Statistical Analysis Plan

Observational study Protocol Identification No.	EMR200136_597
Title:	A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment (MESTRE–MS)
Observational study Protocol Date/ Version	07OCT2016 / Version 2.0
Statistical Analysis Plan Author	PPD, Study Statistician
Statistical Analysis Plan Date and Version	12MAY2017 / Version 1.0
Statistical Analysis Plan Reviewers	PPD 1. PPD, Sr. Statistical Analyst 2. PPD, Principal Biostatistician 3. PPD, Medical Writer. **Merck** 1. PPD, Principal Biostatistician 2. PPD, Medical Manager

1. Signature Page

Statistical Analysis Plan: EMR200136_597

A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment.

PPD

Signature

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Date of Signature

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2. Table of Contents

3. List of Abbreviations and Definition of Terms

AE	Adverse Event
ARR	Annualized Relapse Rate
CI	Confidence Interval
CRF	Case Report Form
EDSS	Expanded Disability Status Scale
HCP	Health Care Professional
ICF	Informed Consent Form
IFNβ	Interferon beta
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
MusiQoL	Multiple Sclerosis International Quality of Life Questionnaire
PT	Preferred Term
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TSQM v II	Treatment Satisfaction Questionnaire for Medication Version II

4. Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
0.1	21OCT2016	PPD	Baseline Version
0.2	03NOV2016	PPD	Based on client comments
0.2	24FEB2017	PPD	Based on client comments
0.2	08MAR2017	PPD	Based on client comments
1.0	12MAY2017	PPD	Final Version

5. Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan (SAP) is to document technical and detailed specifications for the final analysis of data collected for protocol EMR200136_597. Results of the analyses described in this SAP will be included in the Clinical Trial Report (CTR). Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CTR but not identified in this prospective SAP will be clearly identified in the CTR.

The SAP is based upon trial protocol and is prepared in compliance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guidelines. The SAP focused on measuring satisfaction of treatment with Rebif after discontinuing initial treatment of MS using TSQM v II. Statistical analyses for other variables such as Annualized Relapse Rate, Adherence, MusiQoL Questionnaire and Safety (frequency and severity of AEs) are also added in this version of SAP.

6. Summary of Clinical Trial Features

Study Title	A Phase IV, prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of multiple sclerosis (MS) patients on Rebif® after discontinuing initial first-line treatment
Study acronym/Short title	MESTRE–MS (**ME**asuring **S**atisfaction of **T**reatment with **RE**bif after initial treatment of **MS**)
Study Protocol Date / Version	07OCT2016 / Version 2.0
Study Rationale and background	The purpose of this study is to investigate treatment satisfaction in MS patients, who have discontinued first-line MS oral or injectable MS medication, and have initiated treatment with Rebif. MS patients who are starting their first treatment for MS currently can be treated with various oral or injectable medications. When solely considering the route of administration of these medications it may appear that the oral treatments are more patient friendly and convenient than the injectable ones. In addition, certain weekly or daily first-line injection treatments may be preferred over thrice weekly injections for unknown reasons. In clinical trials, discontinuation rates due to adverse events of dimethyl fumarate (Tecfidera®) and of teriflunomide (Aubagio®) treated patients is 16% in both DEFINE and TENERE studies, respectively. Furthermore, injectable treatment discontinuation varies between 14% and 47%. It is important for patients to optimally utilize first-line MS

	treatment options before escalating therapy to more potentially dangerous second line therapies such as natalizumab, fingolimod or alemtuzumab. This Phase IV clinical study is being proposed to support decision making for health care professionals (HCPs) and patients who have decided to initiate MS treatment, and use arguments of patient friendliness and convenience for their decision. Therefore, in this study treatment satisfaction of Rebif is measured in MS patients who have discontinued their initial MS treatment, and who have decided to start Rebif as their Follow-up treatment. Currently there is no information describing the experiences with discontinuation of oral or injectable medication and the initiation of the injectable therapy Rebif. This information is crucial for HCPs and patients to be able to make a well informed decision on what to expect of their treatment. In this study, by measuring treatment satisfaction before and after Rebif treatment we aim to evaluate the difference in treatment satisfaction (as perceived by the patient), reasons to stop initial treatment, and experience after alternative treatment initiation. This study will add the additional data on the perception of treatment convenience and reasons for discontinuation of oral or injectable first-line treatment.
Study objectives	**Primary objective** • To determine the level of treatment satisfaction as measured with the Treatment Satisfaction Questionnaire

