Study title: A Clinical Evaluation of the Safety of Baclofen ER Capsules (GRS) When Administered Once Daily to Subjects with Spasticity due to Multiple Sclerosis (MS): An Open Label, Long Term, Safety Trial

Date of SAP: 30 Oct 2017

NCT number: NCT01797185

Statistical Analysis Plan

Study Title:	A Clinical Evaluation of the Safety of When Administered Once Daily to Subjects with Spasticity Due to Multiple Sclerosis (MS): An Open Label, Long Term, Safety Trial
Protocol Number: **Amendment**	CLR_11_04 Version 01 Amendment 02 17 Dec 2015
Sponsor:	Sun Pharma Advanced Research Company Ltd.,
Sponsor Contact:	Director, Biostatistics
CRO:	
Version No./Date	Version 1.0 / 30Oct2017

Signatory Page

This Statistical Analysis Plan was reviewed and approved by:

Author

10/30/17

Date

Senior Biostatistician

Reviewer

10/30/17

Date

Senior Biostatistician, Director of Programming

Approval

10/30/17

Date

Director, Biostatistics

REVISION HISTORY

Version No.	Version Date	Description of Modifications
0.1	06Mar2017	Original Document
0.2	18Apr2017	Author Updates
0.3	29Oct2017	Sponsor Updates
1.0	30Oct2017	Final Document

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations and Acronyms	Description
AE	Adverse event
BUN	Blood urea nitrogen
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CI	Confidence interval
CNS	Central nervous system
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
ER	Extended release
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter
MS	Multiple sclerosis
ng	Nanogram(s)
PCS	Potentially Clinically Significant
QC	Quality control
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOP	Standard operating procedures
SPARC	Sun Pharma Advanced Research Company
TEAE	Treatment emergent adverse event
TLFs	Tables, Listings and Figures
WBC	White blood cell

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for the analysis of data from Study CLR_11_04, "A Clinical Evaluation of the Safety of When Administered Once Daily to Subjects with Spasticity due to Multiple Sclerosis (MS): An Open Label, Long Term, Safety Trial."

The SAP is prepared to provide a more technical and detailed elaboration of the principal statistical features stated in the protocol. The SAP will ensure that the tables, listings, and figures that will be produced and statistical methods that will be used are complete and accurate and will allow valid conclusions to be drawn. In the development of this SAP, the following documents were used:

- Protocol Number Version 1.0 Amendent 02, 17 Dec 2015
- Electronic Case Report Form (eCRF), 24 Jun 2013

The principles in the following guidance documents are followed in preparation of this SAP:

- International Conference on Harmonisation (ICH) E3 (1995): Structure and Content of Clinical Study Reports
- ICH E6 (1996): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol.

The Biostatistician is responsible for updating the SAP throughout the life of the study as needed. The responsible party at SPARC Ltd. will be required to review and approve all versions of the SAP.

3. STUDY OVERVIEW

3.1 Study Objectives

This is a clinical study designed to investigate the long term safety of
when administered once daily in subjects with spasticity due to multiple sclerosis (MS).

This study is an extension of trial CLR_09_21, which was conducted to demonstrate the efficacy and safety of [redacted] This safety trial will enroll subjects from trial CLR_09_21 as well as subjects who did not participate in that trial [redacted] whose spasticity symptoms are stable, as well as subjects with spasticity who have no previous exposure to [redacted] treatment. Safety data will be collected for at least 26 weeks to examine the long-term safety of [redacted]

3.1.1 Study Objective

The objective of this study is to investigate the long term safety of [redacted] when administered once daily to subjects aged 18 years and older.

3.2 Study Design

This is a multicenter, open-label, safety study in subjects with spasticity due to MS. Approximately 550 subjects will be enrolled in approximately 35-40 centers, in order to obtain safety data from at least 250 subjects who have completed at least 26 weeks of treatment and at least 200 subjects who have completed at least 1 year of treatment. [redacted]

Subjects enrolled in clinical trial CLR_09_21 who complete [redacted] that trial will be eligible to participate in this trial. In addition, subjects not enrolled in trial CLR_09_21 who are on a stable daily dose [redacted] as well as [redacted] naïve subjects will be eligible to participate in this trial.

Informed consent will be obtained from subjects prior to the initiation of any trial-specific procedures.

A Subject Diary (Appendix 1) will be utilized to assess compliance and collect comments regarding any important problems or issues (missed dose, reason for missing dose, disturbing signs/symptoms, etc) associated with this trial. The clinic staff will review the diary during each visit. Comments that may suggest adverse events (AEs) will be reviewed with the subject to determine the presence of AEs. Any missed doses will be recorded in the diary, along with the reason for the missed dose. The diary will help confirm the level of drug compliance in this study.

