STATISTICAL ANALYSIS PLAN

PLATINUM STUDY

Multicenter interventional Phase IV study for the assessment of the effects on patient's satisfaction of Plegridy (pre-filled pen) in subjects with relapsing-remitting multiple sclerosis unsatisfied with other injectable subcutaneous Interferons.

Promotore:	Biogen Italia Srl Via G. Spadolini 5 Centro Leoni A 20141 Milan Italy
Study Identification Number (SIN) :	Progetto n. BIIT0215/NCT02587065 PLATINUM STUDY
Data Management:	[redacted]
Version:	Final 1.0
Date:	03/05/2018

SIGNATURE

Name	Title	Company	Date	Signature
[redacted]	[redacted]	[redacted]		
[redacted]	Statistician	[redacted]		
[redacted]	[redacted]	Biogen		

SIGNATURE

Name	Title	Company	Date	Signature
[redacted]	[redacted]	[redacted]	03 May 2018	[redacted]
[redacted]	Statistician	[redacted]	3 May 2018	
[redacted]	[redacted]	Biogen		

SUMMARY

LIST OF ABBRAVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis Of Variance
APTS	All Patients Treated Set
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CRO	Contract Research Organization
DMT	Disease Modifying Treatments
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
ET	Early Termination
FPI	First Patient In
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl-Transferase
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN	Interferon
IWRS	Interactive Web Response System
LPI	Last Patient In
LPLV	Last Patient Last Visit
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MSTCQ	Adapted Sclerosis Treatment Concerns Questionnaire
MusiQol	Multiple Sclerosis International Quality of Life questionnaire
PHI	Protected Health Information
RBC	Red Blood Cell
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard deviation
SMPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSQM	Treatment Satisfaction Questionnaire to Medication
WBC	White Blood Cell

1. Objective of Sap

This document outlines the statistical methods to be implemented in the analysis of the clinical data of PLATINUM study. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a details of the outcomes of the analysis described in the protocol.

Results from this planned analysis will be used for publication.

2. Sudy design

This is a 6 month, phase IV, open-label, single-arm, interventional, multicentric study, based on self-administered questionnaires and aimed at evaluating patient-reported effects on user's satisfaction of Peg-IFN beta-1a therapy on patients unsatisfied with other injectable, subcutaneous Interferons. The relevant evaluations will be performed at baseline, week 12 and week 24.

Informed consent will be obtained at baseline prior to study enrolment and before collection of all relevant clinical information (i.e., relapses, EDSS).

Clinical evaluation and questionnaire administration will be performed at baseline (within 2 weeks before Peg-IFN beta-1a therapy onset) and after 12 and 24 weeks.

Subjects may elect to discontinue from study treatment at any time, due to medical reasons (contraindications, medical conditions that necessitate drug discontinuation according to the Investigator) or at personal and/or Investigator's discretion. In all cases, reasons for discontinuation from investigational treatment or withdrawal from the study will be recorded in the subject's CRF.

All relevant and required information about any adverse event (serious and non-serious), including laboratory abnormalities and about pregnancy and cases of overdose occurring during the study will be collected and registered in the subject's CRF.

In case of SAE, pregnancy, or cases of overdose, the Investigator will have to notify Biogen Italia Srl's Drug Safety Unit immediately and no later than 24 hours from its occurrence, by fax or e-mail. Any event follow-up will have to be notified to Biogen Italia's Drug Safety Unit within 24 hours from its recording.

3. Study objectives

- Primary objective

The primary objective of this study is to investigate whether Peg-IFN beta-1a improves the satisfaction of RRMS patients unsatisfied with injectable subcutaneous Interferons, as measured by the Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9), at 12 weeks.

- Secondary objective

The secondary objectives of this study are to evaluate in this study population:

- effects of Peg-IFN beta-1a treatment on patients' satisfaction at 24 weeks;
- effects of Peg-IFN beta-1a treatment on short-term patients' adherence;
- effects of Peg-IFN beta-1a treatment on patients' fatigue;
- effects of Peg-IFN beta-1a on disease activity and physical disability;
- impact of Peg-IFN beta-1a treatment on patient-reported health-related quality of life;
- impact of Peg-IFN beta-1a treatment on patients' injection-system satisfaction;
- evaluate the relationship between patients' satisfaction and adherence;
- evaluate the relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc) and clinical characteristics (ARR, disability, etc.)
- evaluate the treatment safety and tolerability.

4. Inclusion/exclusion criteria

Inclusion Criteria

- ✓ Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations.
- ✓ Aged between 18 and 65 years old inclusive, at the time of informed consent.
- ✓ Subjects diagnosed with Relapsing Remitting MS according to 2010 McDonald criteria.
- ✓ Subjects with EDSS score between 0.0 and 5.0 at baseline.

