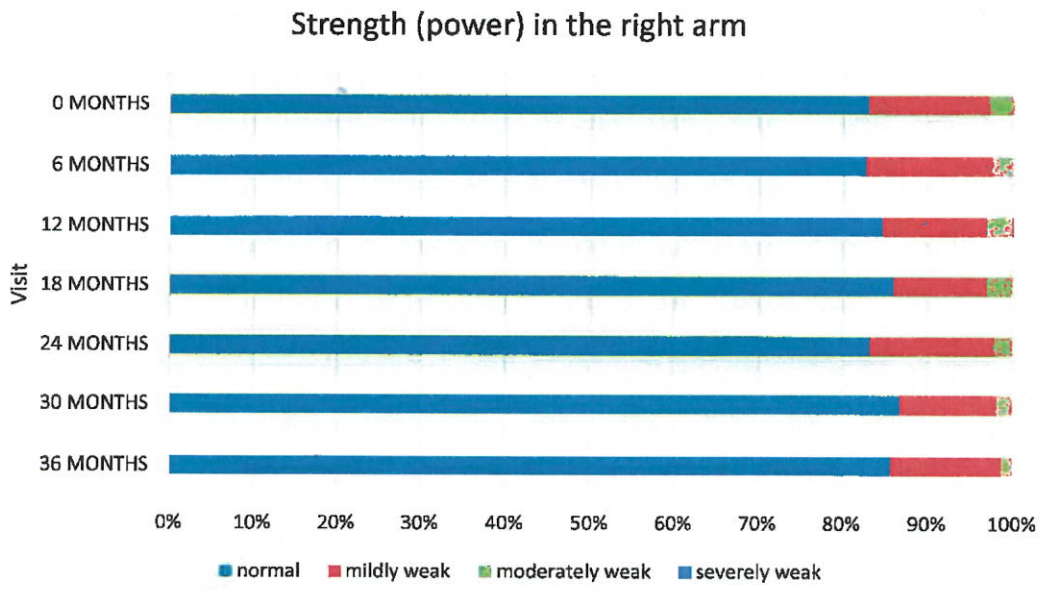


Figure 34: Bar chart of question no. 4 – Which of the following best describes your strength (power) in the right arm?

Table 43: Question no. 4 – Which of the following best describes your strength (power) in the left arm?

Strength (power) in the left arm								
	normal		mildly weak		moderately weak		severely weak	
	N	%	N	%	N	%	N	%
0M	466	84.7%	70	12.7%	13	2.4%	1	0.2%
6M	428	83.3%	77	15.0%	9	1.8%	0	0.0%
12M	402	84.5%	63	13.2%	11	2.3%	0	0.0%
18M	353	85.1%	53	12.8%	9	2.2%	0	0.0%
24M	308	84.6%	51	14.0%	5	1.4%	0	0.0%
30M	280	88.1%	32	10.1%	6	1.9%	0	0.0%
36M	263	87.7%	28	9.3%	9	3.0%	0	0.0%

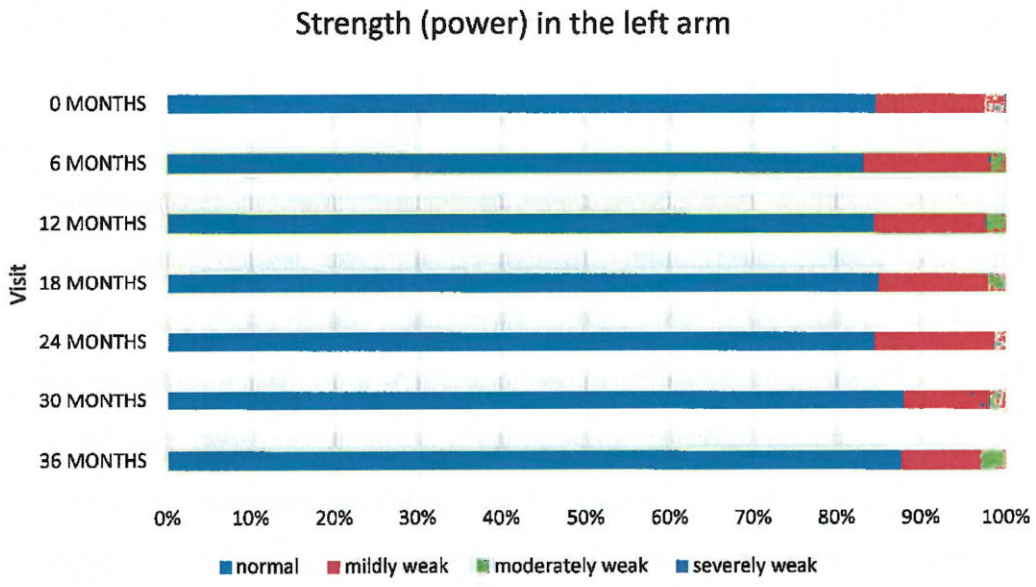


Figure 35: Bar chart of question no. 4 – Which of the following best describes your strength (power) in the left arm?

Table 44: Question no. 4 – Which of the following best describes your strength (power) in the right leg?

Strength (power) in the right leg								
	normal		mildly weak		moderately weak		severely weak	
	N	%	N	%	N	%	N	%
0M	427	77.6%	97	17.6%	25	4.5%	1	0.2%
6M	392	76.6%	91	17.8%	28	5.5%	1	0.2%
12M	365	76.7%	83	17.4%	27	5.7%	1	0.2%
18M	331	80.1%	56	13.6%	24	5.8%	2	0.5%
24M	294	80.5%	54	14.8%	16	4.4%	1	0.3%
30M	266	83.9%	39	12.3%	12	3.8%	0	0.0%
36M	241	80.3%	52	17.3%	7	2.3%	0	0.0%

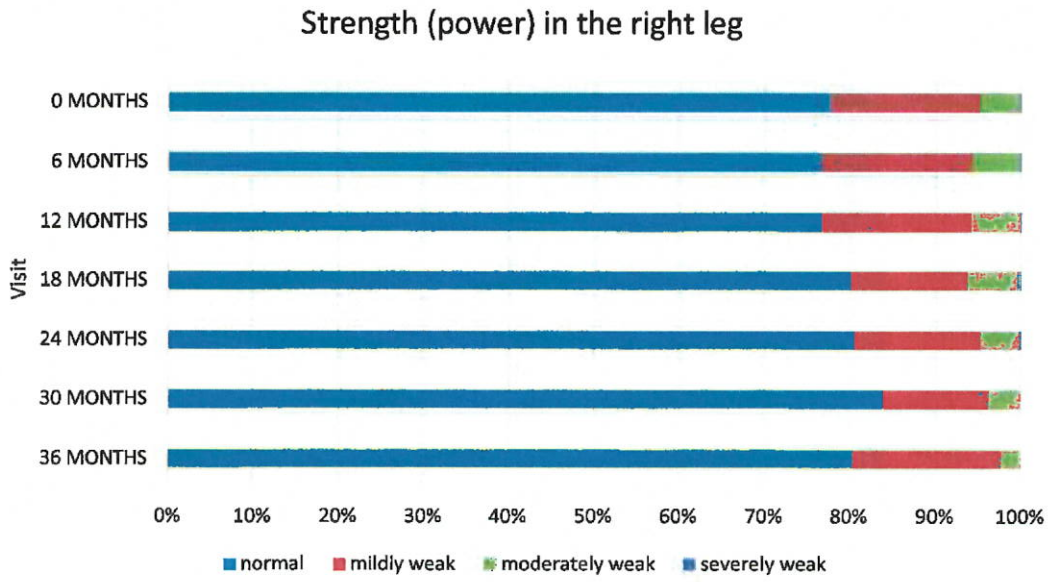


Figure 36: Bar chart of question no. 4 – Which of the following best describes your strength (power) in the right leg?

Table 45: Question no. 4 – Which of the following best describes your strength (power) in the left leg?

Strength (power) in the left leg								
	normal		mildly weak		moderately weak		severely weak	
	N	%	N	%	N	%	N	%
0M	426	77.7%	95	17.3%	21	3.8%	6	1.1%
6M	405	79.1%	81	15.8%	17	3.3%	9	1.8%
12M	372	78.3%	75	15.8%	25	5.3%	3	0.6%
18M	336	81.2%	56	13.5%	19	4.6%	3	0.7%
24M	293	80.5%	52	14.3%	15	4.1%	4	1.1%
30M	268	84.8%	32	10.1%	15	4.7%	1	0.3%
36M	245	81.4%	41	13.6%	13	4.3%	2	0.7%

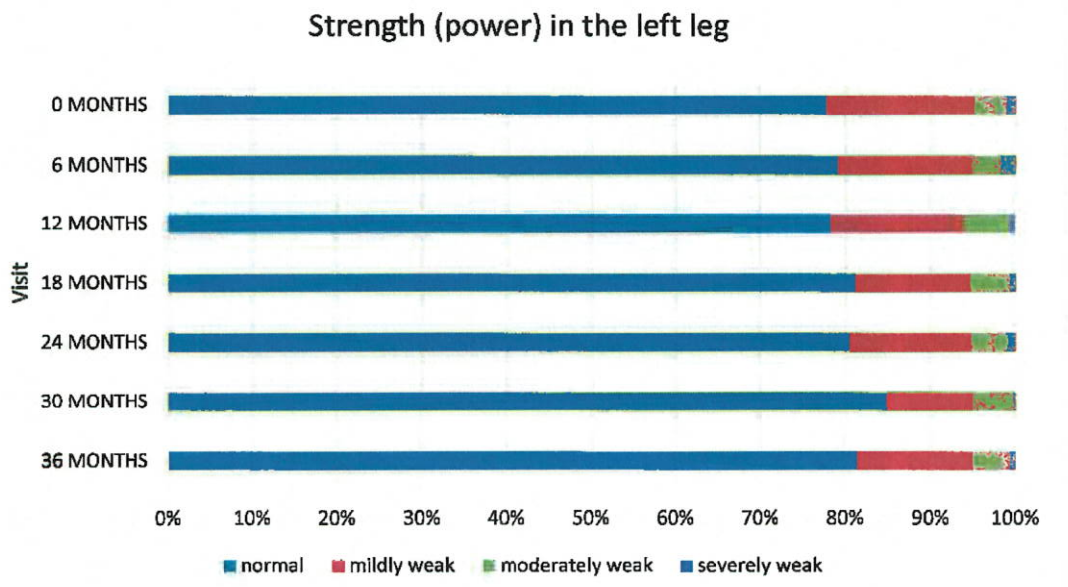


Figure 37: Bar chart of question no. 4 – Which of the following best describes your strength (power) in the left leg?

Table 46: Question no. 4 – Which of the following best describes your strength (power) in the face?

Strength (power) in the face								
	normal		mildly weak		moderately weak		severely weak	
	N	%	N	%	N	%	N	%
0M	518	94.0%	29	5.3%	4	0.7%	0	0.0%
6M	490	96.1%	19	3.7%	0	0.0%	1	0.2%
12M	452	95.4%	20	4.2%	2	0.4%	0	0.0%
18M	393	95.6%	18	4.4%	0	0.0%	0	0.0%
24M	347	95.6%	15	4.1%	1	0.3%	0	0.0%
30M	301	95.9%	13	4.1%	0	0.0%	0	0.0%
36M	282	94.0%	18	6.0%	0	0.0%	0	0.0%

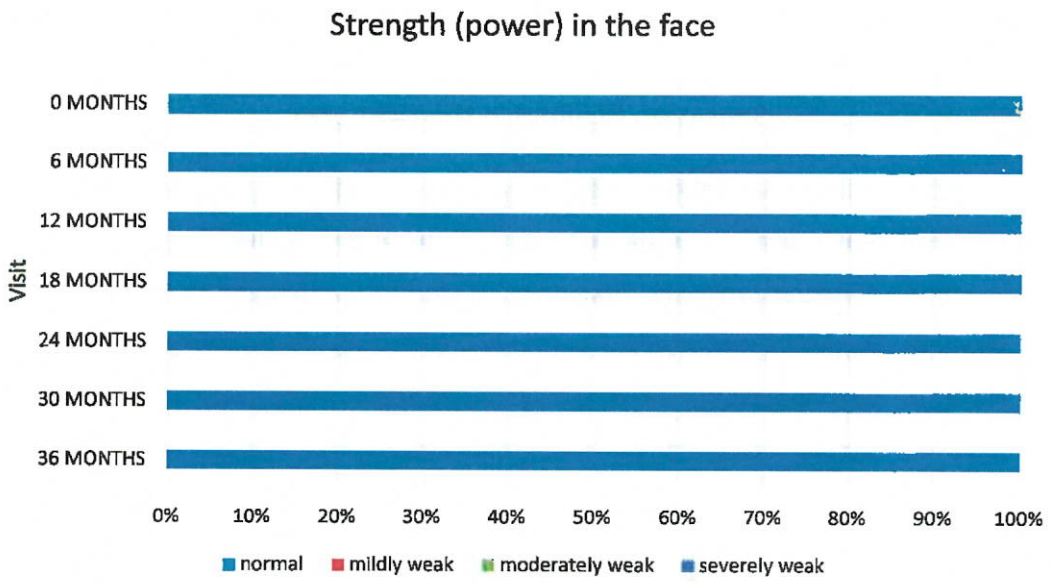


Figure 38: Bar chart of question no. 4 – Which of the following best describes your strength (power) in the face?

8.2.4.2.5 EDSSpts question no. 5

Table 47: Question no. 5 – Which of the following best describes your sensation (feeling) in the right arm?

Sensation (feeling) in the right arm								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	451	82.1%	83	15.1%	14	2.6%	1	0.2%
6M	434	84.1%	68	13.2%	12	2.3%	2	0.4%
12M	396	83.5%	66	13.9%	12	2.5%	0	0.0%
18M	357	85.6%	51	12.2%	9	2.2%	0	0.0%
24M	312	85.5%	41	11.2%	12	3.3%	0	0.0%
30M	275	85.9%	39	12.2%	6	1.9%	0	0.0%
36M	255	84.4%	42	13.9%	5	1.7%	0	0.0%

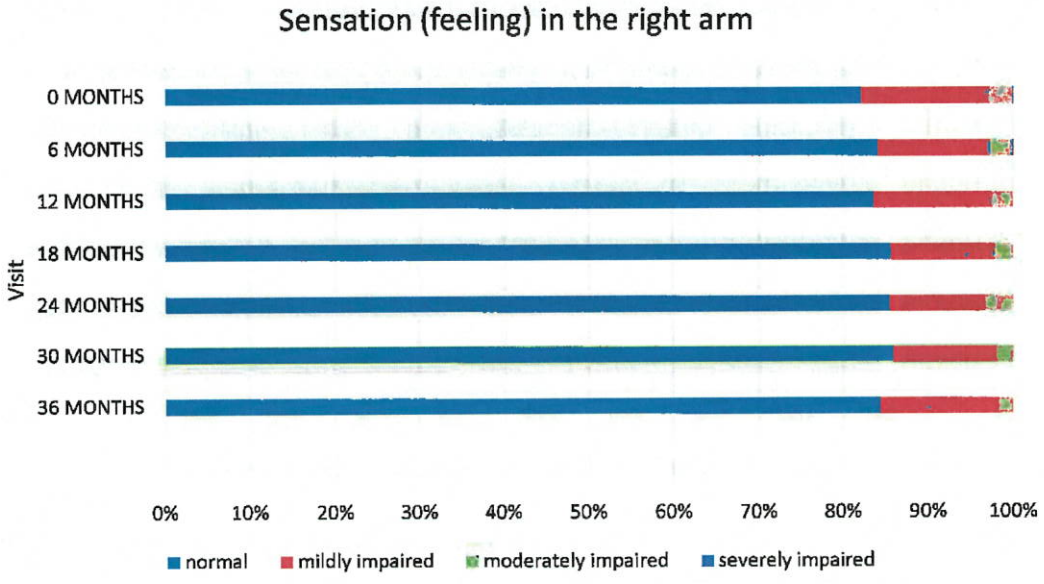


Figure 39: Bar chart of question no. 5 – Which of the following best describes your sensation (feeling) in the right arm?

Table 48: Question no. 5 – Which of the following best describes your sensation (feeling) in the left arm?

Sensation (feeling) in the left arm								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	469	85.3%	70	12.7%	9	1.6%	2	0.4%
6M	452	88.1%	53	10.3%	8	1.6%	0	0.0%
12M	405	85.6%	58	12.3%	9	1.9%	1	0.2%
18M	355	85.5%	56	13.5%	4	1.0%	0	0.0%
24M	317	86.6%	44	12.0%	5	1.4%	0	0.0%
30M	283	89.0%	27	8.5%	8	2.5%	0	0.0%
36M	263	87.1%	32	10.6%	7	2.3%	0	0.0%

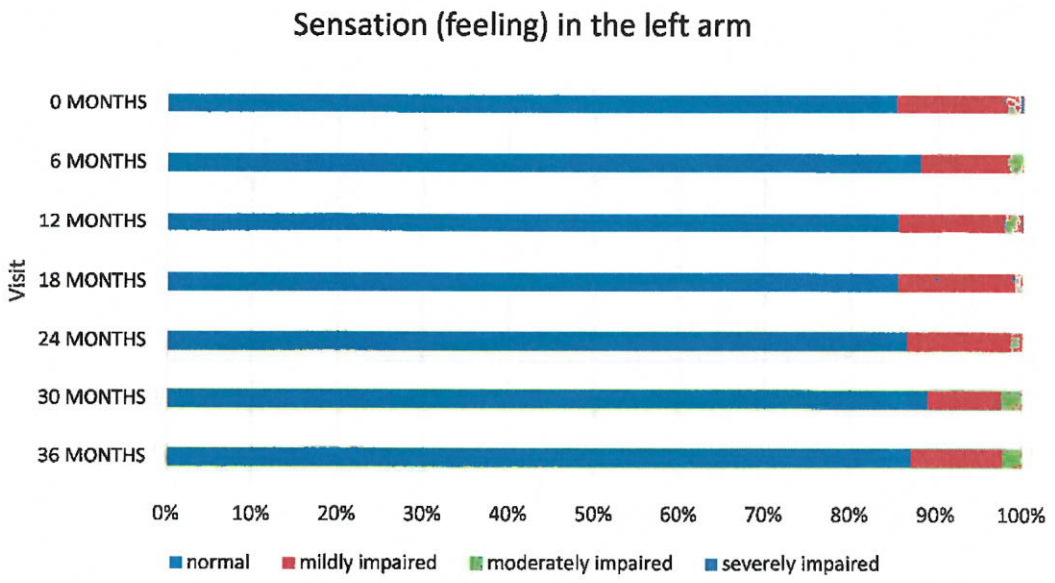


Figure 40: Bar chart of question no. 5 – Which of the following best describes your sensation (feeling) in the left arm?

Table 49: Question no. 5 – Which of the following best describes your sensation (feeling) in the right leg?

Sensation (feeling) in the right leg								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	443	80.5%	93	16.9%	13	2.4%	1	0.2%
6M	409	79.9%	85	16.6%	17	3.3%	1	0.2%
12M	376	79.5%	84	17.8%	12	2.5%	1	0.2%
18M	343	82.9%	58	14.0%	12	2.9%	1	0.2%
24M	303	82.8%	49	13.4%	14	3.8%	0	0.0%
30M	271	85.2%	38	11.9%	9	2.8%	0	0.0%
36M	263	87.1%	35	11.6%	4	1.3%	0	0.0%

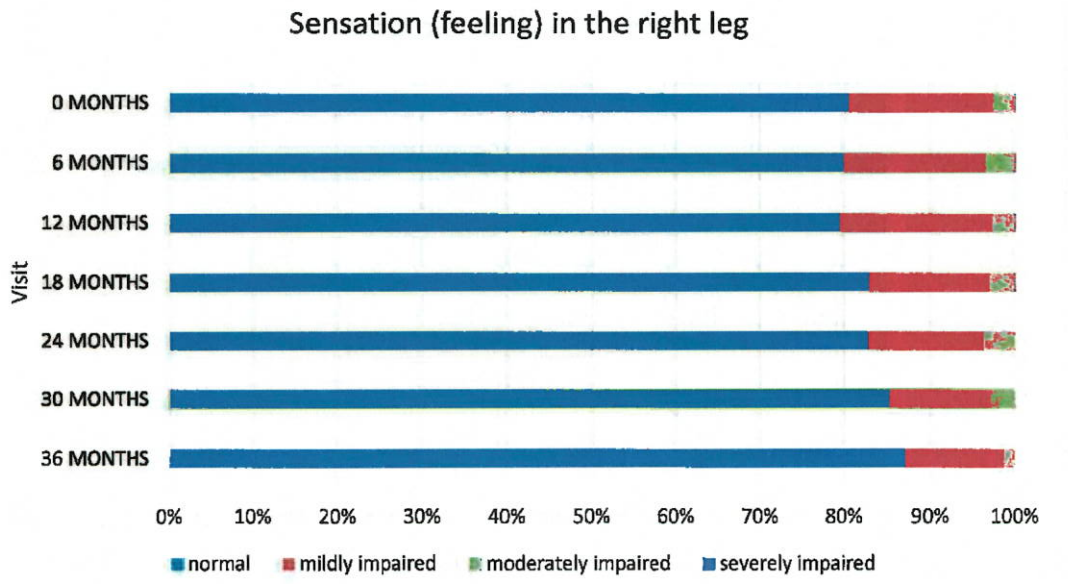


Figure 41: Bar chart of question no. 5 – Which of the following best describes your sensation (feeling) in the right leg?

Table 50: Question no. 5 – Which of the following best describes your sensation (feeling) in the left leg?