Visits are scheduled on: Days -14 (Week -2), 1 (Week 1), 28 (Week 4), 84 (Week 12), 182 (Week 26), and during 3 month interval, follow-up visits.

Table 1 in Section 3.2.3 presents the visit and procedures schedule.

3.2.1 **Sample Size Considerations**

Approximately 550 subjects will be enrolled, in order to obtain safety data from approximately 250 subjects who have completed at least 26 weeks of treatment and at least 200 subjects who have completed at least 1 year of treatment. [redacted]

3.2.2 **Randomization**

No randomization will occur in the study.

3.2.3 Study Assessments Schedules

Study assessments are described in detail in the protocol, and summarized below in Table 1.

Table 1: Visits and Procedures Schedule

Activities	Day -14 Week -2 Visit 1 (Screen)[a]	Day 1 Week 1 Visit 2 (Baseline)	Day 28 Week 4 ± 5 days Visit 3	Day 84 Week 12 ± 5 days Visit 4	Day 182 Week 26 ± 5 Days Visit 5 / Premature Termination Visit[b]	Visits Every 3 Months ± 5 days[c]
Informed consent	X	-	-	-	-	
Medical history and demographics	X	-	-	-	-	
Physical examination	X	-	-	-	X	
Neurologic examination	X	-	-	-	X	
Urine pregnancy test	X	-	X	X	X	X
Vital signs (sitting)	X	-	X	X	X	
Clinical laboratory tests[d]	X	-	-	-	X	
12-lead ECG[e]	X	-	X	X	X[e]	
C-SSRS	X[f]	-	X	X	X	X
Concomitant medication and physical therapy assessments	X	X	X	X	X	X
AE evaluation	X[g]	X[g]	X	X	X	X
Dispense study medication	X[h]	X	X	X	X	X
Collect study medication	-	X[i]	X	X	X	X
Dispense / collect subject diaries	X[j]	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X

[a]Screening Visit assessments in CLR_11_04 which are identical to final visit assessments in CLR_09_21 **do not need to be repeated**. The Screening Visit may be completed simultaneously with the final visit for CLR_09_21, and on the following day, if needed, provided drug supply from CLR_09_21 does not run out. **Subjects cannot enter CLR_11_04 if drug supply runs out prior to the completion of the screening process.**

[b]For subjects not completing the study, all activities scheduled at this visit are to be conducted during the Premature Termination visit with the exception of the ECG (see footnote "e" below) and the physical and neurologic examinations. These three assessments may be conducted during the Premature Termination visit as needed in order to follow the resolution of any adverse events.

[redacted]

[d]Hematology: red blood cell (RBC) count, hemoglobin, total white blood cell (WBC) count, differential WBC count, platelet count; serum chemistry: sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine.

[e]Completed in triplicate two minute intervals during Visit 5. 12-lead ECG should be performed at the Premature Termination visit, as needed, in order to follow adverse events to resolution

[redacted]

[g]AEs recorded for subjects entering from clinical trial CLR_09_21only

[redacted]

4. STUDY ENDPOINTS AND DEFINITIONS

4.1 Study Safety Endpoints

The study endpoints to be evaluated are safety parameters including:

- Vital signs
- Clinical laboratory results
- 12-lead electrocardiogram (ECG) results
- Physical examination results
- Neurological examination results
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Treatment Emergent Adverse Events (TEAEs).

4.2 Study Definitions

4.2.1 Study Day

For purposes of describing days on study drug in data listings, data will be assigned a study day, relative to the start of study drug at either Visit 1 or Visit 2, depending on whether they are roll-over subjects or non roll-over subjects. The following rules will be used (this numbering of days differs from the Study Days as described in the protocol):

Roll-over Subjects

For events that occurred after the Visit 1:

Study Day = visit date – date of Visit 1 + 1

For events occurred before study drug administration:

Study Day = visit date – date of Visit 1

Non [redacted] Roll-over Subjects

For events that occurred after the Visit 2:

Study Day = visit date – date of Visit 2 + 1

For events occurred before study drug administration:

Study Day = visit date – date of Visit 2

Visit numbers as designated on the study eCRFs (Electronic Case Report Forms) will be used. For selected parameters, visit windows will also be calculated for use in descriptive statistics by time.

4.2.2 Baseline and Change from Baseline

The baseline time point for different assessments will be defined in the respective sections. For evaluations that are collected at multiple occasions prior to initiation of study treatment, the latest evaluation will be considered the "Baseline" evaluation for analysis.