- ✓ Treatment with injectable subcutaneous Interferons with score < 58 in the "convenience satisfaction" domain of TSQM-9.
- ✓ Period of stability from last relapse of at least 30 days before the baseline visit.
- ✓ Treatment with intravenous corticosteroids completed at least 30 days before the baseline visit (assumption of oral cortisone allowed as long as within 4 mg per day for no longer than 3 days).

Exclusion Criteria

- ✓ Pregnancy or breast-feeding.
- ✓ Depression or other psychiatric disorders.
- ✓ Unwillingness or inability to comply with the requirements of the protocol.
- ✓ Have any contra-indications to treatment with Peg-IFN-beta 1a according to the Summary of Product Characteristics

5. Study population

Full Analysis Set (FAS) consisting of all enrolled patients who took at least one dose of the study medication.

6. Sample size

Data for estimating the sample size were derived from studies reporting the distribution (mean value and standard deviation) of the TSQM-9 in MS patients treated with IFN (9). Assuming an average value of the overall convenience domain at baseline of 55 (SD=16) (9), with 250 subjects we have a power of 90% to detect a change of 3 points on the overall convenience domain (from 55 to 58) under the conservative hypothesis of a SD=16 (9) for the difference between baseline and week 12. However, by assuming a drop-out rate up to 10% during the study, we consider it appropriate to enrol a total of 275 patients.

7. Software

The analysis will be performed using the software Stata version 14.0.

8. Variables for analysis

This section contains definitions and conventions that will be used for the analysis.

Demographic and baseline characteristics

Demographic (age, gender, education and employment) and medical information (disease duration, previous treatments, comorbidities and concomitant therapies, EDSS score and number of relapses in the previous 12 months) will be obtained at baseline.

Efficacy

Being this a health outcomes research study, the term efficacy refers to the assessment of the following patients' reported parameters, corresponding to the primary and secondary objectives of the study, and to the measurement of the related endpoints:

- overall treatment satisfaction;
- injection system satisfaction;
- adherence to treatment;
- health-related quality of life;
- fatigue.

All the endpoint-related questionnaires, described below, will be administered at baseline and after 12 and 24 weeks of treatment.

Primary variables

a) Patients' Satisfaction assessment

- *Abbreviated Treatment Satisfaction Questionnaire to Medication (TSQM-9)*

The TSQM Version 1.4 is a 14-item psychometrically robust and validated instrument consisting of four scales. The four scales of the TSQM include the effectiveness scale (questions 1 to 3), the side effects scale (questions 4 to 8), the convenience scale (questions 9 to 11) and the global satisfaction scale (questions 12 to 14). In the TSQM-9, the five items related to side effects of medication were not included, which creates a need to psychometrically assess the performance of the abbreviated instrument.

TSQM Scale scores computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provided a transformed score between 0 and 1 that should be multiplied by 100. (see below) [Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent]

EFFECTIVENESS
([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100
If one item is missing
([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100

CONVENIENCE
([Sum(Item 9 to Item 11) – 3] divided by 18) * 100
If one item is missing
([(Sum(Item9? to Item11?)) – 2] divided by 12) * 100

GLOBAL SATISFACTION
([Sum(Item 12 to Item 14) – 3] divided by 14) * 100
If either Item 12 or 13 is missing
([(Sum(Item12? to Item14?)) – 2] divided by 10) * 100
If Item 14 is missing
([(Sum(Item12 and Item13)) – 2] divided by 8) * 100

The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain.

Secondary variables

b) *Patients' adherence assessment*

A questionnaire assessing adherence and the reasons for not taking drug at the recommended frequency of administration.

c) *Patients' Injection-System Satisfaction*

- *Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ)*

The MSTCQ is a validated patient questionnaire developed to address patient concerns with IFN-beta treatment that are not related to efficacy. It has two domains: injection-system satisfaction and side effects. The side-effects domain comprises 3 subscales: ISRs, global side effects, and FLS. All questions in

the MSTCQ have a 5-point response choice, with lower total scores indicating better outcomes. A version adapted for Plegridy will be used.

In scoring of MSTCQ you have a referance to the Scoring manual For Version 3 May 2014.

d) Health Related Quality of Life

- *Multiple Sclerosis International Quality of Life questionnaire (MusiQoL)*

MusiQoL version 5.2 (Multiple Sclerosis International Quality of Life) is a multi-dimensional self-administered questionnaire consisting of 31 items describing nine dimensions of health-related quality of life. The nine dimensions assess many aspect of QoL that are specific to MS patients (activities of daily living, psychological wellbeing, symptoms, relationship with friends, relationship with family, sentimental and sexual life, coping rejection, relationship with healthcare system). Items listed in the MusiQoL questionnaire have responses describing frequency/extent of an event on a five-point scale ranging from never/not at all (option 1) to always/very much (option 5). For some items the scores must be reversed.