	for Medication Version II (TSQM v II), in relapsing remitting MS (RRMS) patients who have discontinued their initial oral or injectable MS treatment, and have initiated treatment with Rebif. **Secondary objectives** • To evaluate the change in annualized relapse rate (ARR) in patients changing from initial oral or injectable forms of treatment to Rebif • To assess therapy adherence to Rebif • To determine the change in quality of life with Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL) between Baseline, Month 6 and Month 12 • To document the reasons for discontinuation of initial MS treatment • To evaluate the potential correlations between the following measurements: TSQM v II, ARR, adherence, reasons for discontinuation, MusiQoL and TSQM v II subscales • To assess the difference between TSQM v II subscales between Baseline, Month 6 and Month 12.
Variables and Study Endpoints	The variables that will be evaluated in this study include demographics, MS history, prior and current medication, pertinent medical history, treatment satisfaction score determined with TSQM v II, ARR, treatment adherence, quality of life determined with MusiQoL questionnaire, reasons for discontinuation of previous therapy and adverse events. **Primary Endpoint:** • Treatment satisfaction score determined with TSQM v II

	from Baseline to Month 6 and to Month 12. **Secondary Endpoints:** • ARR (after 12 months of Rebif treatment) • Adherence (after 6 and 12 months of Rebif treatment) • MusiQoL (compare Baseline with after 6 and 12 months of Rebif treatment) • Reason/s for discontinuation of initial MS treatment (oral or injectable). **Additional Secondary Endpoints:** • Correlation between TSQM v II and ARR; TSQM v II and adherence; TSQM v II and reason for discontinuation • Correlation between MusiQoL and ARR; MusiQoL and adherence; MusiQoL and reason for discontinuation • Correlation between TSQM v II subscales and adherence • Correlation between TSQM v II subscales and reasons for discontinuation • Difference between TSQM v II subscales at Baseline and after 6 and 12 months of Rebif treatment • ARR before study entry compared to ARR at study end • Association between ARR and treatment adherence.
Study Design	This is a prospective, multicenter, open label, uncontrolled, non-interventional, single arm study to measure treatment satisfaction of RRMS patients on Rebif after discontinuing initial first-line treatment. This study consists of three visits: • Visit 1: Baseline

	• Visit 2: Month 6 • Visit 3: Month 12 This study will enroll RRMS patients who have discontinued their oral or injectable first–line MS medication and have decided to initiate subcutaneous Interferon beta-1a (IFN β-1a) (Rebif) treatment before Baseline measurements. MusiQoL and TSQM v II will be measured at Baseline, Month 6 and Month 12. Relapses and adherence will be assessed at Month 6 and Month 12. Adherence to Rebif therapy will be collected electronically using RebiSmart 2.0. Since this is a non-interventional study, there will not be any study required clinical interventions and laboratory assessments.
Study Population and Eligibility Criteria	RRMS patients who have discontinued their initial MS treatment and for whom MS treatment is required according to the decision of the HCP and patient. **Inclusion Criteria:** The patient can be included when the patient • Is male or female, 18 to 65 years of age (both inclusive), at the time of informed consent • Is diagnosed with RRMS according to McDonald criteria 2010 • Has discontinued treatment with dimethyl fumarate (Tecfidera), teriflunomide (Aubagio), glatiramer acetate (Copaxone®), intramuscular IFNβ-1a (Avonex®), pegylated interferon (Plegridy®), subcutaneous IFNβ-1b (Betaferon®) or fingolimod (Gilenya®) within 6 months prior to Visit 1