Unless indicated otherwise, change from baseline (CFB) will be calculated as follows:

- CFB = Value at Visit - Baseline

Percent change from baseline (PCFB) will be calculated as follow:

- PCFB (%) = 100*(Value at Visit - Baseline)/Baseline

5. STATISTICAL ANALYSIS GENERAL CONSIDERATIONS

5.1 Analysis Populations

5.1.1 Safety Population

The safety population will be all subjects who received at least one dose of Baclofen ER Capsules (GRS) during the study and have a subsequent contact with the clinic. Within the Safety Population, the following Safety Groups will be used for all summary and analysis purposes, in addition to an overall summary, derived from the three distinct sources (see Section 5.1.2):

- *Safety Group 1*: Subjects who completed [redacted] Study CLR_09_21
- *Safety Group 2*: Subjects who are on [redacted] at entry
- *Safety Group 3*: Subjects Entering the Trial with no Prior Treatment[redacted]

5.1.2 Safety Groups

5.1.2.1 *Safety Group 1: Subjects who exited the Study CLR_09_21*

Study CLR_11_04 will open for enrollment while study CLR_09_21 is ongoing. Blinded study medication will be temporarily dispensed to all subjects enrolled into CLR_11_04 who have exited study CLR_09_21 [redacted]

[redacted]

All potential subjects will review the informed consent document prior to receiving blinded study medication kits dispensed via IVRS/IWRS. Kits dispensed will be similar in appearance and packaging as dispensed during Part 3 of study CLR_09_21. [redacted] The actual identity of the contents can be obtained only by breaking the blinding code.

During Visit 3, and for the remainder of this study, open label kits will be dispensed to all subjects who completed CLR_09_21. [redacted]

5.1.2.2 ***Safety Group 2:*** [redacted]

Subjects entering the trial [redacted] will complete a Screening period (Visit 1) of up to 14 days to allow all potential subjects to review the informed consent form and complete the procedures [redacted] At Baseline (Visit 2), these subjects will start with [redacted]

5.1.2.3 ***Safety Group 3:*** [redacted]

Subjects [redacted] will complete a Screening period (Visit 1) of up to 14 days to allow all potential subjects to review the informed consent form and complete the procedures [redacted]

Subjects receiving other anti-spasticity medications [redacted] will have the starting dose determined according to the investigator's medical judgment.

5.2 *P*-Values

Data presentations in this safety study will be descriptive. Unless stated otherwise, any significance tests will be two-sided with statistical significance assessed at the alpha (α) 5% level. All p-values will be reported to four decimal places. P-values will not be adjusted to account for multiple comparisons.

5.3 Procedures for Handling Missing Data and Outliers

Every effort will be made to collect all the data and avoid missing data. All missing values will be queried and resolved to the best possible extent. Unless specifically noted otherwise, missing values will not be imputed.

5.4 Interim Analysis

For regulatory purposes, interim reports of safety data accrued will be prepared annually. Post-trial AEs not included in the trial safey database will be included in a separate pharmacovigilance database, which will be used for generating periodic safety reports. No formal interim analyses are planned for the study.

5.5 Final Reporting and Analysis

All analyses outlined in the protocol and in this SAP will be carried out after:

- The SAP has been approved;
- The study database has been authorized by the study clinical team as complete and final;
- All analysis populations are determined;
- Protocol deviations have been identified.

Any post hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the CSR.

5.6 Multi-center Studies

There are expected to be approximately 35-40 study sites in this study. Due to the large number of study sites and the small numbers of subjects per site, the analysis of endpoints will not include adjustments for study site.

6. STATISTICAL ANALYSIS METHODOLOGY

All data collected for this study will be presented in summary tables, listings, and figures (TLFs) as indicated in Appendix 1 of this SAP. Shells for TLFs with enough detail for programming will be provided as a guide to develop the programming SAS codes. These shells will be in sufficient detail to simulate the actual TLFs when they are created from the locked database.

Appropriate descriptive statistics will be computed and displayed (by time point and other key variables as appropriate) for both continuous and categorical variables. For continuous variables, descriptive statistics will include n (the number of subjects with non-missing data), mean, standard deviation (SD), 95% confidence intervals, median, minimum and maximum values. For categorical data, the number and percentage of subjects within each category will be presented. The denominator for percentages will be based on the number of subjects with non-missing data appropriate for summary purposes.

Individual data listings of all data represented on the eCRF and from the clinical laboratory will be presented.

6.1 Study Subjects

6.1.1 Subject Disposition

The following descriptive summaries of subject disposition will be provided:

- Number of subjects who were enrolled
- Number and proportion of subjects who discontinued the trial prior to Visit 5 (Week 26)
- Number and proportion of subjects who discontinued for each of the following categories for why a subject may be prematurely discontinued from the trial:
    - *Discontinued Due to Adverse Event:* Subjects who are discontinued from the trial medication due to the occurrence of an AE will be recorded as dropouts.
    - *Discontinued Due to Major Protocol Violation:* Subjects who are discontinued from the trial due to the occurrence of a major protocol violation will be recorded as dropouts.
    - *Lost to Follow-Up:* Subjects available for evaluation in Visit 1, but not evaluated for subsequent visits will be considered as lost to follow-up.
    - *Discontinued Due to Worsening of Condition:* Subjects can be prematurely discontinued from the trial due to worsening of condition at the discretion of the investigator.
    - *Discontinued Due to Other Reasons:* Subjects who are discontinued from the trial due to any other reason will be recorded as dropouts. The reason for discontinuation will be recorded.