Sensation (feeling) in the left leg								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	452	82.0%	84	15.2%	14	2.5%	1	0.2%
6M	424	82.8%	73	14.3%	14	2.7%	1	0.2%
12M	382	80.6%	73	15.4%	17	3.6%	2	0.4%
18M	333	80.2%	71	17.1%	10	2.4%	1	0.2%
24M	303	82.8%	53	14.5%	10	2.7%	0	0.0%
30M	270	84.9%	38	11.9%	10	3.1%	0	0.0%
36M	261	86.4%	34	11.3%	6	2.0%	1	0.3%

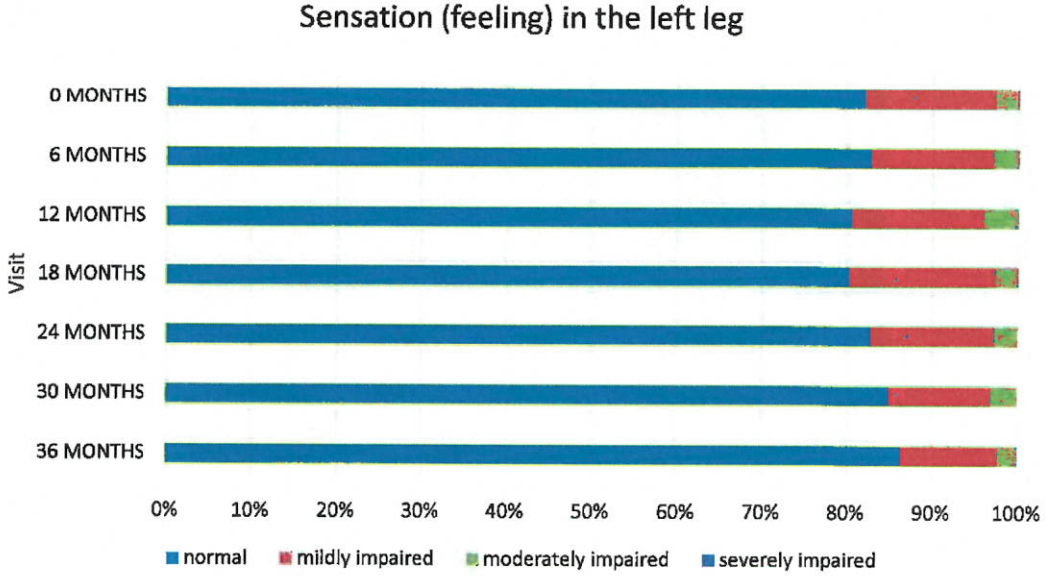


Figure 42: Bar chart of question no. 5 – Which of the following best describes your sensation (feeling) in the left leg?

Table 51: Question no. 5 – Which of the following best describes your sensation (feeling) in the face?

Sensation (feeling) in the face								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	511	93.1%	34	6.2%	4	0.7%	0	0.0%
6M	490	96.3%	17	3.3%	2	0.4%	0	0.0%
12M	441	93.2%	30	6.3%	2	0.4%	0	0.0%
18M	397	95.9%	16	3.9%	1	0.2%	0	0.0%
24M	349	95.4%	17	4.6%	0	0.0%	0	0.0%
30M	299	94.0%	19	6.0%	0	0.0%	0	0.0%
36M	282	93.7%	18	6.0%	1	0.3%	0	0.0%

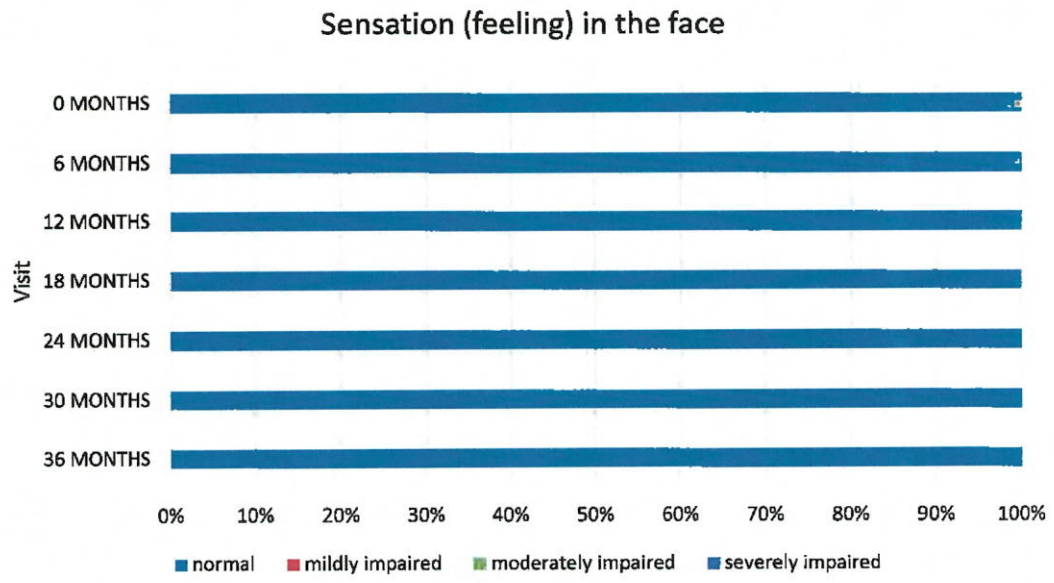


Figure 43: Bar chart of question no. 5 – Which of the following best describes your sensation (feeling) in the face?

8.2.4.2.6 EDSSpts question no. 6

Table 52: Question no. 6 – Which of the following best describes your corrected visual acuity in the right eye?

Corrected visual acuity in the right eye								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	414	76.5%	107	19.8%	16	3.0%	4	0.7%
6M	391	77.3%	95	18.8%	15	3.0%	5	1.0%
12M	370	79.2%	78	16.7%	16	3.4%	3	0.6%
18M	338	81.4%	64	15.4%	8	1.9%	5	1.2%
24M	289	80.5%	58	16.2%	10	2.8%	2	0.6%
30M	252	80.0%	49	15.6%	8	2.5%	6	1.9%
36M	240	79.7%	50	16.6%	9	3.0%	2	0.7%

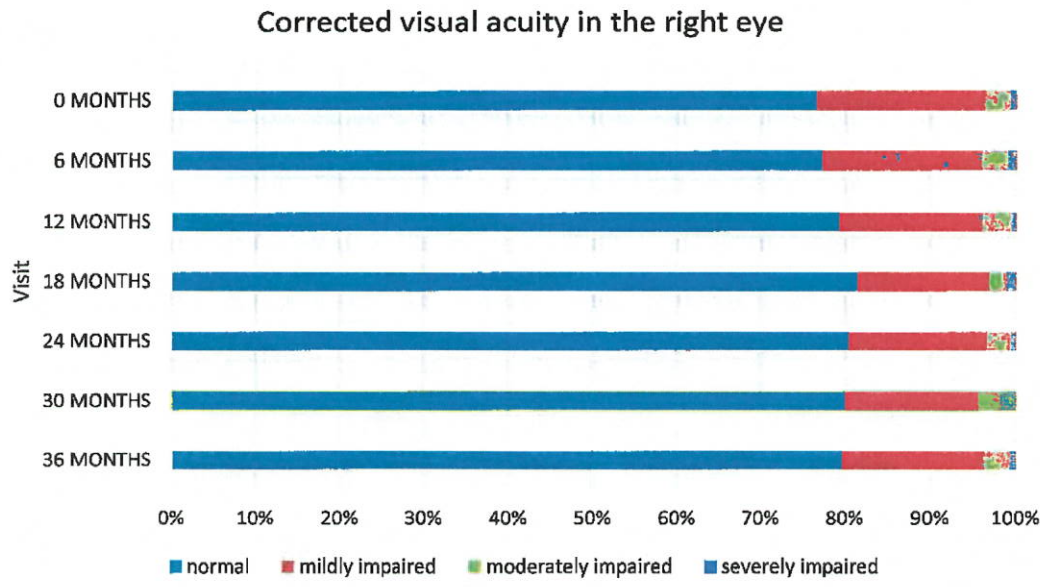


Figure 44: Bar chart of question no. 6 – Which of the following best describes your corrected visual acuity in the right eye?

Table 53: Question no. 6 – Which of the following best describes your corrected visual acuity in the left eye?

Corrected visual acuity in the left eye								
	normal		mildly impaired		moderately impaired		severely impaired	
	N	%	N	%	N	%	N	%
0M	408	75.4%	106	19.6%	21	3.9%	6	1.1%
6M	390	76.9%	93	18.3%	22	4.3%	2	0.4%
12M	370	79.1%	77	16.5%	18	3.8%	3	0.6%
18M	331	80.0%	67	16.2%	13	3.1%	3	0.7%
24M	283	78.6%	65	18.1%	12	3.3%	0	0.0%
30M	251	80.2%	52	16.6%	7	2.2%	3	1.0%
36M	237	79.0%	51	17.0%	11	3.7%	1	0.3%

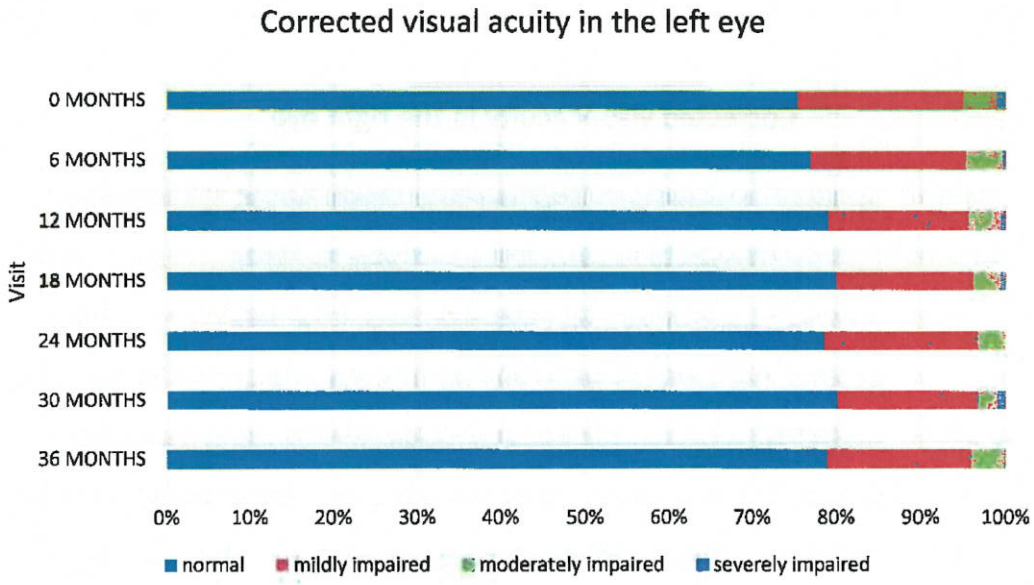


Figure 45: Bar chart of question no. 6 – Which of the following best describes your corrected visual acuity in the left eye?

8.2.4.2.7 EDSSpts question no. 7

Table 54: Question no. 7 – Which of the following best describes your double vision?

Double vision								
	no experience		occasionally		moderately often		most of the time	
	N	%	N	%	N	%	N	%
0M	452	81.6%	87	15.7%	11	2.0%	4	0.7%
6M	427	83.6%	76	14.9%	7	1.4%	1	0.2%
12M	408	86.6%	57	12.1%	5	1.1%	1	0.2%
18M	352	85.4%	55	13.3%	4	1.0%	1	0.2%
24M	315	86.3%	43	11.8%	7	1.9%	0	0.0%
30M	285	89.6%	32	10.1%	1	0.3%	0	0.0%
36M	264	88.3%	29	9.7%	5	1.7%	1	0.3%

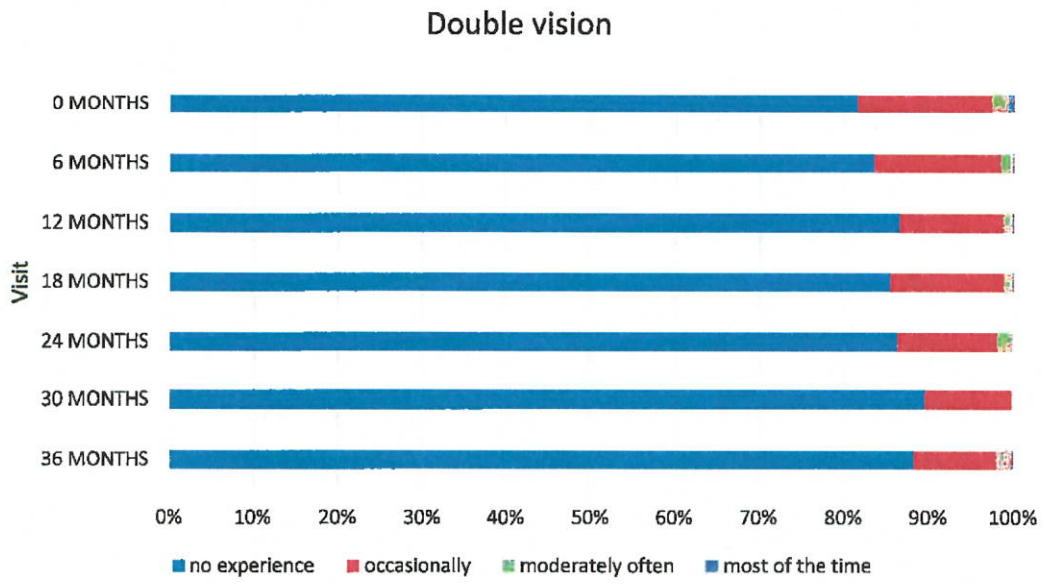


Figure 46: Bar chart of question no. 7 – Which of the following best describes your double vision?

Signature: Michael Smith
Michael Smith (Mar 5, 2017)

Email: mike.smith1@biogen.com

Title: Senior Manager Medical Research

Company: Biogen

Signature: Matthias Meergans
Matthias Meergans (Mar 6, 2017)

Email: matthias.meergans@biogen.com

Title: Medical Director

Company: Biogen

Signature: Emily McIntyre
Emily McIntyre (Mar 6, 2017)

Email: emily.mcintyre@Biogen.com

Title: Associate Director, Medical Research Operat

Company: Biogen

8.2.4.2.8 EDSSpts question no. 8

Table 55: Question no. 8 – Which of the following best describes your coordination in the right arm?

Coordination in the right arm								
	normal		mildly uncoordinated		moderately uncoordinated		severely uncoordinated	
	N	%	N	%	N	%	N	%
0M	488	87.6%	61	11.0%	8	1.4%	0	0.0%
6M	459	88.6%	51	9.8%	8	1.5%	0	0.0%
12M	414	86.8%	57	11.9%	6	1.3%	0	0.0%
18M	367	87.8%	45	10.8%	6	1.4%	0	0.0%
24M	320	87.4%	40	10.9%	6	1.6%	0	0.0%
30M	288	90.0%	29	9.1%	3	0.9%	0	0.0%
36M	263	86.8%	39	12.9%	1	0.3%	0	0.0%

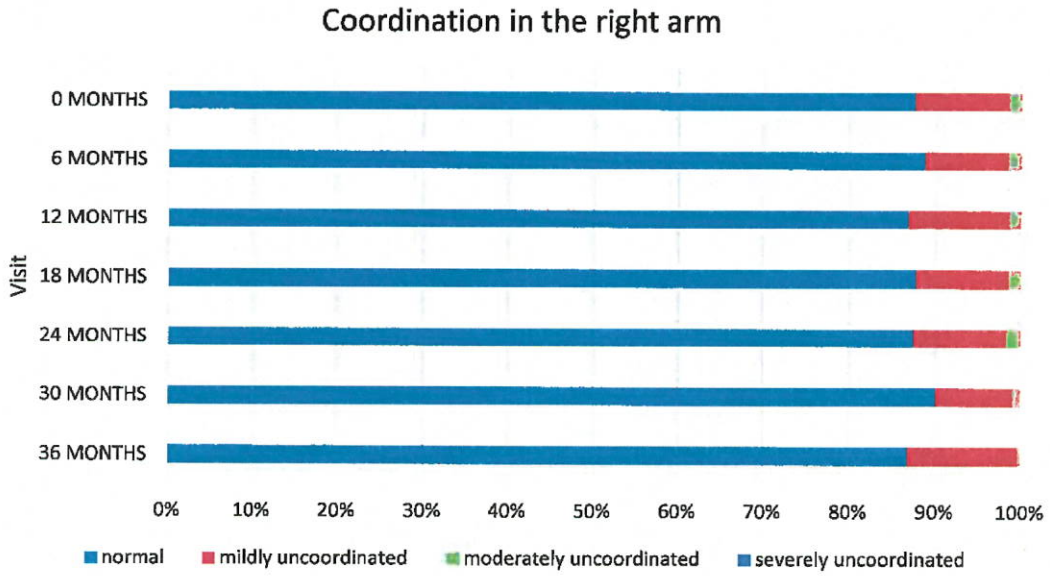


Figure 47: Bar chart of question no. 8 – Which of the following best describes your coordination in the right arm?

Table 56: Question no. 8 – Which of the following best describes your coordination in the left arm?

Coordination in the left arm								
	normal		mildly uncoordinated		moderately uncoordinated		severely uncoordinated	
	N	%	N	%	N	%	N	%
0M	503	90.3%	50	9.0%	3	0.5%	1	0.2%
6M	464	89.7%	48	9.3%	5	1.0%	0	0.0%
12M	418	87.8%	52	10.9%	6	1.3%	0	0.0%
18M	373	89.2%	42	10.0%	3	0.7%	0	0.0%
24M	325	88.8%	40	10.9%	1	0.3%	0	0.0%
30M	285	89.1%	31	9.7%	4	1.3%	0	0.0%
36M	268	88.4%	31	10.2%	4	1.3%	0	0.0%

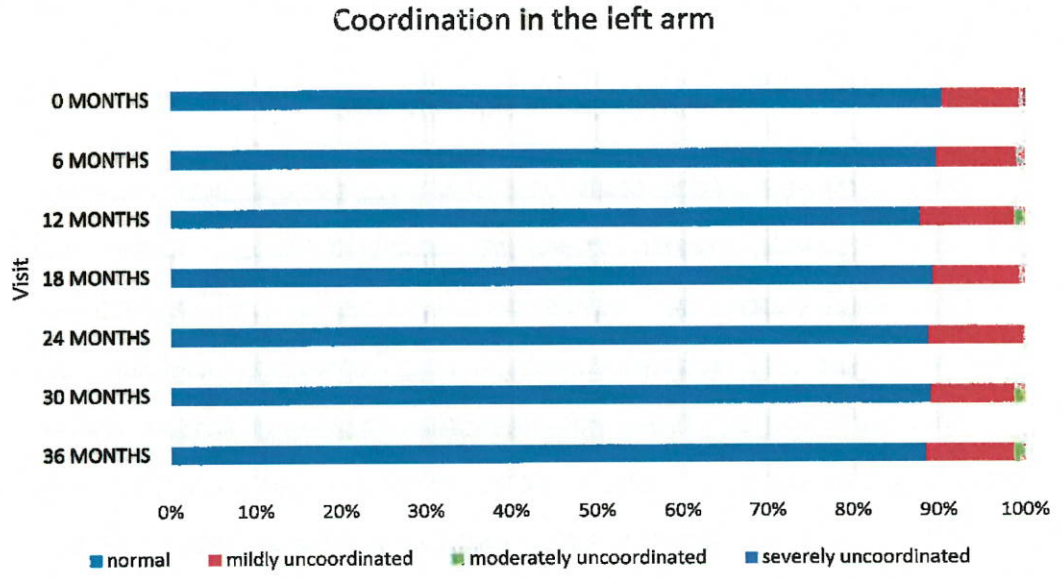


Figure 48: Bar chart of question no. 8 – Which of the following best describes your coordination in the left arm?

Table 57: Question no. 8 – Which of the following best describes your coordination in the right leg?

Coordination in the right leg								
	normal		mildly uncoordinated		moderately uncoordinated		severely uncoordinated	
	N	%	N	%	N	%	N	%
0M	476	85.5%	63	11.3%	18	3.2%	0	0.0%
6M	431	83.5%	70	13.6%	14	2.7%	1	0.2%
12M	391	82.3%	67	14.1%	17	3.6%	0	0.0%
18M	353	84.4%	55	13.2%	8	1.9%	2	0.5%
24M	308	84.2%	47	12.8%	11	3.0%	0	0.0%
30M	278	86.9%	34	10.6%	8	2.5%	0	0.0%
36M	255	84.2%	40	13.2%	8	2.6%	0	0.0%

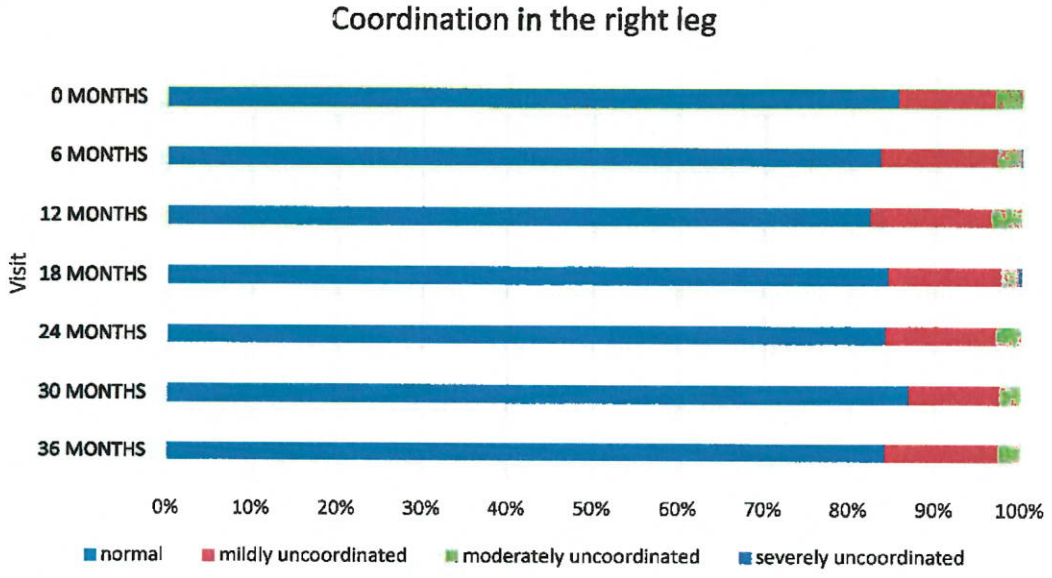


Figure 49: Bar chart of question no. 8 – Which of the following best describes your coordination in the right leg?