	• Is currently treated with Rebif using RebiSmart 2.0, for a maximum of 6 months prior to Visit 1 • Has a score on the Expanded Disability Status Scale (EDSS) between 0 to 5.0 inclusive • Is willing and able to give informed consent. **Exclusion Criteria** The patient cannot be included when the patient • Has known planned surgical procedures at the time of the informed consent that will prevent adherence to treatment with Rebif through RebiSmart 2.0 • Is diagnosed with primary progressive, secondary progressive, or progressive relapsing MS • Is pregnant or lactating, or planning to become pregnant • In the opinion of the Investigator has significant renal or hepatic impairment or other significant disease (e.g., cognitive or visual impairment) that would compromise adherence and completion of the study • Reports any reason that he/she cannot complete the 1 year study • Has a history of hypersensitivity to natural or recombinant interferon, or any other component of the formulation • Is contraindicated for the treatment with subcutaneous IFNβ-1a therapy as per summary of product characteristics or currently approved specific country product information • Has any other factor that in the opinion of the Investigator would make the subject unsuitable for participation in this study

	• Have significant psychiatric symptoms that, in the opinion of the Investigator, would impact patient ability to comply with treatment recommendations.
Study Size	133 patients diagnosed with RRMS will be enrolled (63 in the Netherlands, 40 in Switzerland and 30 in Belgium).
Sample size justification	A sample size of 106 subjects will be required to have 85% power to detect at least an 8 point difference in mean TSQM scores between Baseline and Month 6 or Month 12 measurements, with the standard deviation of 27.5 and a two sided significance level of 5%. Assuming a 20% drop out rate, approximately 133 patients will be enrolled into the study in the Netherlands, Switzerland and Belgium.
Data Analysis	Statistical analysis will be mainly descriptive. Descriptive statistics (n, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], minimum, maximum) will be provided for continuous variables. Frequencies and percentages will be presented for categorical and ordinal variables. Where appropriate, 95% confidence intervals (CIs) will be presented. All analyses will be performed on subjects who received at least one dose of Rebif following enrolment in the study. **Primary Endpoint analysis:** A paired two-sided t-test of the global satisfaction score (TSQM score) will be used to test the null hypothesis that there is no difference in the global satisfaction score (TSQM score) between 6, 12 months and Baseline. The corresponding 95% two-sided CI will be presented.

	Secondary Endpoint analysis: ARR and its associated 95% CI before study entry and after 12 months of Rebif treatment will be summarized overall and by previous MS therapy. Reasons for discontinuation of previous therapy and adherence after 6 and 12 months of Rebif treatment will be summarized descriptively and overall. Changes in MusiQoL after 6 and 12 months of Rebif treatment versus Baseline will be analysed using same methodology as for Primary Endpoint. Additional Secondary Endpoints as correlation analysis between TSQM and MusiQoL versus ARR, adherence and reason for discontinuation will also be analyzed.

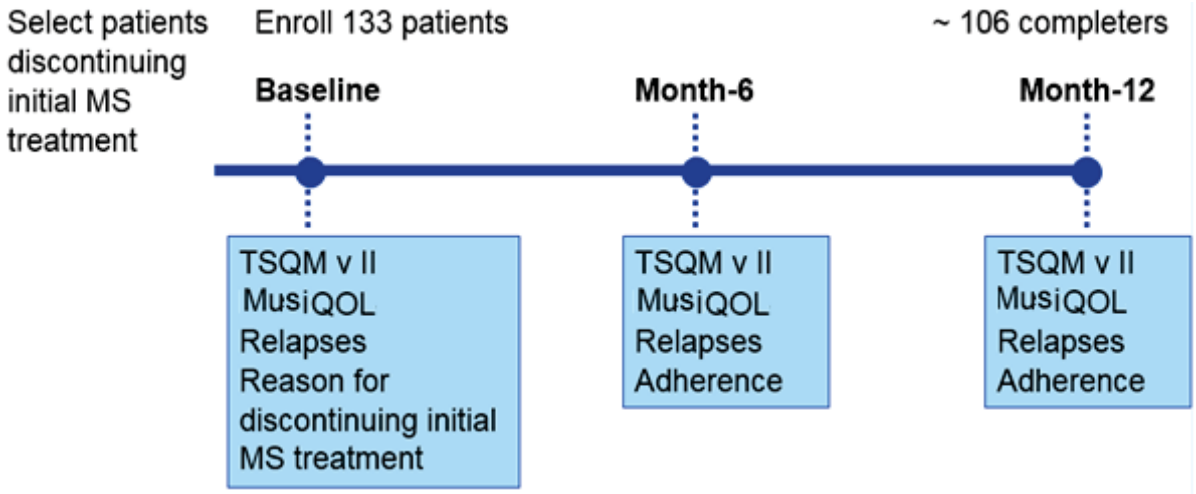
Exposure

Each patient will be observed for 12 months, during this period patients will receive Rebif 22 or 44 mcg three times per week through an electronic autoinjector device (Rebismart 2.0). The details of assessments are available in the flow chart given below.