A listing of subject disposition will be prepared, inclusive of dates of last dose and last contact, and any investigator comments regarding reason for discontinuation. A summary

table will tabulate overall disposition of the subjects. A figure will diagram the overall disposition of the subjects.

A summary of screen failure subjects will be tabulated by reason for screen failure.

6.1.2 **Demographics**

Descriptive statistics of the safety population will be prepared for the demographic and baseline characteristics listed below, including the numbers, means, standard deviations, medians, minimums, maximums and 95% confidence intervals for continuous variables and the numbers and percentages for categorical variables:

- Age (years)
- Age Group (<65 vs. ≥65)
- Sex
- Race/ethnicity
- Renal function
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
- Duration of MS (years)
- Type of MS
- Pregnancy prevention status for femal subjects
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Listings of individual subject's data will also be produced. A summary table of demographics will be produced with descriptive statistics.

6.1.3 **Protocol Deviations**

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

A subset of the protocol deviations can be identified as a major protocol deviation as described below:

Major Protocol Deviation: A major protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Important deviaitons include includion/exclusion criteria violations, cases where withdrawal criteria developed but the subject was not withdrawn, receiving the wrong treatment or incorrect dose, and receiving excluded concomitant medications.

Upon soft lock of database, all documented protocol deviations in the study will be reviewed to identify all important protocol deviations by a data review team including representatives from clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented and databased.

Protocol deviations will be listed by subject with major deviaitons flagged.

6.1.4 Medical and Surgical History

Medical history at Screening Visit (prior conditions and present conditions) will be tabulated using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA®) by System Organ Class and Preferred Term, both with a summary of incidence by diagnosis and the proportion with any abnormality. A by-subject listing will be created.

6.1.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) March 2012. These will be summarized overall and by Safety Group based on Anatomical Therapeutic Chemical Class 3 level (ATC 3), using incidence and percentage.

Neurological and anti-spasticity concomitant medications, identified before data lock, will be summarized separately overall, and for each Safety Group using incidence and percentage, and will be listed for all subjects.

Medications previously used (within 30 days of Visit 1) and before the on-study treatment will be considered Prior Medications. These will be summarized separately.

Physical therapy regimen will be summarized by visit using counts and percentages. Numbers of subjects with changes at post-baseline visits will also be summarized.

When medication start and/or stop dates are missing, the following imputations will be made (subject to medical review):

- Missing Medication Start Dates

  1. If onset date is completely missing, then onset date is set to date of first dose

  2. If year is present and (month and day are missing), or (month is missing but day is present):

     a. If year = year of first dose, then set date to first dose date

b. If year < year of first dose and medication stop month and year are available, then set to first of the end month

c. Otherwise if year < year of first dose, then set month and day to December 31st.

d. If year > year of first dose, then set month and day to January 1st.

3. If month and year are present and day is missing:

a. If year=year of first dose and

i. If month = month of first dose then set day to day of first dose date

ii. If month < month of first dose then set day to last day of month

iii. If month > month of first dose then set day to first day of month

b. If year < year of first dose then set day to last day of month

c. If year > year of first dose then set day to first day of month

4. If the medication start date is completely missing and the corresponding stop date is completely missing, the medication start date will remain missing.

- Missing Medication Stop Dates

  If the stop date is completely missing, the stop day will not be estimated (i.e., the medication will be assumed to be continuing).

  If only the day of Medication stop is unknown, the day will be assumed to be the last day of the month (e.g. ??-JAN-2011 will be treated as 31-JAN-2011).

A by-subject listing comprehensive of prior and concomitant medications will be generated, inclusive of verbatim and coded terms, doses and routes, and start and stop dates. Prior medications will be flagged. Prior and concomitant status with respect to study drug treatment will be determined based on imputed dates as defined above.

6.1.6 Exposure and Compliance

6.1.6.1 *Exposure*

Exposure data at each visit starting with Screening will be summarized overall and for each of the safety groups. Specifically, the numbers of subjects for each dose level will be summarized with counts and percentages, and descriptive summaries (mean, median, mode, and standard deviation) of dose at each visit will be provided.

For each subject, total exposure duration will be calculated as the number of days the subject [redacted]

The exposure duration will be calculated as the date of last dose reported on the final status eCRF– date of first dose + 1. In cases where the date of last dose is not reported or missing, the date of last dose will be considered the date of the last visit with drug return reported. If no visit with drug return reported exists, exposure duration will be set to 1 day.