Table 58: Question no. 8 – Which of the following best describes your coordination in the left leg?

Coordination in the left leg								
	normal		mildly uncoordinated		moderately uncoordinated		severely uncoordinated	
	N	%	N	%	N	%	N	%
0M	486	87.1%	57	10.2%	15	2.7%	0	0.0%
6M	442	85.7%	59	11.4%	13	2.5%	2	0.4%
12M	394	82.8%	68	14.3%	13	2.7%	1	0.2%
18M	349	83.5%	60	14.4%	7	1.7%	2	0.5%
24M	314	85.8%	47	12.8%	5	1.4%	0	0.0%
30M	283	88.4%	30	9.4%	7	2.2%	0	0.0%
36M	264	87.1%	31	10.2%	8	2.6%	0	0.0%

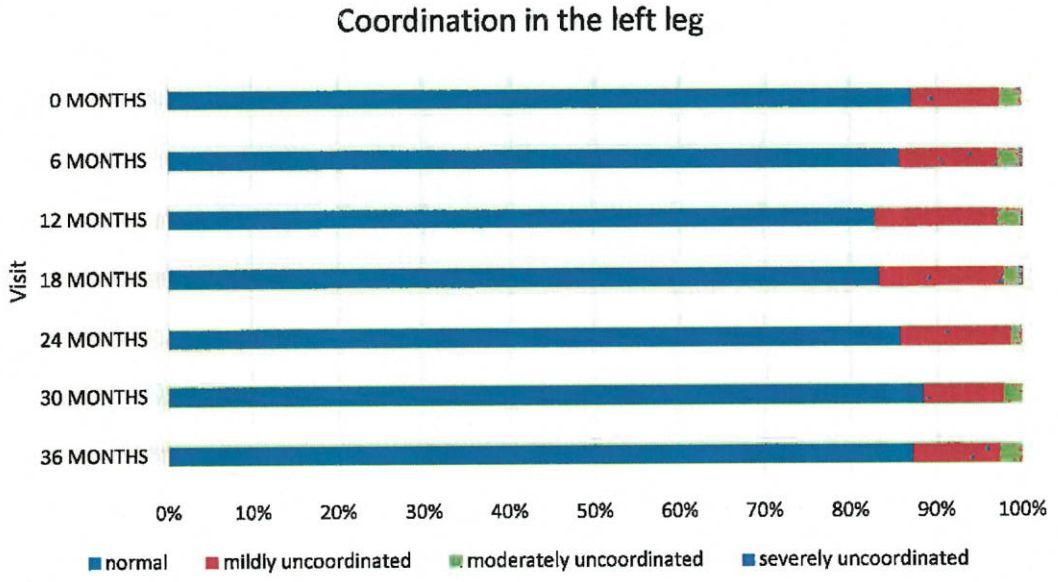


Figure 50: Bar chart of question no. 8 – Which of the following best describes your coordination in the left leg?

8.2.4.2.9 EDSSpts question no. 9

Table 59: Question no. 9 – Do you have difficulty speaking or with your speech?

Difficulty speaking or with speech								
	no difficulty		mild difficulty		moderate difficulty		severe difficulty	
	N	%	N	%	N	%	N	%
0M	502	89.8%	53	9.5%	4	0.7%	0	0.0%
6M	476	91.7%	38	7.3%	5	1.0%	0	0.0%
12M	430	90.3%	44	9.2%	2	0.4%	0	0.0%
18M	377	90.0%	36	8.6%	6	1.4%	0	0.0%
24M	329	89.6%	36	9.8%	2	0.5%	0	0.0%
30M	295	92.2%	24	7.5%	1	0.3%	0	0.0%
36M	276	91.4%	26	8.6%	0	0.0%	0	0.0%

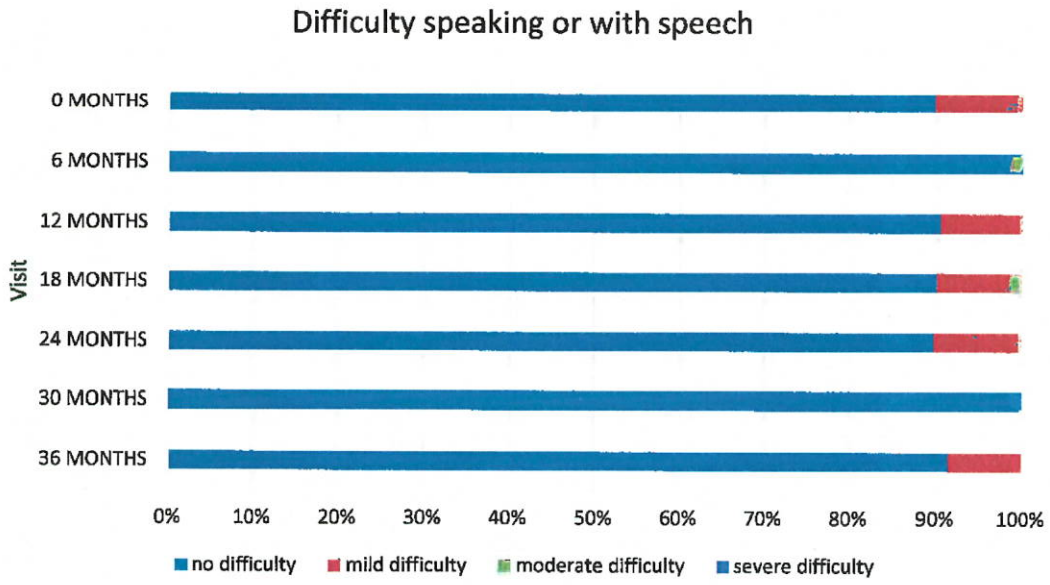


Figure 51: Bar chart of question no. 9 – Do you have difficulty speaking or with your speech?

8.2.4.2.10 EDSSpts question no. 10

Table 60: Question no. 10 – Which of the following best describes your balance?

Balance								
	no difficulty		mild difficulty		moderate difficulty		severe difficulty	
	N	%	N	%	N	%	N	%
0M	366	65.6%	175	31.4%	15	2.7%	2	0.4%
6M	342	65.9%	155	29.9%	19	3.7%	3	0.6%
12M	316	66.5%	141	29.7%	18	3.8%	0	0.0%
18M	293	70.3%	108	25.9%	15	3.6%	1	0.2%
24M	253	68.8%	102	27.7%	12	3.3%	1	0.3%
30M	230	71.9%	80	25.0%	10	3.1%	0	0.0%
36M	214	70.9%	76	25.2%	11	3.6%	1	0.3%

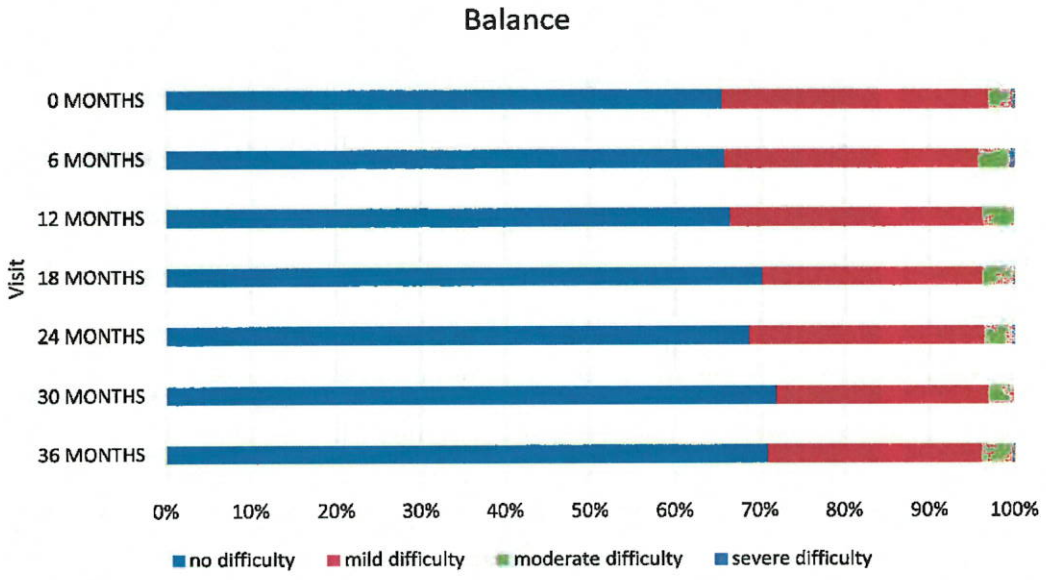


Figure 52: Bar chart of question no. 10 – Which of the following best describes your balance?

8.2.4.2.11 EDSSpts question no. 11

Table 61: Question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the right arm?

Spasticity (stiffness) and/or spasms in the right arm								
	no spasticity		mild spasticity		moderate spasticity		severe spasticity	
	N	%	N	%	N	%	N	%
0M	480	86.3%	69	12.4%	7	1.3%	0	0.0%
6M	454	88.3%	56	10.9%	4	0.8%	0	0.0%
12M	416	87.6%	53	11.2%	6	1.3%	0	0.0%
18M	370	88.3%	44	10.5%	5	1.2%	0	0.0%
24M	324	88.3%	39	10.6%	4	1.1%	0	0.0%
30M	291	90.9%	27	8.4%	2	0.6%	0	0.0%
36M	276	91.4%	22	7.3%	4	1.3%	0	0.0%

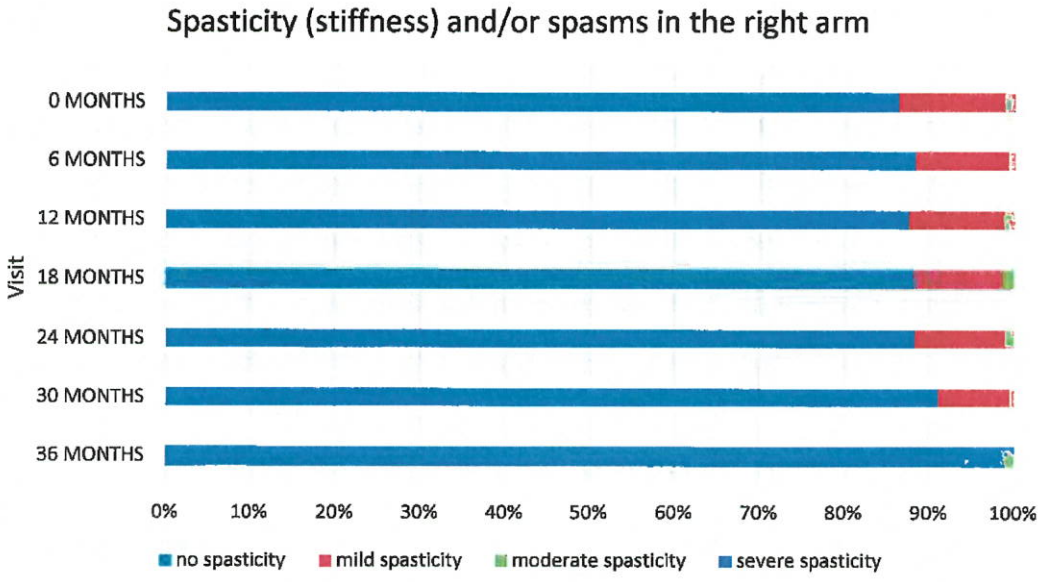


Figure 53: Bar chart of question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the right arm?

Table 62: Question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the left arm?

Spasticity (stiffness) and/or spasms in the left arm								
	no spasticity		mild spasticity		moderate spasticity		severe spasticity	
	N	%	N	%	N	%	N	%
0M	502	90.8%	46	8.3%	5	0.9%	0	0.0%
6M	466	90.8%	43	8.4%	4	0.8%	0	0.0%
12M	424	89.6%	44	9.3%	5	1.1%	0	0.0%
18M	377	90.2%	37	8.9%	4	1.0%	0	0.0%
24M	326	88.8%	37	10.1%	4	1.1%	0	0.0%
30M	291	90.9%	25	7.8%	4	1.3%	0	0.0%
36M	276	91.7%	21	7.0%	3	1.0%	1	0.3%

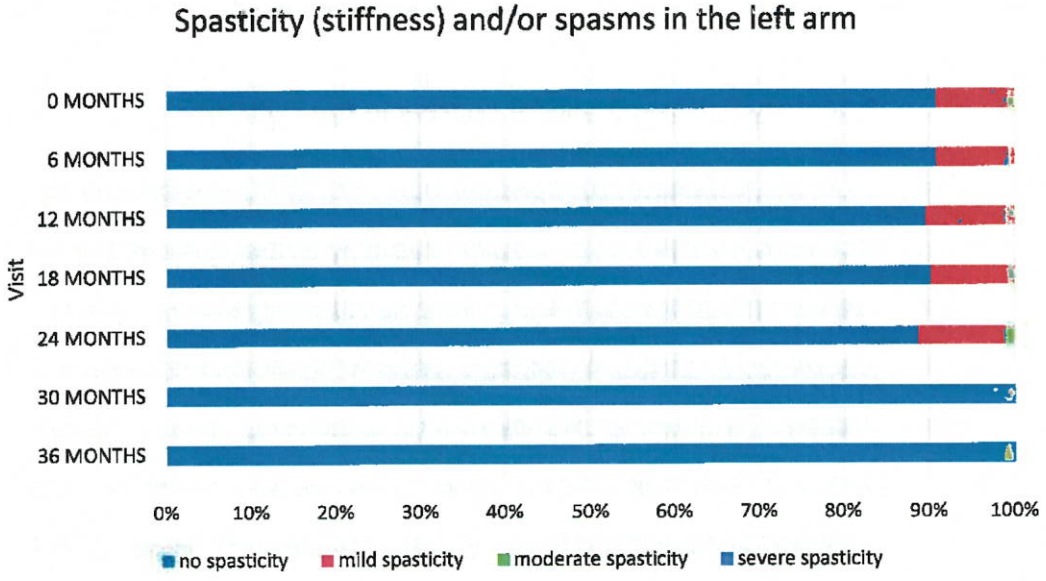


Figure 54: Bar chart of question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the left arm?

Table 63: Question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the right leg?

Spasticity (stiffness) and/or spasms in the right leg								
	no spasticity		mild spasticity		moderate spasticity		severe spasticity	
	N	%	N	%	N	%	N	%
0M	410	74.1%	127	23.0%	15	2.7%	1	0.2%
6M	390	75.6%	104	20.2%	19	3.7%	3	0.6%
12M	363	76.7%	86	18.2%	22	4.7%	2	0.4%
18M	332	79.4%	68	16.3%	16	3.8%	2	0.5%
24M	289	78.7%	60	16.3%	14	3.8%	4	1.1%
30M	262	81.9%	51	15.9%	5	1.6%	2	0.6%
36M	239	79.4%	51	16.9%	11	3.7%	0	0.0%

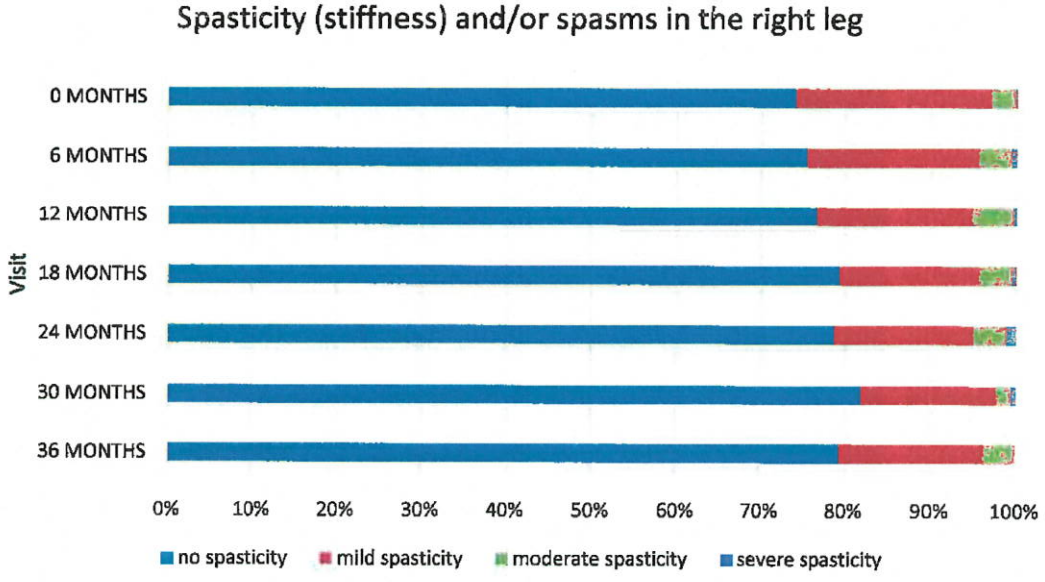


Figure 55: Bar chart of question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the right leg?

Table 64: Question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the left leg?

Spasticity (stiffness) and/or spasms in the left leg								
	no spasticity		mild spasticity		moderate spasticity		severe spasticity	
	N	%	N	%	N	%	N	%
0M	423	76.4%	110	19.9%	20	3.6%	1	0.2%
6M	403	78.6%	87	17.0%	20	3.9%	3	0.6%
12M	372	78.5%	81	17.1%	20	4.2%	1	0.2%
18M	337	80.4%	64	15.3%	18	4.3%	0	0.0%
24M	294	79.9%	63	17.1%	10	2.7%	1	0.3%
30M	263	82.2%	47	14.7%	8	2.5%	2	0.6%
36M	234	77.7%	61	20.3%	5	1.7%	1	0.3%

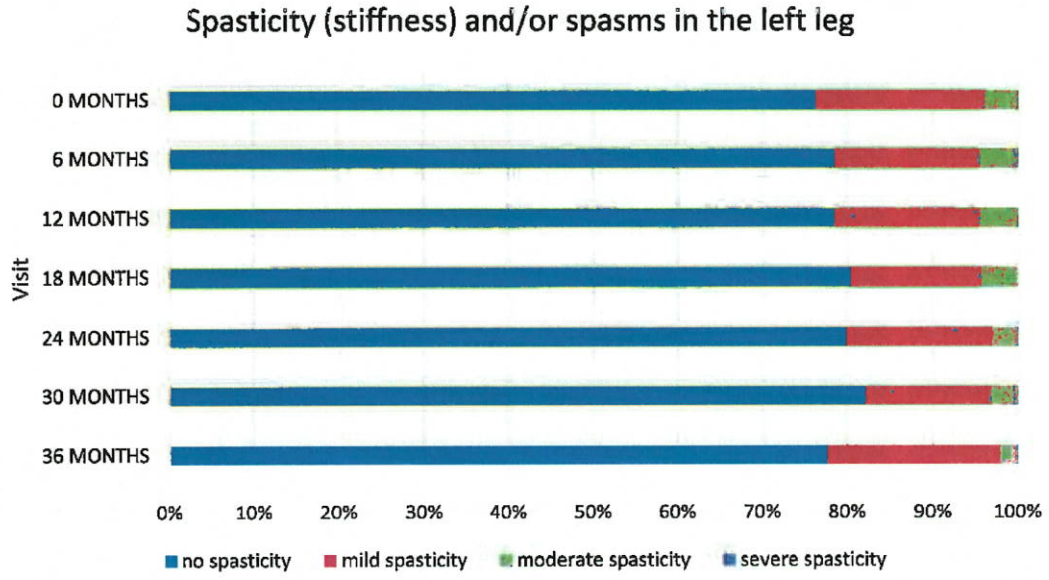


Figure 56: Bar chart of question no. 11 – Which of the following best describes the spasticity (stiffness) and/or spasms of your muscles in the left leg?

8.2.4.2.12 EDSSpts question no. 12

Table 65: Question no. 12 – Which of the following best describes your cognitive (thinking) ability?

Cognitive (thinking) ability										
	no change		mild impairment		moderately impairment		severe impairment		unable to handle my affairs	
	N	%	N	%	N	%	N	%	N	%
0 M	442	79.5%	99	17.8%	14	2.5%	1	0.2%	0	0.0%
6 M	420	81.1%	88	17.0%	9	1.7%	0	0.0%	1	0.2%
12 M	389	81.9%	80	16.8%	6	1.3%	0	0.0%	0	0.0%
18 M	361	86.2%	53	12.6%	5	1.2%	0	0.0%	0	0.0%
24 M	309	84.0%	51	13.9%	8	2.2%	0	0.0%	0	0.0%
30 M	281	87.8%	34	10.6%	5	1.6%	0	0.0%	0	0.0%
36 M	262	86.5%	39	12.9%	2	0.7%	0	0.0%	0	0.0%

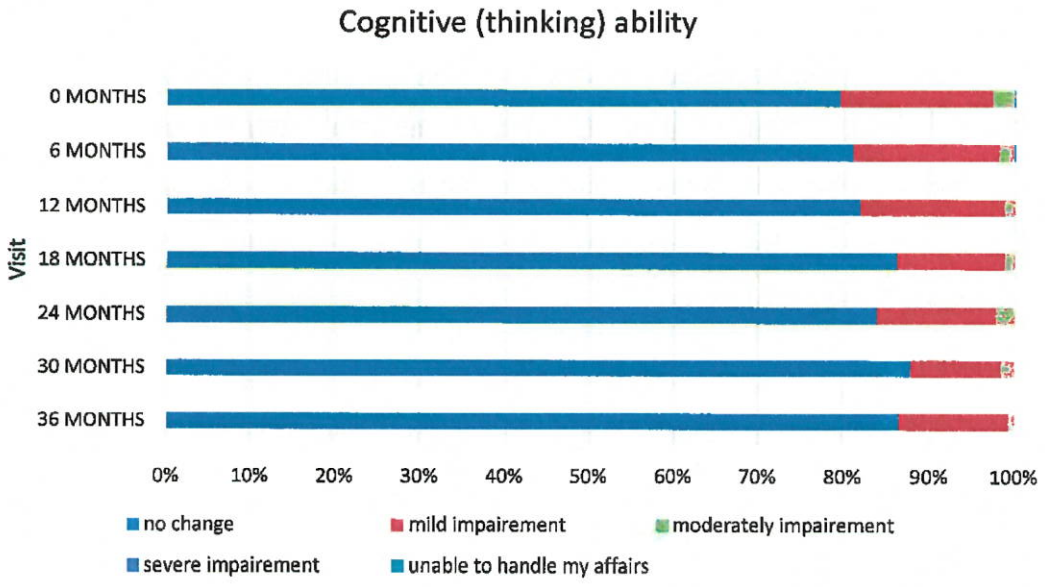


Figure 57: Bar chart of question no. 12 – Which of the following best describes your cognitive (thinking) ability?