To obtain a total score for the entire MusiQoL questionnaire, all nine dimensions must be completed to an extent that is meaningful.

Sometimes a patient may not complete every item on the MusiQoL questionnaire. If this happens, there are simple rules to follow:

- If <50% of the items within a dimension have been answered, the remaining answers are voided and no scoring is possible for that dimension, or for the MusiQoL questionnaire as a whole (i.e. the global index score cannot be calculated).
- If ≥50% of the items within a dimension have been answered, the mean value of these answered items will apply to the entire dimension.
- Some dimensions may still provide valid scores and useful information, as long as the criteria above have been met.

All of the 9 dimensions and the global index are linearly transformed and standardized on a 0-100 scale. Higher scores indicate a better level of health-related QoL for each dimension and for the global index score.

e) Patients' Fatigue

- *Fatigue Severity Scale (FSS)*

This is a specific questionnaire composed of 9 statements on the state of fatigue during the previous week. The answers are within a scale of agreement ranging from 1 to 7, with 1 representing the lowest level of agreement. The total score is obtained summing the number given at each item. An overall score of ≥36 indicates a state of fatigue.

Clinical Safety Assessments

The following safety assessments are provided:

- Medical History
- Physical examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate
- Weight
- Concomitant therapy and procedure recording
- AE and SAE (including laboratory abnormalities), pregnancy and cases of overdose recording

In addition, routine clinical assessments will be performed in order to check the safety of the Peg-IFN ongoing treatment.

Laboratory Safety Assessments

At the Investigator's discretion, the following routine laboratory tests can be carried out, in order to monitor the safety profile of the ongoing treatment based on Peg-IFN:

- Hematology: RBC- WBC –Haemoglobin- Haematocrit- MCV- MCH – MCHC - Platelets Count – Lymphocytes- Monocytes – Neutrophils – Eosinophils – Basophils
- Blood chemistry: creatinine, blood urea nitrogen (BUN), alkaline phosphatase, ALT, AST, gamma-glutamyl-transferase (GGT).

A pregnancy hCG test (blood sample) will be performed at the baseline visit (T0) to exclude pregnancy, if applicable (it is not required if the subject is post-menopausal or surgically sterilized).

9. Missing data

For missing data in TSQM-9, MSTCQ and MusiQol see paragraph Variable of analysis.

For the other variables no imputation technique will be apply.

10. Statistical analysis

The primary and secondary endpoints will be evaluated using a repeated measures ANOVA. The repeated measures ANOVA is used to compare group means on a dependent variable across repeated measurements of time. This statistical method is used for making simultaneous comparisons between two or more means of two or more related, not independent, groups.

However, in addition, it could be useful to apply a general linear mixed model that models for group means as fixed effects while simultaneously modeling for individual subject variables as random effects (12). This kind of model is a subject-specific model and is a choice for analysing longitudinal data. Unlike the repeated measures ANOVA, which requires a complete balanced array of data, the mixed model can accommodate a dataset with a large portion missing. Although the repeated measures ANOVA requires a fixed time schedule among all individual units, the mixed model can accommodate flexible time schedules. Furthermore, rather than treating time as a categorical variable, as in the repeated measures ANOVA, the mixed model is capable of treating time as either a continuous variable or a categorical variable or both.

Spearman's correlation coefficient measures the strength of association between two ranked variables.

Differences will be considered statistically significant if the p-value will be less or equal to a type I error =0.05 (two-sided test).

11. Efficacy data

a. Primary Endpoint Analysis

The primary endpoint is to evaluate the changes from baseline in the score of convenience satisfaction domain of TSQM-9 at 12 weeks. (*Stata instruction*: *anova var1 time, repeated(time)*

b. Secondary Endpoints Analysis

• Changes from baseline in the score of all domains of TSQM-9 at 24 weeks;

• Changes from baseline in patient adherence to study treatment survey at 12 and 24 weeks;

• Changes from baseline in the score of FSS (Fatigue Status Scale) at 12 and 24 weeks;

• Changes from baseline in the score of Adapted Sclerosis Treatment Concerns Questionnaire (MSTCQ) at 12 and 24 weeks;

• Changes from baseline in the score of Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) at 12 and 24 weeks;

• Changes from baseline in clinical measures (ARR, percentage of relapse-free patients), measures at 24 weeks.

All the above primary and secondary endpoints will be analysed by a repeated measures analysis of variance adjusted for baseline factors (age, sex, disease duration, previous treatment duration, EDSS) (*Stata instruction: anova var1 var2 …. time, repeated(time)*).

Correlations between variables will be assessed by a Spearman rank correlation coefficient (*Stata instruction: spearman var1 var2)*).

To evaluate the relationship between patients' satisfaction and social-demographic factors (age, sex, employment working, level of education, etc.) and clinical characteristics (ARR, disability, etc.) generalized linear mixed models for repeated measurements will be performed (*Stata instruction: mixed var1 var2|| patient:*).