Schedule of Assessments

Activity	Visit 1 Baseline	Visit 2 Month 6	Visit 3 Month 12 (End of Study Visit)
Patient Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Demographic information	X		
Medical History / Concomitant diseases / Prior MS medications	X		
Multiple Sclerosis History (including relapses within 2 years before study entry)	X		
MS medication related adverse events and associated concomitant medications	X		
Vital Signs	X	X	X
Physical Examination	X	X	X
Neurological Examination	X	X	X
Relapse Assessment		X	X
TSQM Version II evaluation	X	X	X
MusiQoL evaluation	X	X	X
Document reasons for discontinuation of previous MS therapy	X		
Therapy with Rebif	X	X	X
Evaluation of Adherence to Therapy		X	X
Safety Recording and Reporting		X	X

Study Overview



TSQM v II = Treatment Satisfaction Questionnaire for Medication Version II
MusiQoL = Multiple Sclerosis International Quality of Life Questionnaire
MS = Multiple Sclerosis

7. Sample Size

A sample size of 106 subjects will be required to have 85% power to detect at least an 8 point difference in mean TSQM scores between Baseline and Month 6 or Month 12 measurements, with the standard deviation (SD) of 27.5 and a two sided significance level of 5%. Assuming a 20% drop out rate, approximately 133 patients will be enrolled into the study in the Netherlands, Switzerland and Belgium.

8. Overview of Planned Analyses

This SAP describes final analysis of the study. No interim analyses are planned for this study.

9. Changes to the Planned Analyses in the Observational Study Protocol

The statistical methods as described in the protocol were adopted. There are no changes to the planned analyses.

10. Analysis Set

Safety Analysis Set:

Safety analysis set is defined as all the subjects who provided informed consent and who received at least one dose of study treatment.

All analyses will be performed on safety analysis set.

11. General Specifications for Statistical Analyses

Statistical analysis will be performed using Statistical Analysis System (SAS) version 9.1.3 or higher.

Descriptive statistics such as

- Number of subjects (n), number of subjects with missing values (Missing),
- Mean, Standard Deviation (SD),
- Median, first quartile (Q1), third quartile (Q3),
- Minimum and Maximum

will be provided for all continuous variables.

Mean, median, Q1 and Q3 will have more than one decimal place than the raw data and SD will have 2 decimal places more than the raw data. The decimal place for minimum and maximum values will be same as the raw data.

The frequency (n) and percentage will be calculated for all categorical variables including missing observations and the percentages will be rounded off to one decimal place.

Shapiro-Wilk test / Kolmogorov-Smirnov test will be used for test for normality of the data. All statistical tests are of explorative nature and corresponding p-values will be presented purely descriptive. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as '< 0.0001'.

95% Confidence Interval (CI) will be provided wherever applicable.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 terminology for System Organ Class (SOC) and Preferred Term (PT).

Handling of missing data

Missing information will be captured for quantitative as well as qualitative variables by the category "Missing" in the summary statistics. If there are no missing values, this will be indicated by '0'. Unless otherwise specified missing data will not be replaced.

12. Trial Subjects

12.1 Disposition of Subjects and Discontinuations

A table with

- Number of subjects screened
- Number of screen failure subjects
- Number of subjects enrolled in the study
- Number of subjects in Safety Analysis Set
- Number of Safety Analysis Set subjects who completed the study.
- Number of Safety Analysis Set subjects who discontinued the study together with primary reason for discontinuation (Lost to follow-up, Adverse event/ Serious adverse event, Discontinuation of Rebif is desired or considered necessary by the Investigator and/or the subject, Occurrence of an exclusion criterion, Subject withdraws consent (Reasons for Withdraws consent), Discontinuation of Rebif for any other reason (Reason for discontinuation)).

will be presented. Percentages will be calculated.