8.2.4.2.13 EDSSpts question no. 13

Table 66: Question no. 13 – Which of the following best describes your mood since getting MS?

Mood since getting MS						
	unchanged		depressed		cheerful	
	N	%	N	%	N	%
0M	395	71.6%	131	23.7%	26	4.7%
6M	370	71.8%	120	23.3%	25	4.9%
12M	345	72.6%	110	23.2%	20	4.2%
18M	322	77.4%	72	17.3%	22	5.3%
24M	285	77.7%	61	16.6%	21	5.7%
30M	262	82.1%	42	13.2%	15	4.7%
36M	248	82.1%	47	15.6%	7	2.3%

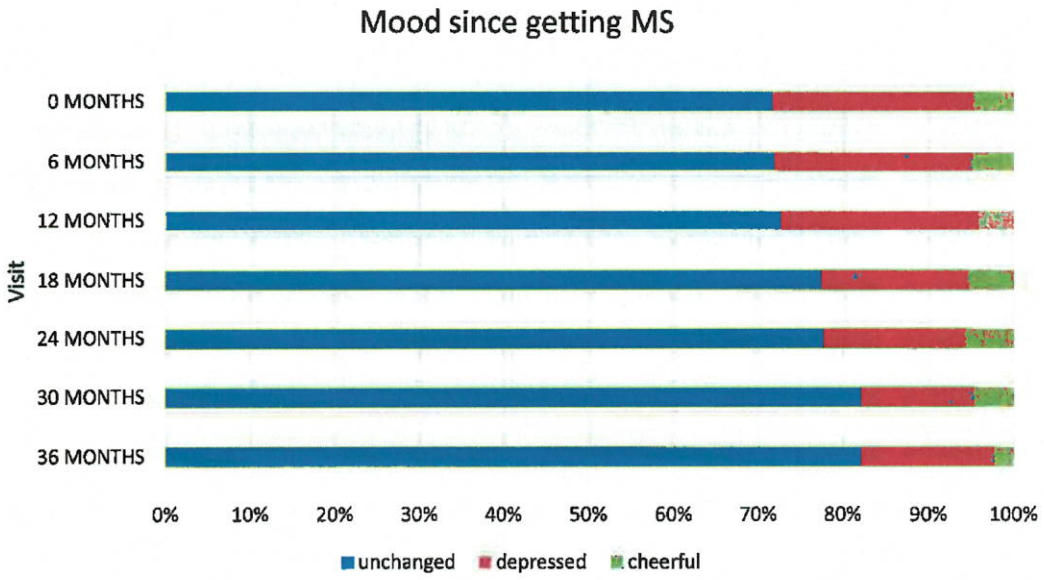


Figure 58: Bar chart of question no. 13 – Which of the following best describes your mood since getting MS?

8.2.4.2.14 EDSSpts question no. 14

Table 67: Question no. 14 – Do you have difficulty swallowing?

Difficulty swallowing								
	no difficulty		mild difficulty		moderate difficulty		severe difficulty	
	N	%	N	%	N	%	N	%
0M	534	96.2%	19	3.4%	2	0.4%	0	0.0%
6M	493	95.4%	24	4.6%	0	0.0%	0	0.0%
12M	452	95.0%	24	5.0%	0	0.0%	0	0.0%
18M	401	95.7%	17	4.1%	1	0.2%	0	0.0%
24M	351	95.6%	16	4.4%	0	0.0%	0	0.0%
30M	308	96.3%	12	3.8%	0	0.0%	0	0.0%
36M	289	95.4%	14	4.6%	0	0.0%	0	0.0%

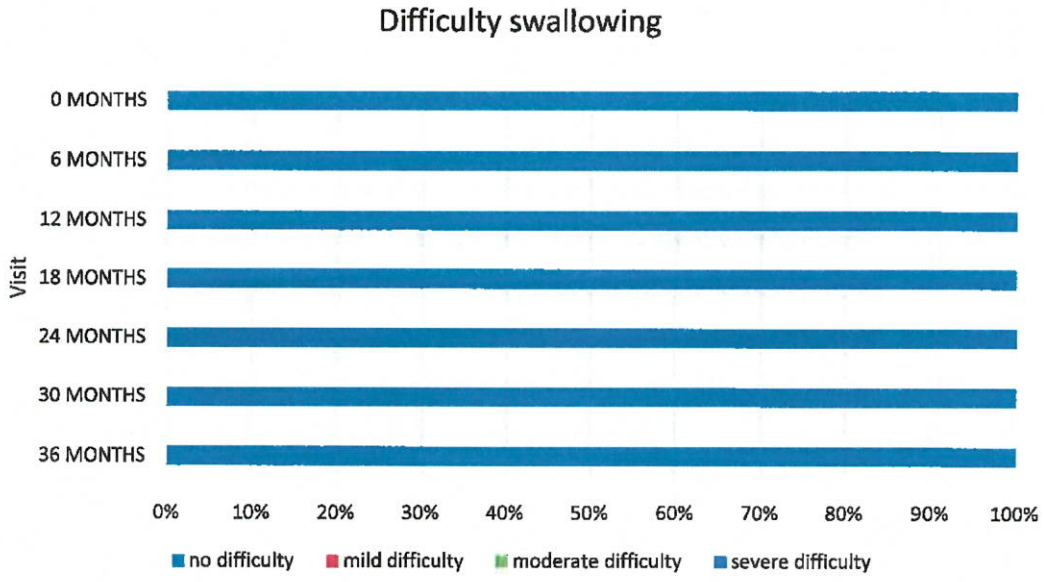


Figure 59: Bar chart of question no. 14 – Do you have difficulty swallowing?

8.2.4.2.15 EDSSpts question no. 15

Table 68: Question no. 15 – Which of the following best describes your bladder function?

Bladder														
	Normal function		Urgency		Frequency		Hesitancy		Occa-sionally inconti-nent		Frequent-ly inconti-nent (weekly)		Frequent-ly inconti-nent (daily)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0M	399	64.5%	122	19.7%	36	5.8%	38	6.1%	19	3.1%	5	0.8%	0	0.0%
6M	361	62.8%	120	20.9%	38	6.6%	35	6.1%	14	2.4%	4	0.7%	3	0.5%
12M	342	65.8%	90	17.3%	31	6.0%	32	6.2%	21	4.0%	4	0.8%	0	0.0%
18M	305	66.9%	85	18.6%	18	3.9%	32	7.0%	16	3.5%	0	0.0%	0	0.0%
24M	269	68.8%	71	18.2%	23	5.9%	17	4.3%	11	2.8%	0	0.0%	0	0.0%
30M	244	69.9%	57	16.3%	17	4.9%	18	5.2%	10	2.9%	3	0.9%	0	0.0%
36M	231	71.7%	55	17.1%	10	3.1%	14	4.3%	10	3.1%	2	0.6%	0	0.0%

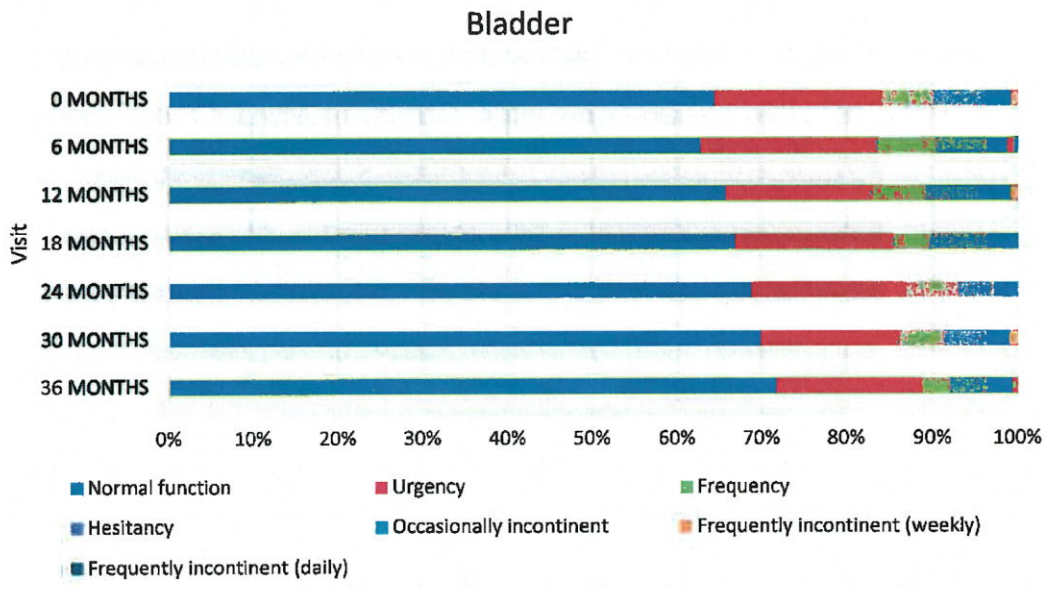


Figure: Bar chart of question no. 15 – Which of the following best describes your bladder function?

Table 69: Question no. 15 – Which of the following best describes your bowel function?

Bowel														
	Normal function		Urgency		Frequency		Hesitancy		Occa-sionally inconti-nent		Frequent-ly inconti-nent (weekly)		Require intermit-tent catheteri-zation	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0M	494	85.5%	42	7.3%	7	1.2%	7	1.2%	4	0.7%	3	0.5%	21	3.6%
6M	461	84.6%	39	7.2%	9	1.7%	11	2.0%	0	0.0%	0	0.0%	25	4.6%
12M	420	85.2%	35	7.1%	3	0.6%	10	2.0%	4	0.8%	0	0.0%	21	4.3%
18M	370	85.1%	26	6.0%	4	0.9%	12	2.8%	2	0.5%	0	0.0%	21	4.8%
24M	321	84.0%	29	7.6%	5	1.3%	9	2.4%	3	0.8%	0	0.0%	15	3.9%
30M	286	88.0%	16	4.9%	2	0.6%	7	2.2%	3	0.9%	0	0.0%	11	3.4%
36M	270	87.9%	22	7.2%	2	0.7%	0	0.0%	2	0.7%	0	0.0%	11	3.6%

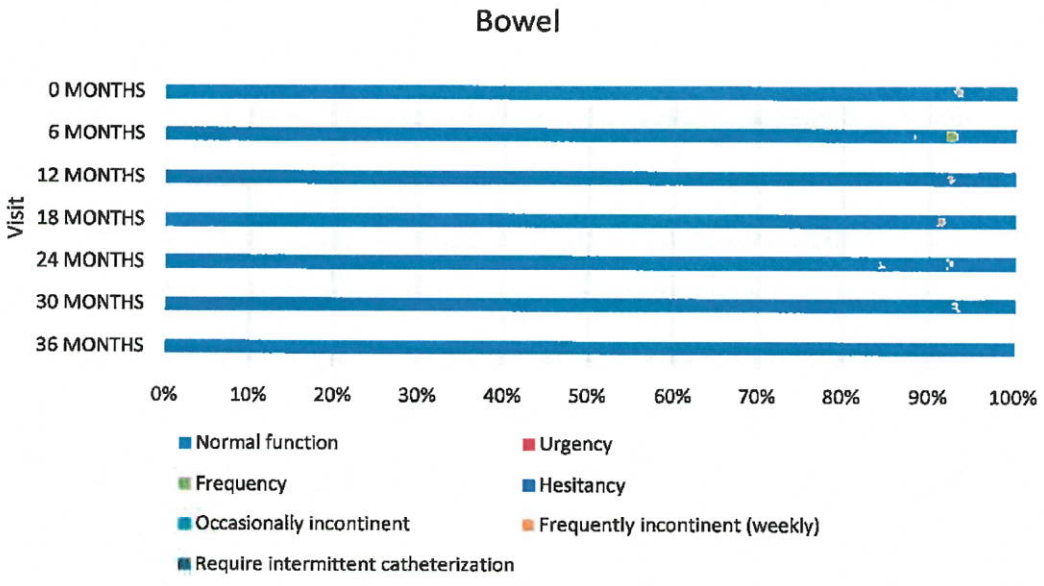


Figure 60: Bar chart of question no. 15 – Which of the following best describes your bowel function?

8.2.4.2.16 EDSSpts question no. 16

Table 70: Question no. 16 – Do you experience vertigo or dizziness?

Vertigo or dizziness								
	no		mild		moderate		severe	
	N	%	N	%	N	%	N	%
0M	362	65.2%	172	31.0%	18	3.2%	3	0.5%
6M	359	69.4%	142	27.5%	13	2.5%	3	0.6%
12M	328	69.1%	134	28.2%	13	2.7%	0	0.0%
18M	308	73.7%	100	23.9%	9	2.2%	1	0.2%
24M	278	75.7%	76	20.7%	12	3.3%	1	0.3%
30M	242	75.9%	72	22.6%	5	1.6%	0	0.0%
36M	230	76.2%	63	20.9%	8	2.6%	1	0.3%

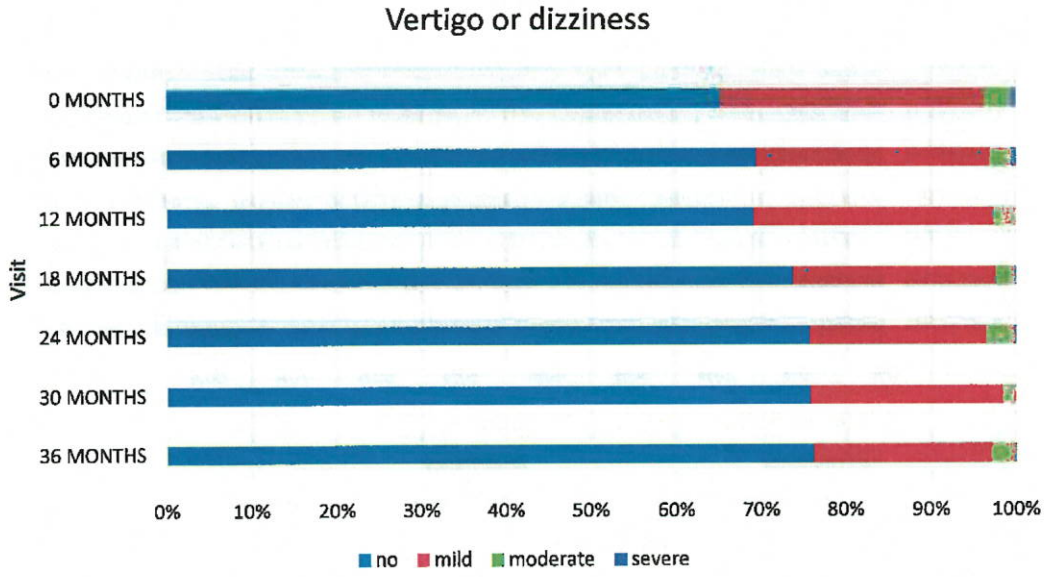


Figure 61: Bar chart of question no. 16 – Do you experience vertigo or dizziness?

8.2.5. Occurrence of relapses in the course of study

Occurrence of relapses in the course of study is provided in Table 72 and on Figure 62. After the first 6 months of treatment in the study, percentage of subjects without MS attack in previous 6 months increased from 34.7% at baseline to 86.7 – 91.2% at the other assessed time points. Similarly, percentage of subjects with one MS attack in previous 6 months dropped from 57.2% at baseline to 8.0 – 12.2% at the other assessed time points. Furthermore, percentage of subjects with two MS attacks in previous 6 months dropped from 7.7% at baseline to 0.3 – 1.8% at the other assessed time points. At last, there were 2 subjects with 3 MS attacks in previous 6 months at baseline and 1 subject with 3 attacks between baseline visit and visit after 6 months, but no case of 3 MS attacks in following months was reported.

Annual relapse rate (ARR) is defined as the total number of confirmed relapses divided by the number of days of observation x 365.25 for each subject. Mean of ARR was improved during the study (from 1.47 to 0.32 relapses per year) in Table 71.

Table 71: Occurrence of Annual Relapse Rate

ARR	N	Mean	Standard Deviation	Median	Minimum	Maximum
prior the study	559	1.4741	1.21621	2.0000	0.00	6.00
during the study	542	0.3202	0.59553	0.0000	0.00	5.40

Table 72: Number of new MS attacks every 6 months

	0		1		2		3	
	N	%	N	%	N	%	N	%
Within last 6 months (0M)	194	34.7%	320	57.2%	43	7.7%	2	0.4%
Since previous visit (6M)	453	86.9%	62	11.9%	5	1.0%	1	0.2%
Since previous visit (12M)	419	86.7%	59	12.2%	5	1.0%	0	0.0%
Since previous visit (18M)	384	90.6%	38	9.0%	2	0.5%	0	0.0%
Since previous visit (24M)	323	87.3%	45	12.2%	2	0.5%	0	0.0%
Since previous visit (30M)	295	90.2%	26	8.0%	6	1.8%	0	0.0%
Since previous visit (36M)	281	91.2%	26	8.4%	1	0.3%	0	0.0%

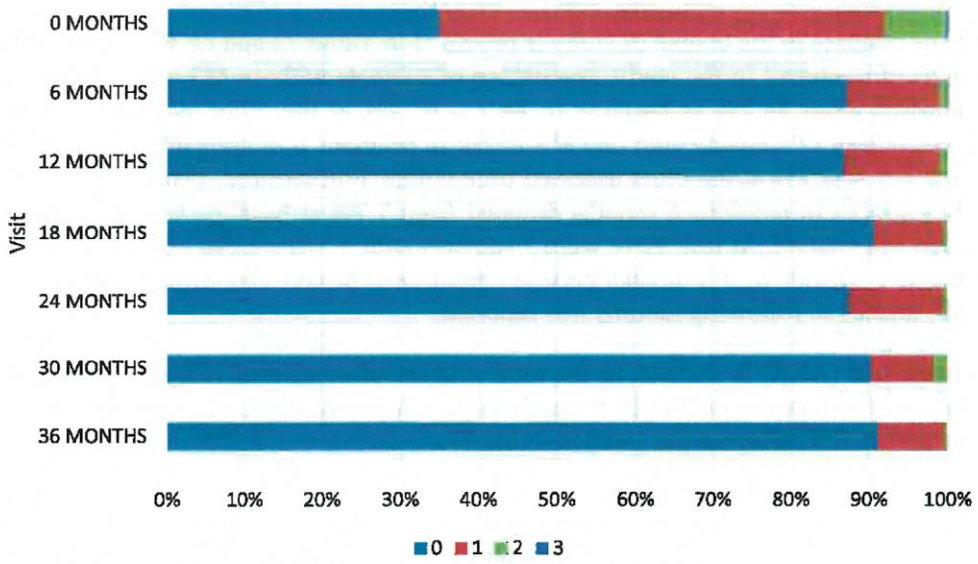


Figure 62: Bar chart of number of new MS attacks every 6 months

8.2.6. Evaluation of weekly injection application by patients (VAS SelfAdmin)

Subjects answered the question "How much does application of Avonex® injection bother you?" every year, i.e. at baseline and visit after 12, 24 and 36 months after ICF signature. The VAS SelfAdmin assesses it in scale from 0 (no problem at all) to 100 (a lot).

As described in Table 74 and on following pictures, VAS varied with following values: 26.6 at baseline, 27.4 at month 12, 23.5 at month 24, and 22.2 at month 36. The median value was 20.0 during the whole study, except month 24 with median value 19.0. In Table 75, there are results of VAS analysis for complete-case analysis only to minimalize influence of withdrawn patients. The mean score increased after the first year and then it was decreasing: 27.3 at baseline, 27.6 at month 12, 23.9 at month 24 and 23.1 at month 36.