This exposure data will be summarized overall for the safety population, and by each of the three safety groups described in Section 5.1.2.

[redacted]

Individual subject listings will be prepared.

6.1.6.2 ***Compliance***

Compliance by Dispense/Return

Treatment compliance will be measured on the basis of a capsule count by the investigator or designee every time drug supplies are returned. Each subject will be instructed to bring the study medication (with the capsules that remain) with him/her to the next scheduled visit. If the subject fails to bring the study medication on the designated day, he/she will be told to bring the study medication within the next 3 days. If the subject fails to do so, the capsule count will be recorded as "not available."

The clinic will fill out the 'Dispense/Return Study Medication' Form, included in the eCRF book. This form will list each bottle dispensed, along with the bottle number, the date the bottle was dispensed, and the dose strength. This form will also list each bottle that was returned, along with the bottle number, the date the bottle was returned, along with the number of capsules returned.

Based on this form, percent compliance will be calculated using the number of capsules dispensed minus the number of capsules returned, divided by the number of capsules intended to be taken.

Average compliance will be summarized descriptively by visit, and for the study overall.

The compliance for each visit is derived by the following. As an example, consider bottles dispensed at Visit X:

1) The expected number of capsules will be determined as the difference between the last return date for all bottles dispensed at the given visit and the Visit X date. The expected capsules calculation takes into account if >1 capsule is taken daily.
2) The capsules that were **assigned at the scheduled visit X** and not any unscheduled visit between visit X and the next scheduled visit are used in the calculation for Visit X

   [redacted]
3) If any bottle from Visit X is not returned/data is not available, the number of capsules returned is not countable and per the protocol will be classified as "not available". The compliance for this visit will be missing in this case.

4) The compliance for Visit X will be calculated as the [number of capsules dispensed - returned]/[number expected]

A further categorical summary of compliance will be provided by visit, and for the study overall, using the following categories: <75%, ≥75% to ≤125%, and >125%.

Secondary Compliance by Diary

A Subject Diary will be utilized to assess compliance and collect comments regarding any important problems or issues (missed dose, reason for missing dose, disturbing signs/symptoms, etc) associated with this trial. The clinic staff will review the diary during each visit. Comments that may suggest AEs will be reviewed with the subject to determine the presence of AEs. Any missed doses will be recorded in the diary, along with the reason for the missed dose. The diary will help confirm the level of drug compliance in this study.

For each subject, based on the subject's diary data, percent compliance will be calculated based on recorded dose information divided by intended dosage. The format of the summary of diary-based compliance information will follow that of the eCRF-based mothod above. This measure of compliance is only meant to endorse the preceding more rigorous measure based on the drug accountability data, which will be collected in the eCRF.

A summary table of compliance by both Dispense/Return eCRF and Diary will be presented by Safety Group and overall.

6.2 Efficacy Analysis

This is a safety trial. Efficacy will not be formally evaluated.

6.3 Safety Analysis

6.3.1 Adverse Events

Adverse events recorded from the time the Informed Consent Form is signed until 30 days after the end of the trial will be captured in the trial safety database. For any AE included in this trial's safety database, follow-up information on the AE up to 30 days from the onset of the AE will also be included in the same database. Post-trial AEs not included in this database will be included in a separate pharmacovigilance database, which will be used for generating periodic safety reports.

Treatment-emergent adverse events (TEAEs) will be used for summary and analysis purposes. [redacted] All TEAEs will be coded by system organ classification and preferred terms according to version 15.0 of MedDRA®.

When AE start and/or stop dates are missing, the following imputations will be made (subject to medical review):

- Missing AE Start Dates

  1. If onset date is completely missing, then onset date is set to date of first dose

  2. If year is present and (month and day are missing), or (month is missing but day is present):

     a. If year = year of first dose, then set date to first dose date

     b. If year < year of first dose and medication stop month and year are available, then set to first of the end month

     c. Otherwise if year < year of first dose, then set month and day to December 31st.

     d. If year > year of first dose, then set month and day to January 1st.

  3. If month and year are present and day is missing:

     a. If year=year of first dose and

        i. If month = month of first dose then set day to day of first dose date

        ii. If month < month of first dose then set day to last day of month

        iii. If month > month of first dose then set day to first day of month

     b. If year < year of first dose then set day to last day of month

     c. If year > year of first dose then set day to first day of month

  4. If the AE start date is completely missing and the corresponding stop date is completely missing, the AE start date will remain missing.

- Missing AE Stop Dates

  If the stop date is completely missing and the event is not ongoing (i.e., an outcome is indicated), the stop day will not be estimated.

  If only the day of resolution is unknown, the day will be assumed to the last of the month (e.g. ??-JAN-2011 will be treated as 31-JAN-2011)

  If the stop date is completely missing and the event is ongoing, the event will be noted as “Ongoing” in the stop date column in the AE listings.