12.2 Outliers

Listing will be provided for subjects with outliers (if data available). Extreme data that are not explainable from clinical point of view are considered as outliers. Subjects with such outliers will be identified before the database lock. These outlier data will not be included in the analysis.

13. Demographics and Other Baseline Characteristics

13.1 Demographics

The quantitative variable

- Age (Years)

will be summarized by descriptive statistics from Safety Analysis Set.

Age (Years) = (Date of Informed Consent- Date of birth + 1) / 365.25

The qualitative variable

- Gender (Male/ Female)

will be summarized as number and percentage from Safety Analysis Set.

13.2 Medical History

Medical History Unrelated to Study Condition:
Listing will be provided for the Medical history unrelated to study condition.

Multiple Sclerosis History:

The quantitative variables

- Time since MS onset (first symptom) (years)
- Time since Second attack (first relapse) (years)
- Number of MS relapses within 24 months prior to written informed consent

will be summarized using descriptive statistics from Safety Analysis Set.

Time since MS onset (first symptom) (years) = (Date of Informed Consent– MS onset (first symptom) date + 1)/365.25.

Time since second attack (first relapse) (years) = (Date of Informed Consent– Second attack (first relapse) date + 1)/365.25.

The qualitative variables

- Degree of recovery from first attack (Complete / Partial / No or minimal recovery)

will be summarized as number and percentage from Safety Analysis Set.

Prior MS Therapy:

The quantitative variable

- Duration of prior MS Therapy (years)

will be summarized using descriptive statistics from Safety Analysis Set.

Duration of prior MS Therapy (years) = (End date of prior MS Therapy – Start date of prior MS Therapy + 1)/365.25.

The qualitative variables

- Received prior MS Therapy (Yes / No)
- Prior MS Therapy details (XXXX/ XXXXX)
- Reason(s) for discontinuation of prior MS Therapy (Adverse event / Lack of efficacy / Other)

will be summarized as number and percentage from Safety Analysis Set.

Prior MS Medication Related AEs and Associated Concomitant medications:

Listing will be provided for the Prior MS Medication Related AEs and Associated Concomitant medications.

13.3 Other baseline characteristics

Expanded Disability Status Scale (EDSS):

The quantitative variable

- EDSS score

will be summarized using descriptive statistics from Safety Analysis Set.

The qualitative variable

- EDSS score (0.0 / 1.0 - 1.5 / 2.0 - 2.5 / 3.0 - 3.5 / 4.0 - 4.5 / ≥5.0)

will be summarized as number and percentage from Safety Analysis Set.

14. Prior or Concomitant Medications/Procedures

Listing will be provided for prior and concomitant medications from Safety Analysis Set. No coding of medication will be done.

15. Treatment Compliance and Exposure

Adherence is one of the secondary endpoint and will be described in section 16.2.

Exposure:

The quantitative variables

- Duration of Rebif Therapy (years)
- Rebif start dose (mcg)

will be summarized using descriptive statistics for Safety Analysis Set.

Duration of Rebif Therapy (years) = (Date of Last Rebif dose administered– Rebif Therapy Start Date + 1)/365.25.
will be summarized as number and percentage from Safety Analysis Set.

Listing will be provided for Rebif therapy record.

16. Endpoint Evaluation

16.1 Primary Endpoint Analyses

TSQM v II was designed as a general measure of treatment satisfaction with medication, suitable for use across a wide variety of medication types and illness conditions. Findings in the development of this questionnaire indicated that the three dimensions on which patients evaluate their medication are: effectiveness, adverse effects and convenience. There was an additional overall satisfaction rating, representing individual balanced judgment across these three specific treatment attributes, potentially most predictive of patient satisfaction and adherence.

TSQM v II dimensions scores will be derived according to TSQM v II Scale Scoring Algorithm mentioned below.

- Global Satisfaction

will be summarized for baseline, Month 6, and Month 12, and change from baseline at Months 6 and 12 using descriptive statistics from Safety Analysis set.

A paired two-sided t-test will be used to test the null hypothesis that there is no difference in the TSQM v II global satisfaction scores between Baseline and Month 6, Baseline and Month 12.

The corresponding 95% two-sided CI will be presented.

Scale Scoring Algorithm: TSQM Scale scores range from 0 to 100 and no computed score should be lower or higher than these limits.