Table 73: Number of collected VAS SelfAdmin assessed by patient

	yes		no	
	N	%	N	%
0 MONTHS	444	79.4%	116	20.6%
12 MONTHS	474	98.1%	9	1.9%
24 MONTHS	364	98.4%	6	1.6%
36 MONTHS	300	97.4%	9	2.6%

Table 74: VAS SelfAdmin assessed by patient every 12 months– available-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	444	26.6	23.90	20	0	100
12 MONTHS	474	27.4	23.53	20	0	100
24 MONTHS	364	23.5	21.27	19	0	100
36 MONTHS	300	22.2	19.57	20	0	95

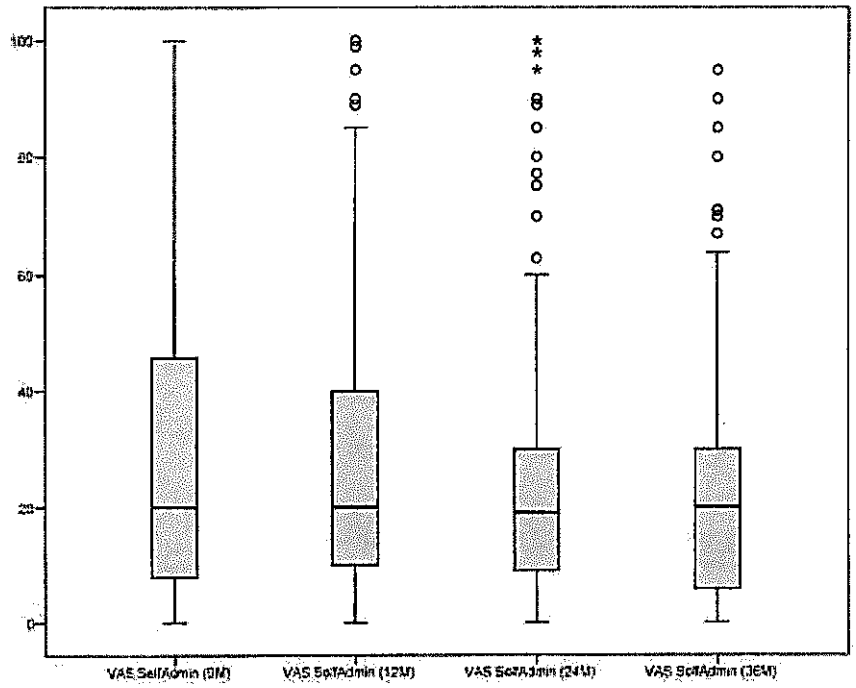


Figure 63: Boxplot of VAS SelfAdmin assessed by patient every 12 months – available-case analysis

Table 75: VAS SelfAdmin assessed by patient every 12 months– complete-case analysis

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	208	27.3	23.02	21	0	90
12 MONTHS	208	27.6	22.55	24	0	100
24 MONTHS	208	23.9	19.67	20	0	100
36 MONTHS	208	23.1	19.56	20	0	95

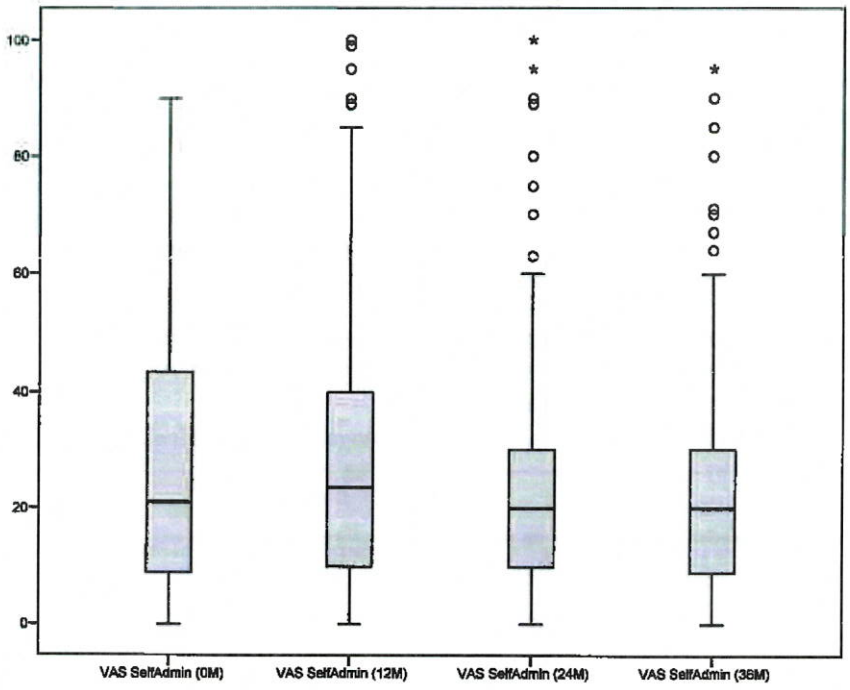


Figure 64: Boxplot of VAS SelfAdmin assessed by patient every 12 months – complete-case analysis (N = 208)

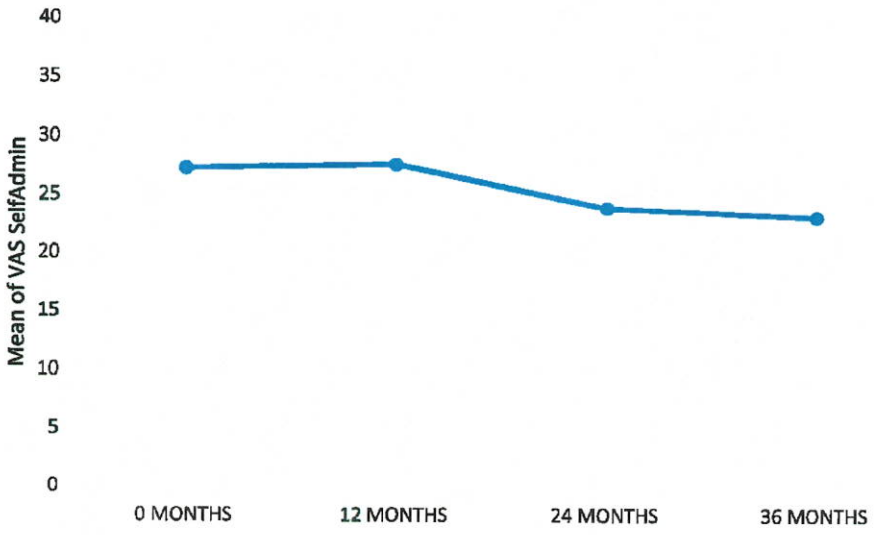


Figure 65: Line chart of mean of VAS SelfAdmin assessed by patient every 12 months (N = 208)

8.2.7. Impact of the disease on subject's employment

A comparison between the number of employed patients at the baseline and at the end of study was made in pairs, all 559 patients had this question complete at both visits. The number of employed or economically active patients slightly increased during the study (80.0% at baseline and 84.3% at end of treatment, EOS visit) as shown in Table 76 and Figure 66. There were changes in characteristics of employment during the study: full time/part time (baseline 93.3%/6.7% and EOS 87.5%/12.5%); manual/intellectual (baseline 38.6%/61.4% and EOS 33.5%/66.5%) as shown in Table 77 and Table 78 and following figures.

Table 76: Number of employed or economically active patients at the baseline and at the end of study

	Employed or economically active (0M)		Employed or economically active (EOS)	
	N	%	N	%
yes	447	80.0%	471	84.3%
no	112	20.0%	88	15.7%

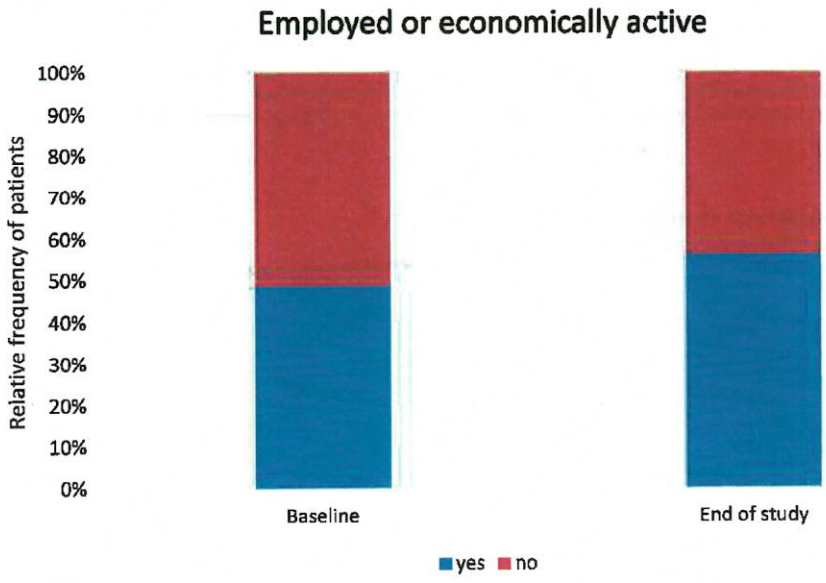


Figure 66: Bar chart of employed or economically active patients at the baseline and at the end of study

Table 77: Number of full-time / part-time employed patients at the baseline and at the end of study

	Employment (0M)		Employment (EOS)	
	N	%	N	%
full time	417	93.3%	412	87.5%
part time	30	6.7%	59	12.5%

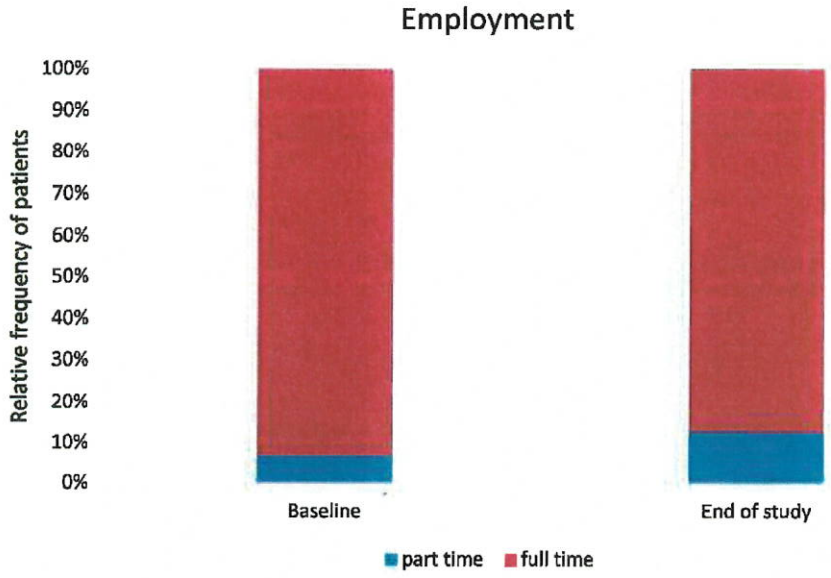


Figure 67: Bar chart of full-time / part-time employed patients at the baseline and at the end of study

Table 78: Last or current employment of patients at the baseline and at the end of study

	Last or current employment (0M)		Last or current employment (EOS)	
	N	%	N	%
manual	192	38.6%	171	33.5%
intellectual	306	61.4%	339	66.5%

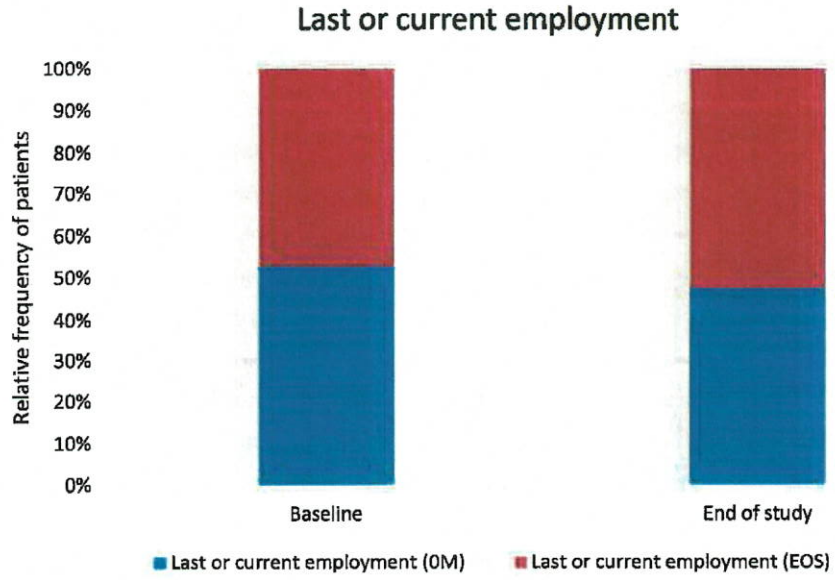


Figure 68: Bar chart of last or current employment of patients at the baseline and at the end of study

8.2.8. Assessment of the development of CDMS in patients with CIS

Physicians had to report whether patient had diagnosis of CIS or CDMS at baseline with the date of respective diagnosis. During the study, physicians recorded newly diagnosed CDMS since the last study visit every 6 months.

Out of 257 patients with CIS, 80 (31%) developed CDMS during the study as it described in Table 79. The mean of time to CDMS diagnosis in patients with CIS was 21.1 months, Table 80). As shown in the Table 81, most of new CDMS diagnosis in the study was determined until 6 months after baseline (6.1%). Frequency of new CDMS diagnosis continually dropped (2.9% until month 12, 1.8% until month 18, 1.1% until month 24, 0.7% until month 30), however last value increased again (1.8 until month 36).

Table 79: Number of patients with CIS or CDMS at the baseline and at the end of study

	Baseline		EOS	
	N	%	N	%
CDMS	302	54%	382	68%
CIS	257	46%	177	32%
Total	**559**	**100%**	**559**	**100%**

Table 80: Time to CDMS diagnosis by patients with CIS diagnosis (in months)

	N	Mean	Std. Deviation	Median	Minimum	Maximum
Time to CDMS diagnosis	80	21.1	22.53	15	1	131

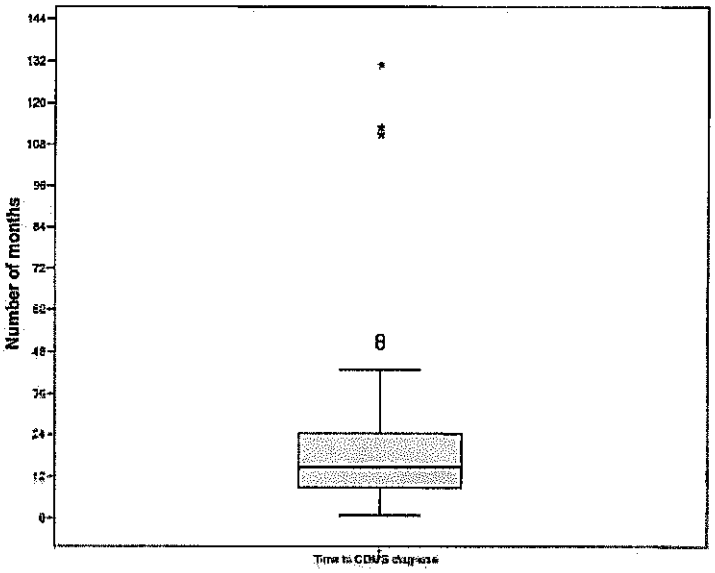


Figure 69: Box plot of Time to CDMS diagnosis by patients with CIS diagnosis at baseline (in months)

Table 81: Frequency of development of CDMS diagnosis during the study

		N	%	Cumulative frequency
Development of CDMS	before start of study	302	54.0%	54.0%
	until 6 months	34	6.1%	60.1%
	between 6 and 12 months	16	2.9%	63.0%
	between 12 and 18 months	10	1.8%	64.8%
	between 18 and 24 months	6	1.1%	65.8%
	between 24 and 30 months	4	0.7%	66.5%
	between 30 and 36 months	10	1.8%	68.3%
CIS at the End of study		177	31.7%	
Total		**559**	**100.0%**	

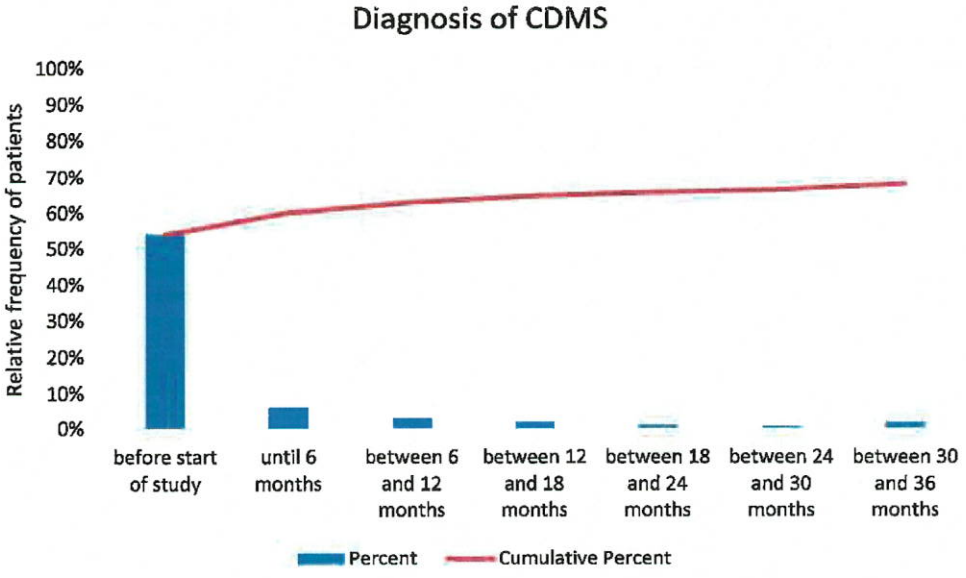


Figure 70: Bar chart of development of CDMS diagnosis during the study

8.2.9. Switches in medication (product and rationale)

Discontinuation of Avonex® treatment resulted in patient withdrawal from study. There were 180 patients who withdrew from the study because of treatment switch as it is stated in Table 6 summarizing reasons for patient withdrawals.

Avonex® was available in two dosage forms – Avonex® 30 µg/0.5 ml sol inj and Avonex® 30 µg plv. (BIO-SET). Table 82 provides the number of patients with each of Avonex® dosage forms who discontinued this type of treatment.

Table 82: Medication switch from Avonex®

	N	%
Avonex® 30 µg/0,5 ml sol inj	169	94%
Avonex® 30 µg plv. (BIO-SET)	11	6%
Total	**180**	**100%**

As described in Table 83 and on Figure 71, new treatments were different interferon beta-1a with combinations (46%), interferon beta-1b (3%) or different DMT (51%). Out of 180 patients who discontinued Avonex® treatment, 47 patients did not receive any further treatment.

Table 83: Medication switch on product

	N	%
Betaferon®	2%	2
Rebif® 22 µg	18%	24
Rebif® 44 µg	26%	34
Copaxone®	26%	34
Aubagio	1%	1
Extavia	2%	2
Flebogamma	1%	1
Gilenya	8%	11
Ocrelizumab	2%	2
Plegridy	2%	2
Rebif 44 x Ocrelizumab	1%	1
Tecfidera	1%	1
Tysabri	14%	18
Total	**133**	**100%**
No medication	**47**	

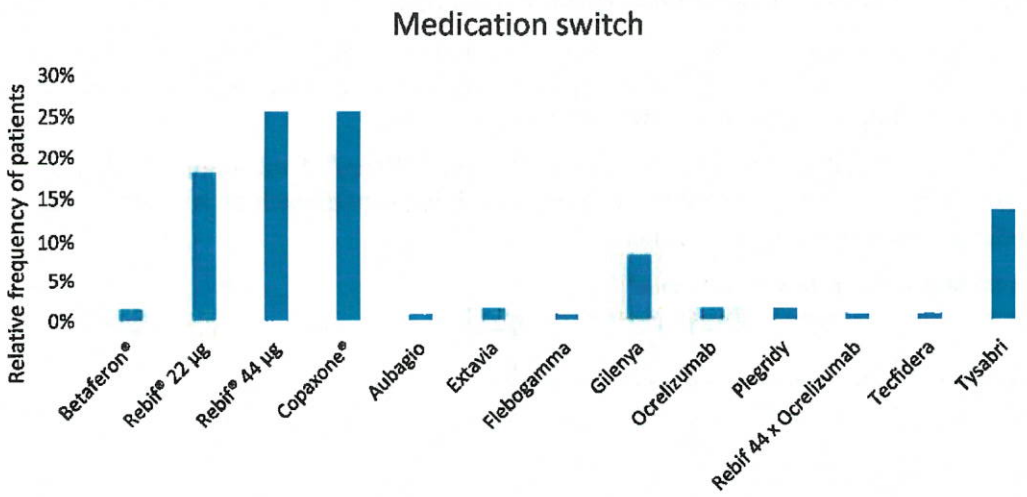


Figure 71: Bar chart of switch medication

The switch between both Avonex® dosage forms was recorded three-times during the study, see Table 84. This type of replacement was not considered to be a medication switch.

Table 84: Avonex® replacement

	N	%
Avonex® 30 µg/0,5 ml sol inj.	0	0%
Avonex® 30 µg plv. (BIO-SET)	3	100%
Total	**3**	**100%**

The most frequent reason (72%) for premature withdrawal was the treatment switch because of low efficacy (41.1%), problems with application (35.6%), patient request (12.8%), and pregnancy (10.6%).

Table 85: Reasons for treatment switch

	N	%
Low efficacy	74	41.1%
Problems with application	64	35.6%
Patient request	23	12.8%
Pregnancy	19	10.6%
Total	**180**	**100.0%**

9. SAFETY RESULTS

All spontaneously reported AEs received through the study regardless of whether the event was serious, were reported to regulatory authorities in accordance with 21 CFR 314.80 in the US and Regulation (EC) No. 726/2004 and Directive 2001/89/E as amended and Volume 9a of the Rules Governing Medicinal Products in the European Union in the E.U. A long-term safety assessment of the Avonex® treatment was performed as a review of SAEs/AEs. All SAEs were documented and reported to responsible organisation in accordance with study protocol.

During the study, 134 cases were collected in Czech Republic and Slovakia. 84 events (48.6%) were recorded as AE, 89 (51.4%) as SAE.

The most frequent events were MS relapse (29.5%), neurological difficulties (15.6%), and flu-like syndrome (8.7%). In more detail among the neurological difficulties were reported events of paresthesis and paraparesis of lower limbs, bilateral tingling of upper limbs, lower limb radicular lumbosacral syndrome and episodes of pain particularly lower back pain, lumbalgia and events of radicular syndrome. Furthermore, neurological difficulties concerning the optic nerve were also reported particularly 3 events of retrobulbar neuritis and 1 event of optic neuritis on the left side. Concerning cognitive functions 1 event of occasional memory problems was reported. Also reported were single events of brainstem syndrome, spinal ataxia, sphincter problems, myoclonus, hemihypesthesia l. sin., spastic paraparesis, and fixatio transpedicularis L5/S1 l. dx. In general, majority of events in the neurological difficulties category were SAE and only two events were reported as AE (benign paroxysmal positional vertigo of the posterior semicircular canal, occasional memory problems).