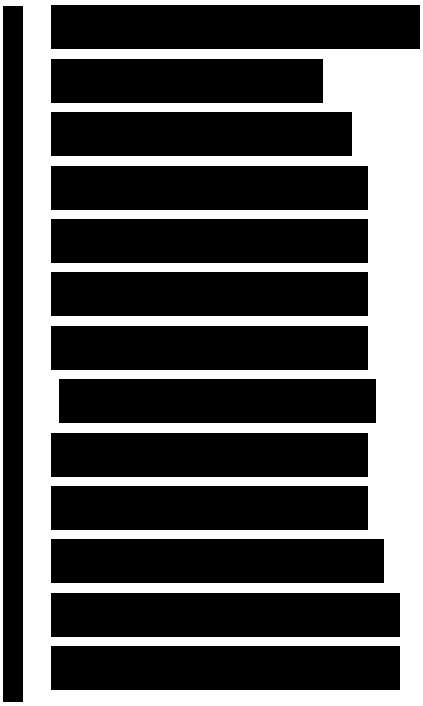
Adverse events will be listed for all subjects, including verbatim and coded terms, duration, severity, and relationship to the study drug. TEAE status will be determined based on the imputed dates as defined above.

The incidence and proportion of subjects with TEAEs and SAEs will be summarized by System Organ Class and Preferred Term overall and by the Safety Groups defined in Section 5.1.2.

An overview of TEAEs will be provided that summarizes the incidence of subjects with one or more AE, the incidence of AEs by highest relationship, the incidence of AEs by highest severity, the incidence of AEs by action taken, the incidence of AEs outcome, the incidence of serious adverse events (SAEs), and the incidence of AEs by type of seriousness.

The incidence and proportion of subjects with TEAEs and SAEs will also be summarized overall and by Safery Groups as follows:

- TEAE by System Organ Class, and Preferred Term
- TEAEs by Preferred Term, in descending order of frequency
- TEAEs by highest severity
- TEAEs by highest relationship
- Treatment-related (defined as at least possibly related) TEAEs by System Organ Class, and Preferred Term
- TEAEs resulting in discontinuation from the study
- Treatment-related (defined as at least possibly related) TEAEs by System Organ Class, and Preferred Term, and severity
- TEAEs by dose at time of onset
- TEAEs by time of onset windows, where the denominator for each visit window is the total number of subjects with exposure to drug as of the first day of the window, defined as:



- Treatment Emergent SAE by System Organ Class and Preferred Term
- Treatment Emergent Fatal SAE by System Organ Class and Preferred Term
- Treatment-related SAE by System Organ Class, Preferred Term, and Severity

TEAEs will also be summarized by subgroups as described in Section 6.4.

6.3.2 **Vital Signs**

Vital sign measurements (seated blood pressure, pulse rate, respiration rate, and temperature) at Visits 1, 3, 4, and 5 will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum, and 95% CI). Similarly, change from Visit 1 at each visit will be summarized using descriptive statistics. For the summary of change statistics, the Baseline mean and standard deviation will be provided for the subset of subjects with available data for the change summary.

Values considered clinically significant by the investigator are to be flagged. Criteria for possibly significant post-baseline changes are presented in Table 3. Number and percentages of subjects with post-baseline values of clinical significance will be summarized by visit.

In addition, vital signs data will be listed for all subjects, inclusive of flags for whether the value is clinically significant in the investigator's judgment and whether it meets pre-specified criteria as being possibly clinically significant post-basesline.

Vital sign values are considered as Possibly Clinically Significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 3 below.

Table 3: Possibly Clinically Significant Vital Sign Criteria

Vital Sign Parameter	***Flag***	***PCS Criteria***	
		Observed Value	*Change from Baseline*
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180 mmHg	Increase of ≥ 20 mmHg
	Low (CL)	≤90 mmHg	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105 mmHg	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50 mmHg	Decrease of ≥ 15 mmHg
Pulse Rate (bpm)	High (CH)	≥ 120 bpm	Increase of ≥ 15 bpm
	Low (CL)	≤ 50 bpm	Decrease of ≥ 15 bpm

Note: A post-baseline value is considered a PCS value if it meets both criteria for observed value and change from baseline.
Note: PCS = potentially clinically significant.
CH = high PCS based on criterion value and percent increase from baseline.
CL = low PCS based on criterion value and percent decrease from baseline

The number and percentage of subjects with a PCS post-baseline vital sign value over all visits will be tabulated. Subjects with baseline and at least one post-baseline assessment will be included in the denominator and subjects who meet the PCS criteria at least once (based on all post-baseline assessments including unscheduled visits) will be included in the numerator. Subjects with a PCS post-baseline value will be flagged in the vital sign listing.