12. Safety Data

a. Adverse events

All events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Type and incidence of all AEs will be tabulated. Severity and drug relatedness of all reported AEs will be tabulated.

b. Clinical Laboratory Tests

For the clinical laboratory data, descriptive statistics will be generated for all tests performed. Laboratory abnormalities will be determined in accordance with the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated.

13. Tables

The following tables will be repeated for each visit, if applicable.

P1. Number and percentage of patients enrolled per center

P2. Number and percentage of patients stratified by gender; mean and median age, range and interquartile range;

P3. Number and percentage of patients stratified by race;

P4. Number and percentage of patients stratified by educational level;

P5. Number and percentage of patients stratified by working status;

P6. Mean and median age, range and interquartile range of time since diagnosis of SM;

P7. Number and percentage of patients undergoing pharmacological treatment for MS by active substance; mean and median, interquartile range and range of the dose and distribution of the frequency of treatment administration;

P8. Number and percentage of patients undergoing concomitant pharmacological treatment by active substance; mean and median, interquartile range and range of the duration;

P9. Mean and median, range and interquartile range of the total number of relapses from the diagnosis;

P10. Mean and median, interquartile range and range of the total number of relapses in the last year;

P11. Number and percentage of patients stratified for relevant previous and / or concomitant diseases; if previous, mean and median, range and interquartile range of duration; if ongoing, number and percentage of the diseases being treated;

P12. Number and percentage of patients stratified by outcome (not performed / normal / abnormal) to physical examination in relation to:

a) General appearence;

b) Skin;

c) Head, neck, thyroid;

d) Ear, nose, throat;

e) Muscolo-skeletal;

f) Respiratory;

g) Heart;
h) Peripheral vascular;
i) Gastrointestinal
j) Abdomen, liver;
k) Renal and genitourinary
l) Endocrine / Metabolic
m) Neurologic;
n) Mental status;
o) Other;

P13. Mean and median, interquartile range and range of height, weight and bmi value

P14. Mean and median, interquartile range and range of temperature, respiration rate, heart rate, maximum and minimum blood pressure;

P15. Mean and median, range and interquartile range of the number of episodes of acute exacerbation since the last visit;

P16. Mean and median, interquartile range and range of EDSS score;

P17. Mean and median, interquartile range and range of TSQM-9, all domains: effectiveness, convenience and global satisfaction;

P18. Change from baseline in the score of convenience satisfaction domain of TSQM-9 at 12 weeks;

P19. Change from baseline in the score of all domains of the TSQM-9 at 24 weeks;

P20. Adjusted repeated measures analysis of variance for change of convenience satisfaction domain of TSQM-9 at 12 and 24 weeks;

P21. Number and percentage of patient who have correctly taken the prescribed doses of treatment within the last 28 days; if don't, mean and median, interquartile range and range of injections have not been performed during the last 28 days;

P22. Number and percentage of patients per reasons to non correctly taken the treatment:
a) Anxiety for injection
b) Skin reaction
c) Forgot to take the dose
d) Pain at the injection site

e) Depression
f) Headhache
g) Fatigue
h) Flu-like symptoms
i) "I did not want to"
j) "I am not sure of the benefits"
k) "I am tired of injections"
l) No one available for injection
m) Uncomfortable dosing
n) "I am pregnant / I have planned a pregnancy"
o) Other

P23. Mean and median, interquartile range and range of injections expected from the therapy taken in the last 28 days;
P24. Mean and median, interquartile range and range of MSTCQ;
P25. Change from baseline in the score of the MSTCQ at 12 and 24 weeks;
P26. Adjusted repeated measures analysis of variance for change of the MSTCQ at 12 and 24 weeks;
P27. Mean and median, interquartile range and range of MusiQol;
P28. Change from baseline in the score of the MusiQol at 12 and 24 weeks;
P29. Adjusted repeated measures analysis of variance for change of the MusiQol at 12 and 24 weeks;
P30. Mean and median, interquartile range and range of FSS;
P31. Change from baseline in the score of the FSS at 12 and 24 weeks;
P32. Adjusted repeated measures analysis of variance for change of the FSS at 12 and 24 weeks;
P33. Mean and median, interquartile range and range of EDSS;
P34. Change from baseline in the score of the EDSS at 12 and 24 weeks;
P35. ARR, Annualized Relapse Rate
P36. Number and percentage of abnormalities in laboratory values per each test;
P37. List of all laboratory abnormalities;
P38. Number and percentage of adverse events stratified by severity;

P39. List of all adverse events with related characteristics;

P40. Number and percentage of patients who discontinued the study and reasons of dicontinuity;

P41. Number and percentage of patients who experienced pregnancy during the study and outcome of pregnancy.