Other infrequently reported events divided into categories were:

Allergy category - 1 AE event of toxoallergic exanthema

Cardiology category - 1 SAE event of dysrhythmia

Dermatology category - 4 AE events of local reactions

Endocrinology - 1 AE event of thyreopathy

Fatigue category - 5 AE events of fatigue

Flu-like syndrome category - 15 AE events of flu-like syndrome

Gastroenterology category - 3 individual AE events of incompetent cardia, gastroduodenal ulcer disease, sliding hiatal hernia, and 2 individual SAE events of hypersplenism, and abdominal pain

Gynecology category - 3 individual SAE events of uterus myomatosus, hematoma in the uterus, and hypermetrorhagia

Hematology category - 5 individual SAE events of leukopenia with bone marrow suppression, secondary thrombocytopenia, autoimmune thrombocytopenia (relaps), thrombocytopenia, and varicocela of the left testis, and 5 individual AE events of drug induced leukopenia, leukopenia of unknown origin, thrombocytopenia, hematoma, and lymphopenia (reported twice)

Hepatology category - 1 SAE event of suspected viral hepatitis and 10 individual AE events of elevated liver function tests (reported twice),unspecified hepatopathy, elevated liver enzymes (reported six times)

Infection category - 2 individual SAE events of uveitis and virus infection, and 6 individual AE events of virosis (reported three times), tonsillitis, influenza, and repeated virus infections of the upper respiratory tract

Injury category - 1 SAE event of chest contusion and 1 SAE event fall of bike

Metabolic disorder category – 1 AE event of hypoproteinemia

MS progression category – 2 AE events of diseases progression according to MRI

Off-label use category – 1 AE event of off-label use (unknown reason)

Oncology category – 1 SAE event of fatty tumor in retroperitoneal space

Ophthalmology category – 1 AE event of scintillating scotoma in stress and longer work at a PC

Otology category 1 SAE event of hearing loss (hypoacusis baso cochlearis on the left)

Psychiatric category – 2 AE events of occasional depression

Skeletal system diseases category – 1 AE event of joint pain and 2 SAE events of hallux valgus and arthralgia

Surgery category – 3 individual SAE events of hollowed chest surgery, knee surgery and splenectomy

Out of 11 pregnancies reported in the Czech Republic during the study, 9 ended with the delivery of a child without any birth defect. 2 pregnancies ended as spontaneous abortion. 1 pregnancy was reported in the Slovak Republic that ended by foetal death for unknown reason. Increased risk of spontaneous abortion is described in Avonex® Summary of Product Characteristics and Avonex® treatment initiation is contraindicated during the pregnancy.

Overview of all categories and severity are shown in Table 86 and Figure 72.

Table 86: Number of AE/SAE

		Seriousness								
		AE			SAE			Total		
		N	Column %	Row %	N	Column %	Row %	N	Column %	Row %
Category	MS relapse	14	16.7%	27.5%	37	41.6%	72.5%	**51**	**29.5%**	**100.0%**
	neurology	2	2.4%	7.4%	25	28.1%	92.6%	**27**	**15.6%**	**100.0%**
	flu-like syndrome	15	17.9%	100.0%	0	0.0%	0.0%	**15**	**8.7%**	**100.0%**
	pregnancy	9	10.7%	75.0%	3	3.4%	25.0%	**12**	**6.9%**	**100.0%**
	hematology	6	7.1%	54.5%	5	5.6%	45.5%	**11**	**6.4%**	**100.0%**
	hepatology	10	11.9%	90.9%	1	1.1%	9.1%	**11**	**6.4%**	**100.0%**
	infection	6	7.1%	75.0%	2	2.2%	25.0%	**8**	**4.6%**	**100.0%**
	fatigue	5	6.0%	100.0%	0	0.0%	0.0%	**5**	**2.9%**	**100.0%**
	gastroenterology	3	3.6%	60.0%	2	2.2%	40.0%	**5**	**2.9%**	**100.0%**
	dermatology	4	4.8%	100.0%	0	0.0%	0.0%	**4**	**2.3%**	**100.0%**
	gynecology	0	0.0%	0.0%	3	3.4%	100.0%	**3**	**1.7%**	**100.0%**
	skeletal system disease	1	1.2%	33.3%	2	2.2%	66.7%	**3**	**1.7%**	**100.0%**
	surgery	0	0.0%	0.0%	3	3.4%	100.0%	**3**	**1.7%**	**100.0%**
	injury	0	0.0%	0.0%	2	2.2%	100.0%	**2**	**1.2%**	**100.0%**
	MS progression	2	2.4%	100.0%	0	0.0%	0.0%	**2**	**1.2%**	**100.0%**
	oncology	0	0.0%	0.0%	2	2.2%	100.0%	**2**	**1.2%**	**100.0%**
	psychiatric	2	2.4%	100.0%	0	0.0%	0.0%	**2**	**1.2%**	**100.0%**
	allergy	1	1.2%	100.0%	0	0.0%	0.0%	**1**	**0.6%**	**100.0%**
	cardiology	0	0.0%	0.0%	1	1.1%	100.0%	**1**	**0.6%**	**100.0%**
	endocrinology	1	1.2%	100.0%	0	0.0%	0.0%	**1**	**0.6%**	**100.0%**
	metabolic disorder	1	1.2%	100.0%	0	0.0%	0.0%	**1**	**0.6%**	**100.0%**
	off label use	1	1.2%	100.0%	0	0.0%	0.0%	**1**	**0.6%**	**100.0%**
	ophtalmology	1	1.2%	100.0%	0	0.0%	0.0%	**1**	**0.6%**	**100.0%**
	otology	0	0.0%	0.0%	1	1.1%	100.0%	**1**	**0.6%**	**100.0%**
	Total	**84**	**100.0%**	**48.6%**	**89**	**100.0%**	**51.4%**	**173**	**100.0%**	**100.0%**

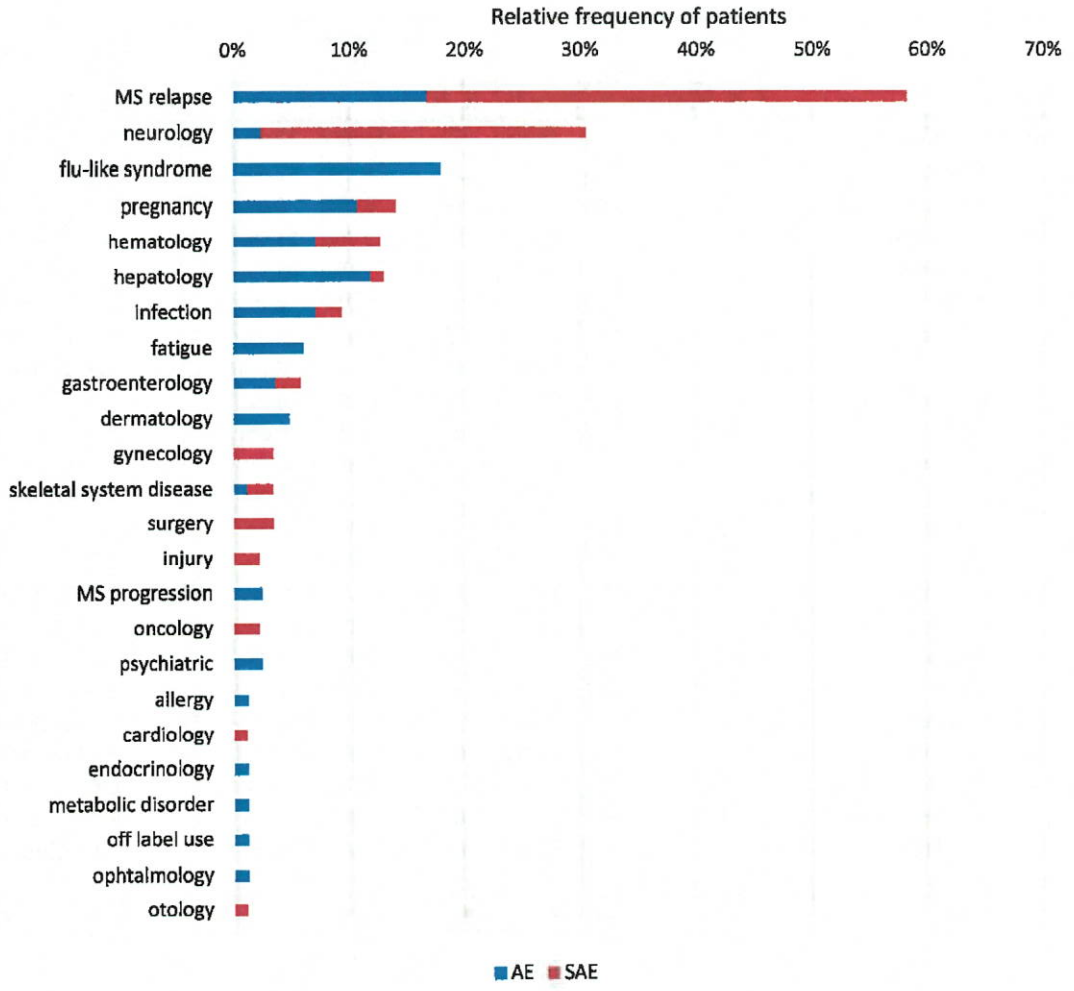


Figure 72: Bar chart of frequency of AE/SAE categories

10. DISCUSSION AND OVERALL CONCLUSIONS

The LD140409 study was conducted in order to clarify the impact of Avonex® therapy on patients' quality of life assessed by patient and physician. Relevant data were obtained from the questionnaires at the beginning of the study (i.e. baseline data) and repeatedly in the course of the study. Furthermore, the effectiveness of the therapy was assessed by objective parameters by physicians (disability, relapses).

Improvement of quality of life was detected during three years of the Avonex® treatment by VAS QoL and SF-36 questionnaires, the primary endpoints of the study. However, this improvement was only mild or negligible in most of SF-36 scores. Furthermore, patients did not report better health status over one previous year more often according to reported health transition. Feeling the same as one year ago was the single answer that was reported with substantially increasing frequency. Although worse health status was reported with higher frequency after baseline, this increase did not continue in the following assessed years. Jongen at al. (2010) described increase of HRQOL in patients with relapsing remitting MS after 2 years of treatment with intramuscular interferon beta-1a, especially in younger patients with low disability. Study of Fernández et al. (2011) included patients with CIS to analysis of factors that determine HRQOL in population with MS. Multivariate multiple regression analyses identified lower educational level, higher EDSS score, cognitive impairment, being single and shorter time since last relapse as significant predictors of lower MS International QoL global index scores ($p < 0.05$). Furthermore, Patti et al. (2014) compared quality of life in patients treated with interferon beta-1a in intramuscular or subcutaneous injections versus untreated group of patients. Interferon treatment irrespective of dosage form was statistically significantly associated with improved quality of life after 2 years.

Quality of life during three years of Avonex® treatment was assessed by VAS administered by physician as well. The results were notably similar to the patient reported quality of life by VAS (29.1/29.4 at baseline, 26.0/26.1 at month 12, 24.9/24.0 at month 24 and 22.2/23.3 at month 36 assessed by patient/ resp. physician). Furthermore, the results in population of patients who completed VAS QoL at all time points (complete-case analysis) were the following: 27.8/28.7 at baseline, 23.5/23.4 at month 12, 24.2/22.9 at month 24 and 21.6/22.9 at month 36 assessed by patient/ resp. physician. To our knowledge, no longitudinal study assessing quality of life using VAS QoL in MS patients during interferon beta-1a treatment has been published yet.

To complete the physician reported outcome, EDSS was examined during the study. The EDSS score was varying around the same level and the median value remained the same for the whole study. Vicrey et al. (2015) demonstrated that EDSS changes after interferon beta-1a treatment are solely associated with physical health domain of HRQOL. During the present LD140409 study, the average score for SF-36 physical functioning was improving (87.48 at baseline to 90.03 at month 36), however median was the same for the whole study (95) what corresponds with EDSS results as median was also the same for the whole present study (1.5).

Cognitive functions assessed by PASAT test were improving for rate #1 what is in accordance with study of Penner et al. (2012) that confirmed improved cognitive performance in patients with a first event suggestive of multiple sclerosis after 2 years of interferon beta-1b treatment.

The correlation between EDSS and EDSSpts is significant at the 0.01 level (2-tailed) with P-value < 0.001 in each visit. The correlation is low positive. In accordance with Goodin (1998), this result indicate that the self-report questionnaire is a valid measure of neurological impairment in MS and, thus, that it can be used to survey this health outcome in an MS population.

Efficacy of the Avonex® treatment was evaluated by occurrence of relapses in the course of the present study. After the first 6 months of treatment in the study, percentage of subjects without MS attack in previous 6 months increased from 34.7% at baseline to 86.7 – 91.2% at the other assessed time points. Similarly, percentage of subjects with one MS attack in previous 6 months dropped from 57.2% at baseline to 8.0 – 12.2% at the other assessed time points. Furthermore, percentage of subjects with two MS attacks in previous 6 months dropped from 7.7% at baseline to 0.3 – 1.8% at the other assessed time points. At last, there were 2 subjects with 3 MS attacks in previous 6 months at baseline and 1 subject with 3 attacks between baseline visit and visit after 6 months, but no case of 3 MS attacks in following months was reported. The Avonex® Summary of Product Characteristics states one-third reduction in annual relapse rate that was observed after more than one year of treatment. In conclusion, the decrease of relapses occurrence in the present study corresponds with the Avonex® Summary of Product Characteristics.

ARR was clearly improved during the treatment with Avonex® (1.47 prior the study and 0.32 during the study). This finding is in accordance with the latest published study of interferon beta-1a efficacy (Saida at el., 2016) likewise with the results of Avonex® clinical study PRISMS-4 (PRISMS, 2001).

Burden of weekly intramuscular injections during Avonex® treatment was evaluated by VAS questionnaire administered by a patient. For selected population of patients who completed the whole study, VAS varied with following values: 27.3 at baseline, 27.6 at month 12, 23.9 at month 24, and 23.1 at month 36. Furthermore, median values copy the same curve (21 at baseline, 24 at month 12, 20 at month 24 and 20 at month 36). Results suggest that after first year of treatment, patients were more reconciled with application form of treatment. PERSIST study (Hupperts et al., 2012) evaluated adherence associated with the intramuscular interferon beta-1a auto injector pen in MS patients over one year. As the result, the auto injector pen was associated with high levels of persistence, compliance, adherence, and satisfaction, little-to-no pain and low need for caregiver assistance. Furthermore, this treatment may reduce barriers to injection therapy, while supporting long-term MS management.

Impact of the disease on patients' employment was analysed by comparison numbers of economically active patients at baseline (80.0%) and EOS (84.3%). Except increase of economically active patients during the study, changes in employment characteristics were detected as well: full time/part time (baseline 93.3%/6.7% and EOS 87.5%/12.5%); manual/intellectual (baseline 38.6%/61.4% and EOS 33.5%/66.5%). These findings are in accordance with comprehensive work of Korchounov et al. (2014) giving evidence that the introduction of disease modifying drugs may have positively influenced the employment with MS.

Delay of CDMS diagnosis after initiation of interferon beta-1a therapy during a first event of MS is well established (Jacobs et al., 2000; Avonex® Summary of Product Characteristics). In present study, 80 (31%) patients with CIS at baseline developed CDMS during the study. The

mean time to CDMS diagnosis in patients with CIS at baseline was 21.1 months and the most of new CDMS diagnosis in the study was determined until 6 months after baseline (6.1%). Frequency of new CDMS diagnosis continually dropped (2.9% until month 12, 1.8% until month 18, 1.1% until month 24, 0.7% until month 30), however last value increased again (1.8 % until month 36).

Out of 180 patients who discontinued Avonex® treatment, 47 patients did not receive immediately any other treatment. For the others, new treatments were different interferon beta 1A (46%), 1B (3%) or different drug (51%). The most frequent reason (72%) for premature withdrawal was treatment switch because of low efficacy (41.1%), problems with application (35.6%), patient request (12.8%), and pregnancy (10.6%). For comparison, Fox et al. (2013) evaluated reasons for treatment discontinuation using data from the North American Research Committee on Multiple Sclerosis (NARCOMS) database. From 739 subjects who discontinued intramuscular interferon beta-1a, following reasons were provided: perceived efficacy 41%, safety 22%, tolerability 37% and burden of drug application 18%.

During the study, the most frequent adverse events were MS relapse (29.5%), neurological difficulties (15.6%), and flu-like syndrome (8.7%) what is in accordance with Avonex® Summary of Product Characteristics. In line with adverse events described in SmPC; no new safety signals were identified.

In conclusion, the present study confirmed significant effect of Avonex® treatment on relapse rate reduction and stabilization of patients' clinical status. The treatment had a positive effect on quality of life assessed both by a patient and a physician using VAS questionnaires and on cognitive functions. The other evaluated endpoints slightly improved or remained stable during the followed three years of treatment.

11. REFERENCE LIST

Alonso A, Herman MA. 2008. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. Jul 8; 71 (2):129-35. doi: 10.1212/01.wnl.0000316802.35974.34.

Avonex® [Biogen Idec] Summary of Product Characteristics

Fernández O, Baumstarck-Barrau K, Simeoni MC, Auquier P; MusiQoL study group. 2011. Patient characteristics and determinants of quality of life in an international population with multiple sclerosis: assessment using the MusiQoL and SF-36 questionnaires. MultScler. Oct; 17(10):1238-49. doi: 10.1177/1352458511407951. Epub 2011 Jun 13.

Fox RJ, Salter AR, Tyry T, Sun J, You X, Laforet G, Campagnolo D. 2013. Treatment discontinuation and disease progression with injectable disease-modifying therapies: findings from the north american research committee on multiple sclerosis database. Int J MS Care. Winter; 15(4):194-201. doi: 10.7224/1537-2073.2012-034.

Goodin DS. 1998. A questionnaire to assess neurological impairment in multiple sclerosis. MultScler October vol. 4 no. 5444-451

Hupperts R, Becker V, Friedrich J, Gobbi C, Salgado AV, Sperling B, You X. 2015. Multiple sclerosis patients treated with intramuscular IFN-β-1a autoinjector in a real-world setting: prospective evaluation of treatment persistence, adherence, quality of life and satisfaction. Expert Opin Drug Deliv. Jan; 12(1):15-25. doi: 10.1517/17425247.2015.989209. Epub 2014 Nov 28.

Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ et al. 2000. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHA MPS Study Group. N Eng J Med; 343(13): 898–904.

Jongen PJ, Sindic C, Carton H, Zwanikken C, Lemmens W, Borm G; Functional composite and quality of Life in Avonex-treated Relapsing multiple sclerosis patients study group. 2010. Improvement of health-related quality of life in relapsing remitting multiple sclerosis patients after 2 years of treatment with intramuscular interferon-beta-1a J Neurol. 2010 Apr;257(4):584-9. doi: 10.1007/s00415-009-5378-x. Epub 2009 Nov 18.

Korchounov A, Tabatadze T, Spivak D2 Rössy W, Krasnianski M. 2014. MS related employment and disease modifying treatment in the German working population: 1994-2009. NeuroRehabilitation. Jan 7. [Epub ahead of print]

Patti F, Pappalardo A, Montanari E, Pesci I, Barletta V, Pozzilli C. 2014. Interferon-beta-1a treatment has a positive effect on quality of life of relapsing-remitting multiple sclerosis: results from a longitudinal study. Neurol Sci. Feb 15; 337(1-2):180-5. doi: 10.1016/j.jns.2013.12.006. Epub 2013 Dec 26.

Penner IK1, Stemper B, Calabrese P, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, Montalbán X, Barkhof F, Pleimes D, Lanius V, Pohl C, Kappos L, Sandbrink R. 2012. Effects of interferon beta-1b on cognitive performance in patients with a first event suggestive of multiple sclerosis. MultScler. Oct; 18(10):1466-71

Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH and Rodriguez M. 2004. Quality of Life Is Favorable for Most Patients with Multiple Sclerosis: a Population-Based Cohort Study. Arch Neurol 61:679-686.

PRISMS. 2001. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001 Sep 25;57(6):1146.

Putzki N, Fisher J, Gottwald K, Reifschneider G, Ries S, Siever A, Hoffmann F, Kafferlein W, Kausch U, Liedtke M, Kirchmeier J, Gmund S, Richter A, Schicklmaier P, Niemczyk G, Wernsdorfer C and Hartung HP. 2009. Quality of Life in 1000 Patients with Early Relapsing-Remitting Multiple Sclerosis. Eur J Neurol16:713-720.

Saida T, Kira J, Ueno Y, Harada N, Hirakata T. 2016. Long-term efficacy and safety of intramuscular interferon beta-1a: Randomized postmarketing trial of two dosing regimens in Japanese patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2016 May;7:102-8.

Shmueli A. 2005. The visual analog rating scale of health-related quality of life: an examination of end digit preferences. Health Qual Life Outcomes. 3: 71. Published online 2005 Nov 14. doi: 10.1186/1477-7525-3-71

Štourač P, Horáková D, Mavrov I, Turčáni P. 2014. AMETYST Observational Phase IV Study Following the Influence of Intramuscularly Administered Interferon Beta-1a in Patients with Clinically Isolated Syndrome/Clinically Definite Multiple Sclerosis. CeskSlovNeurol N. 77/110 (4): 465-472 [in Czech language]

Twork S, Wiesmeth S, Spindler M, Wirtz M, Schipper S, Pohlau D, Klewer J and Kugler J. 2010. Disability Status and Quality of Life in Multiple Sclerosis: Non-Linearity of the Expanded Disability Status Scale (EDSS). Health Qual Life Outcomes8:55.