6.3.3 Clinical Laboratory Tests

The following tests will be performed at Screening (Week -2), Visit 5 (Week 26), and the Premature Termination visit (if applicable):

- Hematology:
  - RBC, including RBC count and hemoglobin
  - Total WBC count
  - Differential WBC count
  - Platelet count

- Serum chemistry: o
  - Sodium
  - Potassium
  - Chloride
  - BUN
  - Creatinine

Clinical laboratory testing (hematology and chemistry) results at Visit 1 relative to Visit 5 (Week 26) based on Conventional Units will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, and 95% CI). Change from Visit 1 to Visit 5 will also be summarized. For the summary of change statistics, the Baseline mean and standard deviation will be provided for the subset of subjects with available data for the change summary.

Values outside the laboratory normal range are to be flagged as L (low) and H (high). Shift tables displaying the shift from laboratory normal range between Visit 1 and Visit 5 will be

generated. Criteria for possibly significant changes for selected parameters appear in Tables 4 and 5. The numbers and percentages of subjects meeting these criteria will be summarized by visit.

Table 4: Possibly Clinically Significant Hematology Values

Parameter	PCS values	
	S.I. Units	Conventional Units
White blood cells (WBC)	≤ 2.8 or ≥ 16 × 10^3/L	≤ 2.8 or ≥ 16 × 10^3/L
Lymphocytes	≤ 0.5 or ≥ 4.5 × 10^3/L	≤ 0.5 or ≥ 4.5 × 10^3/L
Monocytes	≥ 1.5 × 10^3/L	≥ 1.5 × 10^3/L
Neutrophils	≤ 1.0 × 10^3/L	≤ 1.0 × 10^3/L
Eosinophils	≥ 0.7 × 10^3/L	≥ 0.7 × 10^3/L
Basophils	≥ 0.4 × 10^3/L	≥ 0.4 × 10^3/L
Red blood cells (RBC)	M: ≤ 2.5 × 10^{12}/L F: ≤ 2.0 × 10^{12}/L	M: ≤ 2.5 × 10^6/mm^3 F: ≤ 2.0 × 10^6/mm^3
Hemoglobin	M: ≤ 115 g/L F: ≤ 95 g/L	M: ≤ 11.5 g/dL F: ≤ 9.5 g/dL
Hematocrit	M: ≤ 0.37 F: ≤ 0.32	M: ≤ 37% F: ≤ 32%
Platelet count	≤ 75 or ≥ 700 × 10^3/L	≤ 75 or ≥ 700 × 10^3/L

S.I. = International System of Units

Table 5: Possibly Clinically Significant Serum Chemistry Values

Parameter	PCS values	
	S.I. Units	Conventional Units
Sodium	≤ 115 or ≥ 155 mmol/L	≤ 115 or ≥ 155 mEq/L
Potassium	≤ 3.0 or ≥ 5.8 mmol/L	≤ 3.0 or ≥ 5.8 mEq/L
Glucose (random)	≤ 2.775 or ≥ 9.99 mmol/L	≤ 50 or ≥ 180 mg/dL
BUN	≥ 30 mg/dL	> 30 mg/dL
Creatinine	≥ 176.8 µmol/L	≥ 2.0 mg/dL
Calcium, plasma	≤ 1.75 or ≥ 3.875 mmol/L	≤ 7 or ≥ 15.5 mg/dL
ALT / SGPT	≥ 3 × ULN	≥ 3 × ULN
AST / SGOT	≥ 3 × ULN	≥ 3 × ULN
Alkaline phosphatase (ALK-P)	≥ 3 ×ULN	≥ 3 × ULN
Total bilirubin	≥ 34.2 µmol/L	≥ 2.0 mg/dL
Total protein	≤ 45 or ≥ 90 g/L	≤ 4.5 or ≥ 9.0 g/dL
Albumin	≤ 25 or ≥ 65 g/L	≤ 2.5 or ≥ 6.5 g/dL
Creatinine clearance	< 70 mL/min	< 70 mL/min

S.I. = International System of Units; ULN = upper limit of the [normal] reference range
Medium = serum, unless otherwise noted

The number and percentage of subjects with a PCS post-baseline laboratory value over all visits will be tabulated. Subjects with baseline and at least one post-baseline assessment will be included in the denominator and subjects who meet the PCS criteria at least once (based on all post-baseline assessments including unscheduled visits) will be included in the numerator. Subjects with a PCS post-baseline value will be flagged in laboratory listings.

Clinical laboratory results will be listed for all subjects, inclusive of flags for whether or not the value is outside the laboratory normal range, considered significant by the investigator, or met the pre-specified criteria for being possibly clinically significant.