- **Effectiveness**: ([(Item 1 + Item 2) − 2] divided by (12) × 100
- **Side Effects**: ([Sum of Item 4 to Item 6) − 3] divided by 12) × 100
- If one item is missing: ([(Sum of the two completed items) − 2] divided by (8) × 100
- **Convenience**: ([Sum of Item 7 to Item 9) − 3] divided by 18) × 100
- If one item is missing: ([(Sum of the two completed items) − 2] divided by (12) × 100
- **Global Satisfaction**: ([Sum of Item 10 to Item 11) − 2] divided by 12) × 100

16.2 Secondary Endpoint Analyses

Annualized Relapse Rate (ARR):

The quantitative variables,

- Annualized Relapse Rate before study entry
- Number of relapses during the study
- Annualized Relapse Rate on study

will be summarized for prior MS Therapy categories and overall using descriptive statistics from Safety Analysis Set.

Annualized Relapse Rate before study entry = (No. of Relapses within 24 months prior to written informed consent / (30.4375*24)) * 365.25

Annualized Relapse Rate on study = (Sum of No. of Relapses at month 6 and month 12/ Time on Study) * 365.25

where,

Time on Study (days) = (Date of Study Completion or Date of study discontinuation - Date of first Rebif administration +1)

95% Confidence Interval (CI) will also be provided for Annualized Relapse Rate before study entry and on study.

Adherence to Rebif Therapy:

The qualitative variables

- Injections been missed since last visit (Yes / No)
- Reason(s) for missed injections
  - Forgot to inject
  - Pain at injection site
  - Did not want injection
  - Injection site reaction other than pain
  - Flu like symptoms

- Fear of injection
- Fatigue
- Other

will be summarized for month 6 and month 12 as number and percentage from Safety Analysis Set.

The quantitative variable

- Estimated missed injections

will be summarized for month 6, month 12 and overall using descriptive statistics from Safety Analysis Set.

Adherence Evaluation:

Adherence (%) will be calculated for each subject as 100 x the number of injections the subject administered divided by the expected number of injections over 6 or 12 Months. If the subject terminates earlier than 12 months, the expected number of completed injections will be based on the subject's time on study.

The quantitative variable

- Adherence (%)

will be summarized for month 6 and month 12/End of treatment using descriptive statistics from Safety Analysis Set.

Adherence (%) = (No. of injections the subject administered / Expected No. of injections over 6 or 12 Months) x 100.

Number of injections the subject administered = Expected number of injections over 6 or 12 Months - Total No. of estimated missed injections since baseline visit.

The expected number of injections 3 times weekly (i.e. 3*24 weeks (6 months) = 72 expected injections over 6 months and 144 expected number injections over 12 months).

MusiQoL Questionnaire

The effect of MS on quality of life (QOL) will be measured using the Multiple Sclerosis International QoL (MusiQoL) questionnaire to reflect subject's view points on the impact of MS in their daily lives.

MusiQoL Overall and MusiQoL dimensions scores will be derived according to MusiQoL scoring algorithm (Refer Appendices). Descriptive statistics will be presented for the MusiQoL overall score at baseline, Month 6, and Month 12, and change from baseline at Months 6 and 12 from Safety Analysis set. Same descriptive statistics will be presented for the following MusiQoL dimensions.

- Activities of Daily Living (ADL)
- Psychological Well-Being (PWB)
- Relationships with friends (FR)
- Relationships with family (FA)
- Self-Esteem (SE)
- Relationship with Health Care System (RHCS)
- Sentimental & Sexual life (SSL)
- Coping (COP)
- Rejection (REJ)

MusiQoL Overall score = Sum of all MusiQoL dimension scores / No. of MusiQoL dimensions.

MusiQoL Overall score will be computed as the mean of the dimension scores, when none of the 9 dimension scores is missing.

A paired two-sided t-test will be used to test the null hypothesis that there is no difference in the MusiQol Overall and dimensions scores between 6, 12 months and Baseline.

Reason(s) for discontinuation of Prior MS therapy:

The qualitative variables

- Reason(s) for discontinuation of prior MS Therapy (Adverse event / Lack of efficacy /Other)

will be summarized by prior MS Therapy categories and overall as number and percentage from Safety Analysis Set.