Vickrey BG, Lee L, Moore F, Moriarty P. 2015. EDSS Change Relates to Physical HRQoL While Relapse Occurrence Relates to Overall HRQoL in Patients with Multiple Sclerosis Receiving Subcutaneous Interferon β-1a. MultScler Int. 2015: 631989. Published online 2015 Jul 5. doi: 10.1155/2015/631989

12. APPENDICES

APPENDIX A. LISTING OF ETHICS COMMITTEES

Listing 1: Ethics Committees

Site No.	Investigator / Institution Name	Name / Address of Ethics Committee
CZ01	MUDr. Dana Horáková/ Neurologická klinika1.LF UK Karlovo nám. 32 120 00 Praha	Etická komise Všeobecné fakultní nemocnice v Praze/ Na Bojišti 1 128 08 Praha
CZ02	MUDr. Eva Meluzínová/ Neurologická klinika FN Motol V Úvalu 84 150 06 Praha	Etická komise pro multicentrické klinické hodnocení FN v Motole/ V úvalu 84 150 06 Praha 5 - Motol
CZ03	Doc. MUDr. Martin Vališ, Ph.D./ Neurologická klinika FN HK Sokolská 581 500 05 Hradec Králové	N/A
CZ04	Doc. MUDr. Pavel Štourač, Ph.D./ Neurologická klinika FN Bohunice Jihlavská 20 630 00 Brno	Etickákomise FN Brno-Bohunice/ Jihlavská 20 62500 Brno
CZ05	Ing. MUDr. David Zeman, Ph.D./ Neurologická klinika FN Ostrava ul.17 listopadu 1790 708 52 Ostrava	Etická komise Fakultní nemocnice Ostrava/ 17. listopadu 1790 708 52 Ostrava-Poruba
CZ06	MUDr. Michal Dufek/ Neurologická klinika FN u Svaté Anny Pekařská 53 656 91 Brno	Etická komise Fakultní nemocnice u sv. Anny/ Pekařská 53 65691 Brno

Site No.	Investigator / Institution Name	Name / Address of Ethics Committee
CZ07	Doc. MUDr. Jan Mareš, Ph.D./ Neurologická klinika FN Olomouc I.P.Pavlova 6 775 20 Olomouc	N/A
CZ08	MUDr. Alena Novotná/ Neurologická klinika nemocnice Pardubice Kyjevská 44 532 03 Pardubice	Etická komise Nemocnice Pardubického kraje, a.s,/ Pardubická nemocnice Kyjevská 44 53203 Pardubice 1.1.2
CZ09	MUDr. Romana Vančurová/ Neurologická klinika TN Vídeňská 800 140 00 Praha	Etické komise IKEM a Thomayerova nem./ Vídeňská 800 140 59 Praha 4 Krč
CZ10	MUDr. Libuše Lhotáková/ Neurologické oddělení B. Němcové 585/54 370 87 České Budějovice	Etická komise Nemocnice České Budějovice, a.s./ B. Němcové 54 305 01 ČeskéBudějovice
CZ11	Prim. MUDr. Jiří Fiedler, Ph.D./ Neurologická klinika FN Plzeň Alej Svobody 80 304 60 Plzeň	Etická komise Fakultní nemocnice Plzeň/ E. Beneše 13 305 99 Plzeň
CZ12	MUDr. Marta Vachová/ Neurologické oddělení Duchcovská 53 415 28 Teplice	N/A
CZ13	Doc. MUDr. Ivana Štětkářová, CSc./Neurologická klinika FNKV, Šrobárová 50 100 34 Praha	Etická komise Fakultní nemocnice Královské Vinohrady/ Šrobárova 50 100 34 Praha 10

Site No.	Investigator / Institution Name	Name / Address of Ethics Committee
CZ14	MUDr. Radek Ampapa/ Neurologická klinika Nemocnice Jihlava Vrchlického 59 58633 Jihlava	Etická komise Nemocnice Jihlava, p.o./ Vrchlického 59 586 33 Jihlava
SK01	Prof. MUDr. Peter Turčáni/ I. Neurologická klinika UNB Nemocnica Staré Mesto Mickiewiczova 13 813 69 Bratislava	Etická komisia Bratislavského samosprávneho kraja/ Sabinovská 16, P.O. Box 106 820 05 Bratislava 25
SK02*	Doc. MUDr. VladimírDonáth, Ph.D./ Neurologická klinika FNsP F.D. Roosevelta Námestie L. Svobodu 1 975 17 Banská Bystrica	Etická komisia FNsP F.D. Roosevelta/ Nám. L. Svobodu 1 975 17Banská Bystrica
SK03	Doc. MUDr. Eleonóra Klímová, CSc./FNsP J. A. Reimana a FZ PU Hollého 14 081 81 Prešov	Etická komisia FNsP J. A. Reimana/ Hollého 14 081 81 Prešov
SK04	MUDr. Ľubica Procházková, CSc./II. Neurologická klinika UNB Nemocnica akad. L. Dérera Limbová 5 833 05 Bratislava	Etická komisia UNB Nemocnica ak. L. Dérera/ Limbová 5 833 05 Bratislava
SK05	Prof. MUDr. Ľubomír Lisý, DrSc./Neurologická klinika UNB Nemocnica Ružinov Ružinovská 6 826 06 Bratislava	Etická komisie UNB Nemocnica Ružinov/ Ružinovská 6, 826 06 Bratislava
SK06	MUDr. Jarmila Szilášiová, PhD./ARTROMAC n.o. Toryská 1 040 01 Košice	Etická komisia Košického samosprávneho kraja Námestie Maratónu mieru 1 042 66 Košice

Site No.	Investigator / Institution Name	Name / Address of Ethics Committee
SK07	MUDr. Anna Šaffová/ Neurologická klinika ÚVN SNP Ružomberok FN, Generála Miloša Vesela 21 034 26 Ružomberok	Etická komisie UVN SNP Ružomberok –FN/ Generála Miloša Vesela 21 034 26 Ružomberok
SK08	MUDr. Georgi Krastev, PhD./FN Trnava A. Žarnova 11 917 75 Trnava	Etická komisia FN Trnava/ A. Žarnova 11 917 75 Trnava
SK09	Doc. MUDr. Miroslav Brozman, CSc./FN Nitra Špitálska 6 949 01 Nitra	Etická komisia FN Nitra/ Špitálska 6 949 01 Nitra
SK10	MUDr. Milan Grofík/ Neurologická ambulancia Karola Kalocsaya 12 038 61 Vrútky	Etická komisia Žilinského samosprávneho kraja/ Komenského 48 011 09 Žilina

* Site did not enroll any subject.

APPENDIX B. LISTING OF INVESTIGATORS

Listing 2: Listing of Investigators

Site No.	Investigator Name	Institution and Address	Number of Subjects
CZ01	MUDr. Dana Horáková	Neurologická klinika1.LF UK Karlovo nám. 32 120 00 Praha	103
CZ02	MUDr. Eva Meluzínová	Neurologická klinika FN Motol V Úvalu 84 150 06 Praha	18
CZ03	Doc. Martin Vališ, Ph.D.	Neurologická klinika FN HK Sokolská 581 500 05 Hradec Králové	25
CZ04	Doc. MUDr. Pavel Štourač, Ph.D.[1]	Neurologická klinika FN Bohunice Jihlavská 20 630 00 Brno	19
CZ05	Ing. MUDr. David Zeman, Ph.D.	Neurologická klinika FN Ostrava ul.17 listopadu 1790 708 52 Ostrava	8
CZ06	MUDr. Michal Dufek	Neurologická klinika FN u Svaté Anny Pekařská 53 656 91 Brno	14
CZ07	Doc. MUDr. Jan Mareš, Ph.D.	Neurologická klinika FN Olomouc LP.Pavlova 6 775 20 Olomouc	35
CZ08	MUDr. Alena Novotná	Neurologická klinika nemocnice Pardubice Kyjevská 44 532 03 Pardubice	38

Site No.	Investigator Name	Institution and Address	Number of Subjects
CZ09	MUDr. Romana Vančurová	Neurologická klinika TN Vídeňská 800 140 00 Praha	18
CZ10	MUDr. LibušeLhotáková	Neurologické oddělení B.Němcové 585/54 370 87 České Budějovice	49
CZ11	Prim. MUDr. Jiří Fiedler, Ph.D.	Neurologická klinika FN Plzeň Alej Svobody 80 304 60 Plzeň	37
CZ12	MUDr. Marta Vachová	Neurologické oddělení Duchcovská 53 415 28 Teplice	16
CZ13	Doc. MUDr. Štětkářová Ivana, CSc.	Neurologická klinika FNKV, Šrobárová 50 100 34 Praha	10
CZ14	MUDr. RadekAmpapa	Neurologická klinika Nemocnice Jihlava Vrchlického 59 58633 Jihlava	10
SK01	Prof. MUDr. Peter Turčáni, PhD.[1]	I. Neurologická klinika UNB Nemocnica StaréMesto Mickiewiczova 13 813 69 Bratislava	9
SK02	Doc. MUDr. VladimírDonáth, PhD.	Neurologická klinika FNsP F.D. Roosevelta Námestie L. Svobodu 1 975 17 Banská Bystrica	0
SK03	Doc. MUDr. Eleonóra Klímová, CSc[1]	FNsP J. A. Reimana a FZ PU Hollého 14 081 81 Prešov	5

Site No.	Investigator Name	Institution and Address	Number of Subjects
SK04	MUDr. ĽubicaProcházková, CSc.	II. Neurologická klinika UNB Nemocnica akad. L. Dérera Limbová 5 833 05 Bratislava	7
SK05	Prof. MUDr. ĽubomírLisý, DrSc.	Neurologická klinika UNB Nemocnica Ružinov Ružinovská 6 826 06 Bratislava	19
SK06	MUDr. JarmilaSzilášiová, PhD.	ARTROMAC n.o. Toryská 1 040 01 Košice	45
SK07	MUDr. Anna Šaffová	Neurologická klinika ÚVN SNP Ružomberok FN, Generála Miloša Vesela 21 034 26 Ružomberok	20
SK08	MUDr. GeorgiKrastev, PhD.	FN Trnava A. Žarnova 11 917 75 Trnava	11
SK09	Doc. MUDr. Miroslav Brozman, CSc	FN Nitra Špitálska 6 949 01 Nitra	16
SK10	MUDr. Milan Grofik	Neurologická ambulancia Karola Kalocsaya 12 038 61 Vrútky	27

[1] Scientific Coordinators for the study.

APPENDIX C. STASTISTICAL ANALYSIS PLAN

STATISTICAL ANALYSIS PLAN

Final version

Tracking number: 4.0

Study Title: LD140409 AMETYST

Start of Study Date:	12 December 2009
End of Study Date:	05 February 2016

Study Sponsor:	Biogen MA Inc. 225 Binney Street Cambridge, MA 02142 United States	Biogen Research Limited Innovation House 70 Norden Road Maidenhead, Berkshire SL6 4AY United Kingdom

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

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

Table 87: List of Abbreviations

AE	Adverse event
CDMS	Clinically definitive multiple sclerosis
CIS	Clinically isolated syndrome
CRF	Case report form
CRO	Contract research organisation
DMT	Disease-modifying treatment
EDSS	Expanded disability status scale
HRQOL	Health-related quality of life
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent ethics committee
ITT	Intention-to-treat
MCS	Mental component summary
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PASAT	Paced auditory serial addition test
PCS	Physical component summary
PP	Per protocol
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	Short form questionnaire 36
US	United States
VAS	Visual analogue scale
VAS SelfAdmin	Visual analogue scale of self-administration
SD	Standard deviation
df	Degrees of freedom

1 ESSENTIAL PROTOCOL-BASED INFORMATION

The study follows the Protocol LD140409 – AMETYST, version 1.0 dated 7th September 2009 in Slovakia and Protocol LD140409 – AMETYST, version 1.0_CZ dated 14th August 2009 in the Czech Republic. Additionally, Protocol Amendment 1 – LD140409 – AMETYST, version 1.0_CZ dated 6th August 2010 has been requested by the Association of Innovative Pharmaceutical Industry (AIFP) for sample size justification in the Czech Republic.

1.1 Study objectives

1.1.1 Primary objectives

To evaluate the impact of Avonex® treatment on the quality of life of patients with CIS/CDMS. Quality of life assessed (VAS QoL and SF-36) every 12 months.

1.1.2 Secondary objectives

- Quality of life assessed by the physician (VAS QoL, EDSS, PASAT) every 12 months (unless indicated otherwise);
- Correlation of quality of life as assessed by the patient and the physician (EDSS and EDSSpts) every 6 months;
- Occurrence of relapses in the course of the study every 6 months;
- Evaluation of weekly injection application by the patient (VAS SelfAdmin) every 12 months;
- Impact of the disease on patient employment status;
- Assessment of the development of CDMS in patients with CIS;
- Switches in medication (product and rationale).

1.2 Study design

The LD140409 study is an international, observational, prospective, longitudinal, multicentre, non-interventional clinical study.

After having obtained informed consent from a subject, the investigator will collect demographic data including information on employment, date of CIS/CDMS diagnosis, date of the last MS attack and date of Avonex® treatment initiation. The other relevant data will be obtained from questionnaires at the beginning of the study (baseline data) and then repeatedly in the course of the study. Any interventional assessment will be performed as an inseparable part of standard medical care and therapy. Data of eligible subjects will be repeatedly collected every 6 months during their regular visits conforming to standard medical care. Participation in the study shall continue until completion of the month 36 visit, discontinuation of Avonex® treatment for any reason, withdrawal of consent by the patient, loss to follow-up or death of the patient.

1.2.1 Study population

Patients fulfilling the eligibility criteria below, treated in specialized neurology sites in the Czech Republic and Slovakia will be enrolled in the study.

Inclusion criteria:

- Signed written informed consent form
- ≥ 18 years of age
- Diagnosis of CIS or CDMS
- Beginning of Avonex® treatment according to medical guidelines (SPC) no earlier than 3 months prior to enrolment
- No other DMT treatment of CIS/CDMS than Avonex® used prior to enrolment
- The last attack more than 30 days prior to enrolment.

Exclusion criteria:

- Legal incapability or limited legal capability
- Any medical or psychological condition which, in the opinion of the investigator, would not permit the patient to complete the study or sign a meaningful informed consent form
- Pregnancy.

Number of subjects planned in the Czech Republic: 400 subjects

Number of subjects planned in Slovakia: 200 subjects

1.2.2 Study exposure

Estimated duration of recruitment: 3 years

Estimated duration for one subject: 36 months

Overall estimated duration of the study: 6 years

1.3 Methods and procedures

1.3.1 Subjects identification and allocation to study treatment

Every subject shall obtain an original identification code containing CZ or SK as country identifier, 2 numbers as site identifier, dash, and 3 numbers based on the order of enrolment of the subject. The ID may look like CZ01-001.

1.3.2 Study assessments

The following data shall be recorded in CRFs according to **Table 88:**

- Demographic data:
  - Date of birth
  - Sex
  - Pregnancy (yes/no) at the baseline visit for women
  - Employment status (economically active yes / no, full / part time employment, manual / intellectual work)
  - Date of signing the informed consent form
  - Date of CIS or CDMS diagnosis
  - CDMS diagnosis (yes / no) at the baseline
  - CDMS diagnosis within the last 6 months during the study (yes/no and date of diagnosis if yes)
  - Date of the last MS attack
  - Start of Avonex® treatment
  - End of Avonex® treatment, if applicable
  - Number of attacks within the last 6 months
- Questionnaires:
  - VAS QoL assessed by the patient
  - VAS SelfAdmin assessed by the patient
  - EDSSpts assessed by the patient
  - SF-36 assessed by the patient
  - VAS QoL assessed by the physician
  - EDSS assessed by the physician
  - PASAT assessed by the physician
- End of study:

- Patient withdrawn (yes / no)
- Reason for withdrawal (ICF withdrawal / Death of patient / Lost of contact)
- Treatment switch:
  - Medication
  - Beginning of the treatment
  - End of Avonex® treatment
  - Reason for switching the treatment (problem with application / patient request / pregnancy / low efficacy).

1.3.2.1 *Effectiveness assessment*

The Visual Analog Scale (VAS) has been extensively used in the assessment of health-related quality of life (HRQOL) [1]. VAS QoL assesses the influence of MS on everyday life using the scale from 0 (no influence at all ~ positive effect) to 100 (a high influence ~ negative effect). The scale will be self-administered by the patient.

The SF-36 v2 Health Survey [2] includes 36 questions to measure functional health and well-being from the patient's point of view. The SF-36v2® provides scores for each of the eight health domains. The survey uses norm-based scoring ranging from 0 (very low QoL) to 100 (very high QoL). The questionnaire will be self-administered by the patient.

The Kurtzke Expanded Disability Status Scale (EDSS) [3] provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to a loss of ambulatory ability. The main categories range from (0) = normal neurologic exam; (5) = ambulatory without an aid and without resting for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS.

The Paced Auditory Serial Addition Test (PASAT) [4] is a measure of the cognitive function that specifically assesses auditory information processing speed and flexibility, as well as the ability to calculate. The test score is the total number of correct sums given (out of 60 possible) in each summation task. The resulting tables present the percentage of correct answers (0 is the worst and 100 is the best score).

The EDSS score assessed by the patient is measured using an instrument designed by Goodin [5]. A subset of questions of this instrument is used in the CRF (EDSSpts). To compare both outcomes (EDSS and EDSSpts), Section 1 of the EDSSpts questionnaire will be used and the following relationships will be applied:

- Answer 1 is equivalent to EDSS score 0.0;
- Answer 2 is equivalent to EDSS score 4.0;

- Answer 3 is equivalent to EDSS score 4.5;
- Answer 4 is equivalent to EDSS score 5.0;
- Answer 5 is equivalent to EDSS score 5.5;
- Answer 6 is equivalent to EDSS score 6.0;
- Answer 7 is equivalent to EDSS score 6.5;
- Answer 8 is equivalent to EDSS score 7.0;
- Answer 9 is equivalent to EDSS score 7.5; and
- Answer 10 is equivalent to EDSS score 8.0.

The number of relapses since the previous visit will be obtained every 6 months.

Subjects will answer the question "How much does the application of Avonex® injection bother you?" every year, i.e. at the baseline and at visits after 12, 24 and 36 months from signing the ICF. It is assessed using the VAS SelfAdmin on the scale from 0 (no problem at all) to 100 (the worst problem).

A comparison between the number of employed patients at the baseline and at the end of the study will be made in pairs. Frequencies of employed or economically active patients, full time or part time employed subjects and subjects with manual or intellectual work will be compared at the baseline and at the end of the study.

The physician shall record whether the patient had the diagnosis of CIS or CDMS at the baseline, with the date of the respective diagnosis. During the study, physicians shall record newly diagnosed CDMS since the last study visit every 6 months.

Switches in medication will be recorded at every study visit. The medication (Betaferon, Rebif, Copaxone, other product) and reasons for switching the treatment (problems with application, patient request, pregnancy, low efficacy) will be recorded.

1.3.2.2 *Safety assessment*

All serious adverse events (SAEs) and related adverse events (AEs) will be documented and collected. The investigators will be responsible for forwarding all SAEs and AEs to the Pharmacovigilance vendor who is responsible for safety reporting. Safety assessment will provide a summary of SAE and AE obtained from the Pharmacovigilance vendor.

Occurrence of relapses in the course of the study as the number of attacks since the previous visit and the reason for switching the treatment will be assessed as secondary objectives.

Date of the last MS attack before the baseline will be assessed as a demographic and baseline characteristic.

1.3.2.3 *Other assessments*

Demographic and baseline characteristics:

- Gender distribution
- Age of enrolled subjects
- Duration of CIS/CDMS diagnosis at the baseline (in months)
- Time from last attack to subject's enrolment (in months)

No medical and surgical history, previous and concomitant medication or pharmacokinetics will be recorded in the study.

1.3.2.4 *Withdrawal/discontinuation*

If a patient has been withdrawn from the study, one or more reasons for the withdrawal have to be selected (e.g. ICF withdrawal, Death of patient, Lost to follow-up).

1.3.3 Schedule of assessments

Study assessments done during the whole trial are clearly arranged in the Study Flowchart below **(Table 88)**:

Table 88: Study flowchart

Study Parameters		Prestudy Phase	Study Phase (Months)							
			0/Baseline	6	12	18	24	30	36	EOS
Informed Consent		x								
Demography			x							
patient's self-evaluation	VAS QoL		x		x		x		x	
	VAS SelfAdmin		x		x		x		x	
	EDSSpts		x	x	x	x	x	x	x	
	SF-36		x		x		x		x	
physician's evaluation of patient	VAS QoL		x		x		x		x	
	EDSS		x	x	x	x	x	x	x	
	PASAT		x		x		x		x	
Information on employment			x							x
Development of CDMS			During the course of the study							
Switches in medication			During the course of the study							
Occurrence of clinical relapses			During the course of the study							

1.3.4 Planned sample size

Patients fulfilling the eligibility criteria below and treated in specialized neurology sites in the Slovak Republic will be enrolled in the study. The estimated number of subjects is 200. The study enrolment phase will last 3 years or until the target number of patients is reached.

Patients fulfilling the requirements and treated in specialized neurology sites in the Czech Republic will be enrolled in the study. The required number of subjects is 400. The study enrolment phase will last 3 years or until the target number of patients is reached.

2 SUBJECT POPULATION (ANALYSIS SETS)

2.1 Effectiveness

2.1.1 Intention-To-Treat population

The ITT population refers to all treated subjects.

Any subject who has previously been recruited will only be included in the ITT population for the first occasion in the study. Data from subsequent occasions in the study will be excluded from the analysis and listed separately. Details of the subjects' status and outcomes will be included in the report.

The ITT population will be analysed using the subjects as enrolled.

2.1.2 Per Protocol population

The PP population is defined as all subjects in the ITT population for whom no major protocol violations / deviations have occurred. No PP population is defined for this study.

2.2 Safety

The safety population comprises patients who received at least one dose of study medication.

2.3 Pharmacokinetics

No pharmacokinetics population is defined for this study.

2.4 Primary population

The primary effectiveness analysis will be based on the ITT population. No supportive analysis will be done.

Safety assessment will be based on the Safety population.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [6] and will be based on the pooled data from the individual study sites, unless mentioned otherwise.

Statistical analysis of effectiveness and safety will be performed by CRO, NEOX s.r.o.

3.1.1 Primary effectiveness endpoints

Primary effectiveness endpoints include:

a) VAS QoL assessed by the patient every 12 months;

b) Particular domains (physical and social functioning, bodily pain, role limitation due to physical health and emotional problems, mental health, vitality, general health, reported health transition) from the SF-36 questionnaire as assessed by the patient every 12 months.