Additional Secondary Endpoints Analyses:

Correlation between TSQM v II and ARR; TSQM v II and Adherence

Correlation between TSQM v II (Global satisfaction score) and ARR; TSQM v II (Global satisfaction score) and Adherence will be evaluated by using either Pearson's correlation procedure or Spearman's rank correlation procedure based on normality of the data from Safety Analysis Set.

The results from the correlation analysis will be presented in the table with correlation coefficient (r), 95% CI and p-value.

TSQM v II and reason for discontinuation

The qualitative variable

- Global satisfaction score

will be summarized using descriptive statistics by reasons for discontinuation i.e. Adverse event, Lack of efficacy and others from Safety Analysis Set.

Correlation between MusiQoL and ARR; MusiQoL and Adherence;

Correlation between MusiQoL (Overall Score) and ARR; MusiQoL (Overall Score) and Adherence will be evaluated by using either Pearson's correlation procedure or Spearman's rank correlation procedure based on normality of the data from Safety Analysis Set. The results from the correlation analysis will be presented in the table with correlation coefficient (r), 95% CI and p-value.

MusiQoL and reason(s) for discontinuation

The qualitative variable

- MusiQoL Overall score

will be summarized using descriptive statistics by reasons for discontinuation i.e. Adverse event, Lack of efficacy and others from Safety Analysis Set.

Correlation between TSQM v II subscales and adherence

Correlation between TSQM v II Subscales (Effectiveness, Side Effects and Convenience) and Adherence will be evaluated by using either Pearson's correlation procedure or Spearman's rank correlation procedure based on normality of the data from Safety Analysis Set.

The results from the correlation analysis will be presented in the table with correlation coefficient (r), 95% CI and p-value.

TSQM v II subscales and reason for discontinuation

The quantitative variables

- Effectiveness
- Side Effects
- Convenience

will be summarized using descriptive statistics by reasons for discontinuation i.e. Adverse event, Lack of efficacy and others from Safety Analysis Set.

TSQM v II subscales at Baseline and after 6 and 12 months of Rebif treatment

TSQM v II dimensions scores will be derived according to TSQM v II Scale Scoring Algorithm (Refer Section 16.1) mentioned below.

- Effectiveness
- Side Effects
- Convenience

will be summarized for baseline, Month 6, and Month 12, and change from baseline at Months 6 and 12 using descriptive statistics from Safety Analysis set.

A paired two-sided t-test will be used to test the null hypothesis that there is no difference in the TSQM v II dimensions scores between 6, 12 months and Baseline.

The corresponding 95% two-sided CI will be presented.

Association between number of relapses and treatment adherence:

Univariate negative binomial regression analysis will be performed to identify the factors contributing to number of relapses. The number of relapses as dependent variable and following variables will be the independent variables for the regression analysis.

- Adherence (%)
- Log (Time on Study (days))
- Age (years)
- Sex (male/female)
- Number of MS relapses within 24 months prior to written informed consent

Further, multiple negative binomial regression analysis will be performed for all independent variables listed above to identify the factors contributing to number of relapses from safety analysis set. All independent variables with a p-value ≤ 0.15 in univariate negative binomial regression analysis only will be considered for multiple negative binomial regression analysis. Method of regression will be the forward stepwise addition method.

Diagnosis of Multicollinearity:

In SAS version 9.1.3, the variance inflation factor (vif) option will be used to detect the multicollinearity. The variables whose VIF values are greater than 10 may merit further investigation. Tolerance, defined as 1/VIF, is used to check on the degree of collinearity. A tolerance value < 0.1 is comparable to a VIF of 10. It means that the variable could be considered as a linear combination of other independent variables. The tol option on the model statement gives these values.

Further, the independent variables which are having vif < 10 and tol > 0.1 will be included in the final model.

The results of univariate and multivariate negative binomial regression analysis will be reported with the following items

- Estimate

- Standard Error
- 95% CI
- P-value

The above mentioned negative binomial regression analysis will be performed when the outcome variable is over-dispersed, i.e., when the situation like data show extra variation that is greater than the mean. Otherwise, Poisson regression analysis will be performed as an alternative method.