3.1.2 Secondary effectiveness endpoints

Secondary effectiveness endpoints are:

a) VAS QoL assessed by the physician every 12 months;

b) EDSS assessed by the physician every 6 months;

c) PASAT assessed by the physician every 12 months;

d) Correlation between EDSS assessed by the physician and EDSSpts assessed by the patient every 6 months;

e) EDSSpts assessed by the patient every 6 months;

f) Number of relapses since the previous visit every 6 months;

g) VAS SelfAdmin assessed by the patient every 12 months;

h) Number of employed subjects at the baseline and at the end of the study;

i) Number of full-time or part-time employed subjects at the baseline and at the end of the study;

j) Number of subjects with manual or intellectual employment at the baseline and at the end of the study;

k) Number of subjects with CIS or CDMS diagnosis during the study;

l) Number of switches in medication during the study, frequency of particular products and reason for switching the treatment.

3.1.3 Safety endpoints

Safety endpoints are AEs and SAEs occurring during the study.

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

The statistical analysis of primary and secondary endpoints is only descriptive and therefore no formal statistical significance testing will be performed except correlation. Correlation will be two-sided at the 5% level of significance.

3.2 Analysis methods

3.2.1 Effectiveness

3.2.1.1 *Primary effectiveness analysis*

Primary endpoints listed in Section 3.1.1 will be analysed only descriptively. For this purpose, the mean, standard deviation (SD), median, minimum, and maximum will be calculated. Categorical variables will be summarized using frequency counts (n) and percentages.

A summary table of questionnaires collected at each visit will be provided for both primary variables.

Change from the baseline in months 12, 24 and 36 will be calculated for the endpoint VAS QoL assessed by the patient. The number of available cases will be provided at every time-point. Available case analysis and complete case analysis will be done for this endpoint.

Every SF-36 domain will be analysed separately and the means of the domains will be compared using a line graph. Available case analysis will be done for these domains.

3.2.1.2 *Secondary effectiveness analysis*

Secondary endpoints stated in Section 3.1.2 Secondary effectiveness endpoints will be analysed only descriptively, except Correlation between EDSS assessed by the physician and EDSSpts assessed by the patient every 6 months. For descriptive purposes, the mean, standard deviation (SD), median, minimum, and maximum will be calculated. Categorical variables will be summarized using frequency counts (n) and percentages (%).

A summary table of questionnaires collected at each visit will be provided for every secondary variable.

The distribution of each score will be analysed for the Correlation between EDSS assessed by the physician and EDSSpts assessed by the patient every 6 months using Kolmogorov-Smirnov and Shapiro-Wilk tests and it the statistical value, degrees of freedom (df) and p-value will be computed. Furthermore, the Pearson correlation coefficient (parametric approach) or Spearman correlation coefficient (non-parametric approach) will be used for the analysis.

Every question will be analysed separately in EDSSpts assessed by the patient every 6 months.

The Number of subjects with CIS or CDMS diagnosis during the study will be summarized using frequency counts (n) and percentages. Additionally, cumulative frequency of new CDMS diagnoses during the study will be calculated.

The form of Avonex, a new treatment product and reasons for switching the treatment will be analysed for the item Number of switches in medication during the study, frequency of particular products and reason for switching the treatment. If Avonex dosage form is replaced, frequency counts (n) and percentages will be reported.

3.2.2 Safety

All safety data will be included in the data listings, and summary tables will be based on the safety population.

3.2.2.1 *Adverse events*

Adverse events are not coded against any dictionary. Classification of AEs/SAEs to appropriate categories will be done by the pharmacovigilance officer.

Listings will be presented and sorted by subject ID, gender, age, starting time of AEs, classification of PV officer and verbatim text for all AEs recorded during the study.

Listings of SAEs, AEs leading to withdrawal and listings of deaths will also be presented.

An overall summary table of all adverse events will be presented.

3.2.3 Missing data and outliers

3.2.3.1 *Missing data*

No imputation of missing data will be performed. For all time points, subjects without any documentation of other events will be censored at the date of last contact.

The available case analysis (pairwise deletion) shall seek to minimize the loss that occurs in listwise deletion. Thus, pairwise deletion maximizes all data available by an analysis. This analysis is used to describe every endpoint.

The complete case analysis (listwise deletion) will remove all data for a case that has one or more missing values. This technique is commonly used if the researcher is conducting a treatment study and wants to compare a completed analysis (listwise deletion) vs an intent-to-treat analysis (includes cases with missing data imputed or taken into account via an algorithmic

method) in a treatment design. This analysis is used to described primary the endpoint a) VAS QoL assessed by the patient every 12 months and the secondary endpoints VAS QoL assessed by the physician every 12 months, EDSS assessed by the physician every 6 months, PASAT assessed by the physician every 12 months, and VAS SelfAdmin assessed by the patient every 12 months.

3.2.3.2 *Missing or incomplete dates*

In this study, complete dates are not necessary in all date variables. Partial dates are allowed in Date of CIS/CDMS diagnosis, Last date of MS attack, and the beginning and end of the treatment.

Any missing day will be replaced with day 1 and any missing month will be replaced with January.

3.2.3.3 *Outliers*

No outliers will be analysed.

3.2.4 Subject disposition

A summary table and a flow chart will be presented for each subject population presenting the number of subjects at each assessment and identifying the number of subjects who withdraw over time.

A summary table will present the extent of subject exposure in the study. The exposure length is defined as time from the date of consent to the last application during the study.

3.2.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdraw from the study and the reasons for withdrawal will be presented.

3.2.6 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by subject.

Summary statistics will be provided for demographic and baseline characteristics (sex, age, duration of CIS/CDMS diagnosis at the baseline (in months), time from the last attack to subject's enrolment (in months)) for the ITT population.

No statistical comparison of the treatment groups will be performed.

3.2.7 Medical and surgical history

No medical and surgical history will be obtained.

3.2.8 Subject compliance

No compliance or drug administration will be recorded during the study.

3.2.9 Prior and concomitant therapies

No prior and concomitant therapies will be obtained.

3.2.10 Derived data

The age is defined as the time from the date of birth to the date of consent in years.

The duration of CIS/CDMS diagnosis is defined as the time from the date of CIS or CDMS diagnosis at the baseline to the date of consent in months.

The diagnosis at the end of the study is CDMS, if the diagnosis at the baseline is CDMS or if at some study visit CDMS is newly diagnosed. Other subjects with CIS at the baseline will have CIS at end of study.

The time from the last attack to subject's enrolment is defined as time from the date of the last attack at the baseline to the date of consent in months.

Change from the baseline (e.g. VAS QoL) is defined as the difference between VAS QoL value at a particular visit and the baseline value.

The PASAT rate (percentage) is defined as PASAT total score / 60 *100%.

The time to CDMS diagnosis during the study is defined as the time from the date of consent to the date of newly diagnosed CDMS in months.

The development of CDMS is defined in 8 categories:

- If CDMS is diagnosed at the baseline, the value is "before start of study";
- If time to CDMS diagnosis is until 6 months (including 6), the value is "until 6 months";
- If time to CDMS diagnosis is until 12 months (including 12), the value is "between 6 and 12 months";
- If time to CDMS diagnosis is until 18 months (including 18), the value is "between 12 and 18 months";
- If time to CDMS diagnosis is until 24 months (including 24), the value is "between 18 and 24 months";
- If time to CDMS diagnosis is until 30 months (including 30), the value is "between 24 and 30 months";

- If time to CDMS diagnosis is until 36 months (including 36), the value is "between 30 and 36 months";
- If time to CDMS diagnosis is after 36 months, the value is "more than 36 months".

3.2.11 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation time points may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected, then the visit nearest to the scheduled date of a particular visit should be used.

The time interval of +/- 60 days will be used for all study phases. Study visits with the time interval longer or shorter than 60 days from the scheduled date of a particular visit should be marked as missing.

3.2.12 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and deprived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined based on general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented: n, arithmetic mean, standard deviation, median and the range (minimum and maximum).

The number of decimal places used to report mean values will be one decimal place greater than that used for the raw/derived data summarised by the means. The number of decimal places used to report standard deviations will be two decimal places greater than that used for the raw data. Median, minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place and 0% will be presented. Percentages will be calculated using the denominator of all subjects in a specified population. For clarity, the denominator will be specified in the footnote to the tables if necessary.

P-values will be reported to three decimal places (e.g. $p = 0.034$), rounded. P-values lower than 0.001 will be presented as "0.001".

Generic or trade names of medications must be justified and standardised.

All other text fields must be left justified, and those numeric or numeric with some text specification (e.g. not done, UNK, unknown, < 4.5 ...) must be decimal justified. Dates will be presented in the format [DD-MMM-YYYY] and times in the 24-hour format [hh:mm].

3.2.13 Pooling of centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.14 Interim analysis

The first interim analysis will be performed when 100 enrolled subjects have completed 12 months on the primary effectiveness parameter. Other interim analyses will be carried out according to the Sponsor's requirements.

3.2.15 Role of independent data monitoring committee

No independent data monitoring committee will be used in this study.

3.2.16 Covariates and analysis of subgroups

No covariates and analyses of subgroup are planned.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

Statistical analysis will be performed using HP ProBook 430 G2.

4.2 Software

Tables, figures and listings will be produced; computation and statistical analysis will be done using the operating system Windows 7, IBM SPSS v. 23. S tables, listings and figures will be created in Microsoft Office 2016. All collected data will be available in SAS format (sas7bdat), IBM SPSS syntax (SPS) and data file (DAT - TSV) or IBM SPSS (SAV). All results will be available in IBM SPSS format (SPV), Microsoft Excel format (XLSX) and Microsoft Word format (DOCX).

4.3 Validation programs

Copies of internal QC forms produced for the validation process and CRO's sign-off forms can be provided to the Sponsor to support the validation.

5 CHANGES FROM PROTOCOL

Original Protocol LD140409 – AMETYST, version 1.0_CZ dated 14th August 2009 was amended and sample size justification was added for the Czech Republic.

No other changes were performed.

5.1 Sample size justification

Two-sided paired t-test will be used to evaluate the size of change in the quality of life. Assuming that the effect size would be similar to that observed in [7, 8, 9], a sample size of 400 subjects is proposed to be included. The sample size is sufficient to detect at the significance level of 0.05 a mean difference of 0.02 from the baseline in the utility value assessed by the VAS, SF-36 and EQ-5D questionnaire, based on the standard deviation of 0.13 and the power of 80%, with the estimated drop-out rate of 20%.

6 REFERENCES

[1] Shmueli A. The visual analog rating scale of health-related quality of life: an examination of end digit preferences. Health Qual Life Outcomes 2005; 3:71. Published online 2005 Nov 14. doi: 10.1186/1477-7525-3-71.

[2] Ware JE. User's Manual for the SF-36v2 Health Survey. Lincoln, RI: QualityMetric Incorporated, 2007. ISBN: 1-891-810-16-2.

[3] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983 Nov; 33(11):1444-52.

[4] Fisher JS, Jak AJ, Kniker JE, Rudick RA, Cutter G. Multiple sclerosis functional composite: Administration and scoring manual. National Multiple Sclerosis Society, 2001.

[5] Goodin DS. A questionnaire to assess neurological impairment in multiple sclerosis. Mult Scler October 1998; 4:5444-451.

[6] International Conference on Harmonisation. E9: Statistical principles for clinical trials. 1998. Available from:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

[7] Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH and Rodriguez M. Quality of Life Is Favorable for Most Patients with Multiple Sclerosis: a Population-Based Cohort Study. Arch Neurol 2004; 61:679-686.

[8] Putzki N, Fisher J, Gottwald K, Reifschneider G, Ries S, Siever A, Hoffmann F, Kafferlein W, Kausch U, Liedtke M, Kirchmeier J, Gmund S, Richter A, Schicklmaier P, Niemczyk G, Wernsdorfer C and Hartung HP. Quality of Life in 1000 Patients with Early Relapsing-Remitting Multiple Sclerosis. Eur J Neurol 2009; 16:713-720.

[9] Twork S, Wiesmeth S, Spindler M, Wirtz M, Schipper S, Pohlau D, Klewer J and Kugler J. Disability Status and Quality of Life in Multiple Sclerosis: Non-Linearity of the Expanded Disability Status Scale (EDSS). Health Qual Life Outcomes 2010; 8:55.

7 DATA PRESENTATION

Data listings are presented for all screened subjects with available CRFs.

The title of each generated table, listing and figure should appear bookmarked within Word (one single bookmark per table/listing/figure) to allow document publishing by the Sponsor.

7.1 Listings index

7.1.1 Discontinued subjects

Listing 16.2.1.1: Subject disposition – All subjects

Listing 16.2.1.2: Subject disposition – Study withdrawals

Listing 16.2.1.3: Inclusion criteria

Listing 16.2.1.4: Exclusion criteria

Listing 16.2.1.5: Screening failures

Listing 16.2.1.6: Assessment times

7.1.2 Protocol deviations

Listing 16.2.2.1: Subject eligibility for the study

Listing 16.2.2.2: Protocol deviations and reasons for exclusion from the study populations

7.1.3 Subjects

Listing 16.2.3: Subjects excluded from the effectiveness analysis

7.1.4 Demographic data

Listing 16.2.4.1: Demographics

7.1.5 Adverse event listings

Listing 16.2.7.1: All adverse events

Listing 16.2.7.2: Serious adverse events

Listing 16.2.7.4: Deaths

7.2 Listing template

Listing 3: Listing template

		ID	Date of consent	Date of withdrawal	Reason for withdrawal
END OF STUDY	Withdrawn	01-001	01-Jan-2000	01-Jan-2000	Other
		01-002	01-Jan-2000	01-Jan-2000	Lost to follow-up
		99-999	01-Jan-2000	01-Jan-2000	Death
	Total	99	99	99	99

7.3 Table templates

Table 89: Absolute and relative frequency

	Yes		No	
	N	%	N	%
0 MONTHS	999	99.9%	1	0.1%
12 MONTHS	999	99.9%	1	0.1%
24 MONTHS	999	99.9%	1	0.1%
36 MONTHS	999	99.9%	1	0.1%

Table 90: Summary statistics

	N	Mean	Standard Deviation	Median	Minimum	Maximum
0 MONTHS	999	99.9	9.99	99	99	99
12 MONTHS	999	99.9	9.99	99	99	99
24 MONTHS	999	99.9	9.99	99	99	99
36 MONTHS	999	99.9	9.99	99	99	99

7.4 Figure templates

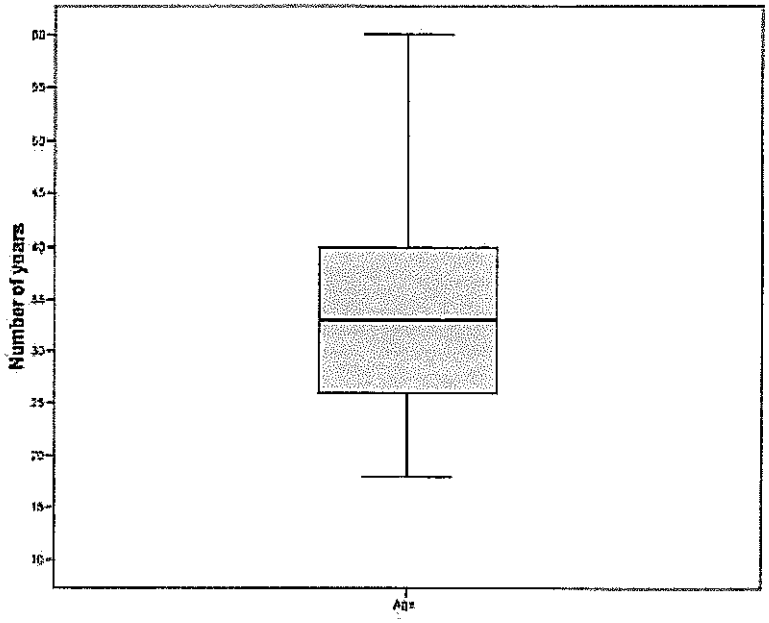


Figure 73: Boxplot

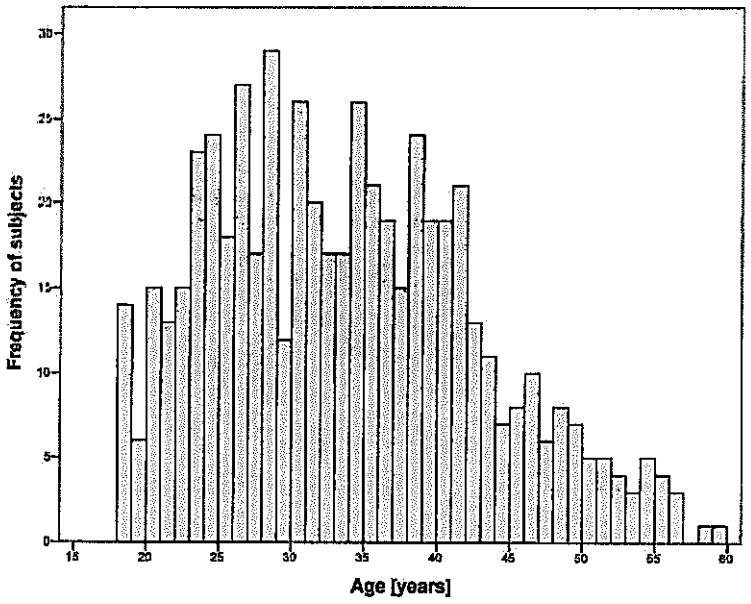


Figure 74: Histogram

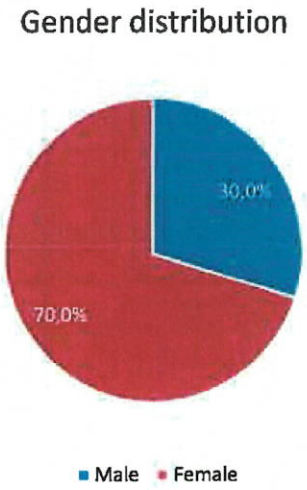


Figure 75: Pie chart

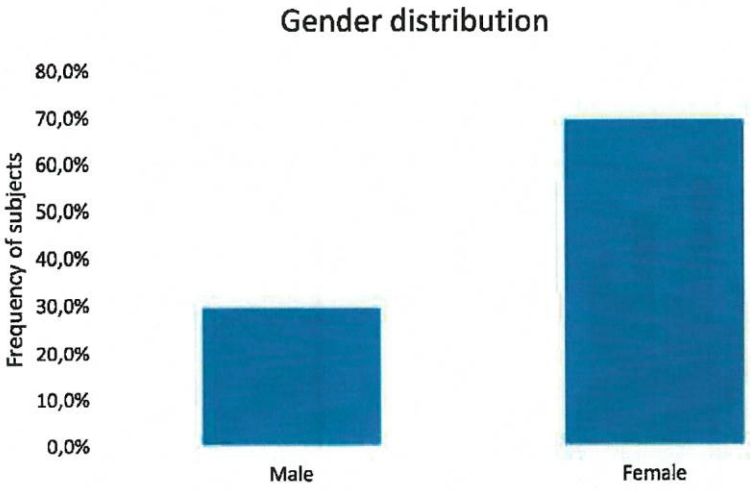


Figure 76: Bar chart

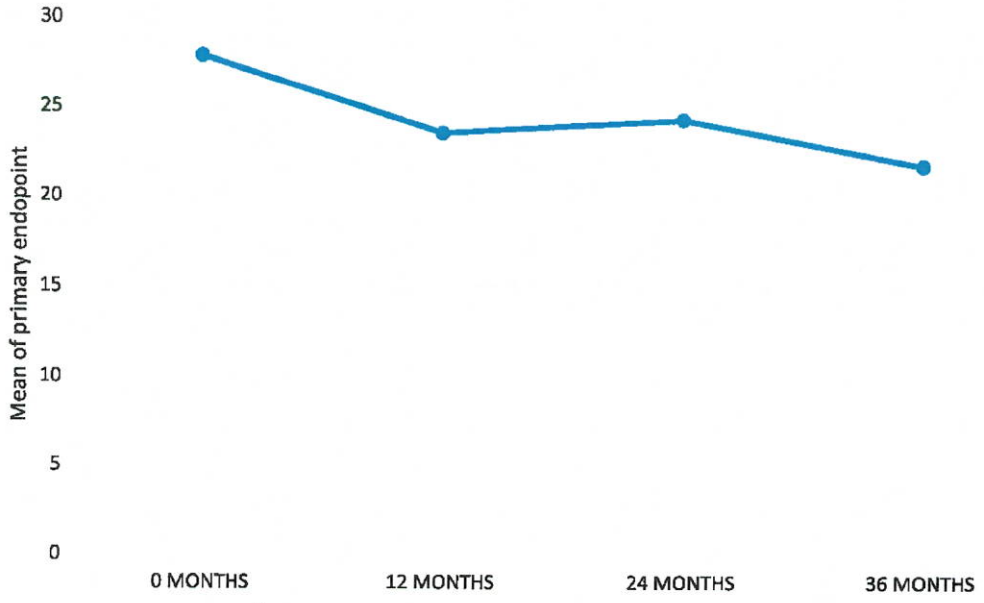


Figure 77: Line graph

APPENDIX D. INVESTIGATOR SIGNATURE PAGE

Investigator Signature Page

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of AMETYST Study (LD140409).

_____ 10/FEB/2017

Coordinating Investigator's Signature Date

Coordinating Investigator's Name: Prof. MUDr. Peter Turčáni, PhD.

Coordinating Investigator's Affiliation: I. Neurologická klinika LF UK a UNB

Signature: Michael Smith (Mar 5, 2017)

Email: mike.smith1@biogen.com

Title: Senior Manager Medical Research

Company: Biogen

Signature: Matthias Meergans (Mar 6, 2017)

Email: matthias.meergans@biogen.com

Title: Medical Director

Company: Biogen

Signature: Emily McIntyre (Mar 6, 2017)

Email: emily.mcintyre@Biogen.com

Title: Associate Director, Medical Research Operat

Company: Biogen