16.3 Other Endpoint Analyses

Relapse Assessment:

The qualitative variables

- Subject experienced any MS relapses since last visit (Yes / No)

will be summarized for month 6, month 12 using descriptive statistics from Safety Analysis Set.

The quantitative variable

- No. of Relapses since last visit

will be summarized for month 6, month 12 as number and percentage from Safety Analysis Set.

Listing will be provided for Relapse assessment.

17. Safety Evaluation

Safety evaluation includes the summary of safety endpoints such as adverse events, vital signs, physical examination and neurological examination during the study based on Safety Analysis Set.

17.1 Adverse Events

Adverse events will be summarized per subject using number and percentage by SOC and PT from Safety Analysis Set. If an adverse event is reported for a subject more than once during

treatment, the worst severity and the worst relationship to trial treatment will be tabulated. Listings will also be provided for all the adverse events.

Adverse events will be coded using MedDRA version 19.1.

17.1.1 All Adverse Events

All Adverse events will be summarized using number and percentage by MedDRA-SOC and PT within SOC for relationship, severity and Action taken with Study Medication. The adverse events reported under the category 'Related' will be considered as treatment-related adverse events. Missing will also be considered as related to the treatment. PT within SOC and primary SOC will be given in alphabetical order from Safety Analysis Set.

17.1.2 Adverse Events Leading to Trial and Treatment Discontinuation

AEs leading to treatment discontinuation and study termination will be summarized using number and percentage by MedDRA-SOC and PT within SOC from Safety Analysis Set.

If the primary reason for discontinuation is "Discontinuation of Rebif is desired or considered necessary by the Investigator and/or the subject" and "Discontinuation of Rebif for any other reason" will be considered for the treatment discontinuation reasons.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

If any death is reported it will be presented as case narrative. Listing will be provided for death cases.

17.2.2 Serious Adverse Events

Serious adverse events (SAEs) will be summarized per subject using number and percentage by SOC and PT from Safety Analysis Set.

All SAEs will be summarized using number and percentage by MedDRA-SOC and PT within SOC for relationship and Action taken with Study Medication. The SAEs reported under the

category 'Related' will be considered as treatment-related SAEs. Missing will also be considered as related to the treatment. PT within SOC and primary SOC will be given in alphabetical order from Safety Analysis Set.

17.3 Clinical Laboratory Evaluation

Not applicable

17.4 Vital Signs

Vital sign parameters such as Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg), Weight (Kg) and Height (Cm) will be assessed at all available visits. These parameters will be summarized using descriptive statistics. Listings will also be provided for individual subjects.

Unit Conversion:
Weight (Kg) = 0.4536* Weight (lb)
Height (Cm) = 2.54* Height (In)

17.5 Physical Examination

Listing will be provided for the Physical examination.

17.6 Neurological Examination

Neurological examination parameters for systems affected

- Pyramidal function (Yes / No)
- Cerebellar function (Yes / No)
- Brain stem function (Yes / No)
- Sensory function (Yes / No)
- Bowel and bladder function (Yes / No)
- Visual (optic) function (Yes / No)
- Cerebral (mental) function (Yes / No)

will be summarized as number and percentage at all available visits from Safety Analysis Set. Listings will also be provided for the individual subjects.

18. Benefit risk assessment

Not applicable

19. References

1. Protocol Number: EMR200136_597, dated 07OCT2016, Version 2.0
2. CRF - Version 3.0 dated 18 JAN2017.
3. ICH E3 - “Structure and Content of Clinical Study report” and E9- “Statistical Principles for Clinical Trials”.
4. Hierarchical Construct Validity of the Treatment Satisfaction Questionnaire for Medication (TSQM Version II) among Outpatient Pharmacy Consumers, Mark J. Atkinson, MEd, PhD, Ritesh Kumar, MS, PhD, Joseph C. Cappelleri, MPH, MS, PhD, Steven L. Hass, PhD.
5. MuSIQOL Questionnaire, VERSION 5.4, Professeur Pascal Auquier, Dr Marie Claude Simeoni, Laboratoire de Santé Publique – EA 3279, Faculté de Médecine - 27, bd Jean Moulin. 13 385 Marseille – France.

20. Appendices

- TSQM Version II Analysis
- MusiQoL scoring algorithm