6.3.4 **12-Lead ECG**

ECGs will be assessed at visit 1 (screening), visit 3 (week 4), visit 4 (week 12), and visit 5 (week 26). ECG measurements will be collected in triplicate 2 minues apart and read at the investigator site. The following intervals will be collected: HR, PR, RR, QRS, QT, and QTc. The QTc interval will be presented by both the Bazett ($QTcB = QT/(RR)^{1/2}$) and the Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections. For QTcF and QTcB at each study visit, the distribution of maximum values (≤ 450, >450 - ≤ 480, >450 males, >470 females, >480 - ≤ 500, and > 500 msec) as well as the distribution of the greatest change from visit 1 (0 or less [no increase], 1-29 msec, 30-60 msec, > 60 msec, and >60 msec increase or >500 msec) will be presented. Appropriate visit windows for categorizing results will be established prior to database lock and unblinding. When more than one value is available within a given visit window, the latest value will be used for tabulation purposes.

For the purposes of summary and analysis, results from the triplicate measurements at each visit will be averaged. ECG results will be summarized by visit using counts and percentages for abnormalities noted by the investigator and T-wave abnormalities, and using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, and 95% CI) for interval data. For abnormality designations collected in triplicate, the worst outcome will be selected in the following order: Abnormal, Clinically Significant>Abnormal, Clinically Non-Significant>Normal. Any ECG abnormalities, based on clinical interpretation, will be reviewed for any emergent abnormalities that could be attributed to the new dosage form. Continuous ECG parameters will be summarized as change from Baseline (visit 1). For the summary of change statistics, the Baseline mean and standard deviation will be provided for the subset of subjects with available data for the change summary.

ECG results, including clinical interpretation and a flag for whether or not the value meets criteria for being possibly clinically significant, will be listed for all subjects.

6.3.5 **Physical and Neurological Examinations**

Physical and neurological exminations will be performed at screening (visit 1) and week 26 (visit 5). Normal and abnormal physical and neurological exam results will be summarized by visit, using counts and percentages. Physical and neurological examination findings will be listed. These will be reviewed for any emergent abnormalities that could be attributed to the new dosage form.

6.3.6 **Suicidality Assessment Using C-SSRS**

Results of the C-SSRS, assessed at each visit, will be evaluated and reported according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for the Safety Population. [redacted]

6.4 Subgroup Analysis

Subset analysis will be stratified by anti-spasticity and MS medications used (ie, tizanidine, fampridine, etc) at Visit 1 if the percentage of subjects in these stratification groups is ≥10% of the total number of subjects enrolled.

The effects of any other medications and/or medical conditions present at Visit 1 will also be explored. Should any medications be used by or conditions be present in 20% or more of the subjects overall, subjects will be stratified accordingly and the incidence of TEAEs in each part summarized.

The incidence of TEAEsh will be summarized by the following subgroups: sex, age (below 65 years of age and 65 years of age and older), and race.

7. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs will be written in SAS® version 9.3, or later. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per standard operating procedure (SOP). In addition, SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in the Clinical Data Management System (CDMS) database. Further all tables, listings, and figures (TLFs) will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent with the analysis methods described in this SAP, and accurately reflects the data stored in CDMS.

7.1 Programming Specifications for TLFs

Appendix 1 provides a list of the TLFs that are planned to be produced.

7.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text Files (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 1.5 inches on top, and 1 inch for right, left, and bottom.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

Portion of Output	Preferred	Minimum
Page Header	10 pt	8 pt
Title	10 pt	8 pt
Column header	10 pt	8 pt
Cells	10 pt	8 pt
Footnote	10 pt	8 pt
Page Footer	10 pt	8 pt

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.
- Column headings should be in initial capital characters. For numeric variables, include “unit” in the column heading when appropriate.
- In figures, axes will be labeled appropriately.

7.3 Standard Text Conventions

7.3.1 Header

All output (table, listing, or figure) will have the following header:

Sun Pharma Advanced Research Company Ltd.
Protocol CLR_11_04 Page xx of XX

All output will have the date and time (date and time output was generated) and internal page number in the footer. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

7.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis population descriptor.
  - Population(s) represented on the tables will be clearly identified in the last row of the table Title. Consistent terminology will be used to identify a population.
  - Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., Safety Group 1 Subjects from Study Site 1, Safety Group 2 Subjects from Study Site 2) used for analysis in a table, figure, or a data listing.

All titles will be centered, as shown in the following example:

Table 14.3.2.1
Overall Incidence of Safety Events
Safety Population

7.3.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "Note: followed by 2 spaces, then the footnotes", as shown in the following example:

  Note: SD = Standard Deviation; SEM = Standard Error of the Mean.

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears for the first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the study statistician to decide whether there is a need to repeat the same footnote for the rest of TLFs.
- A footnote serves as a brief explanation/clarification /definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- All footnotes will be at the lowest line of the page immediately above the footer. There will be one space between the last footnote and the footer.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

7.3.4 **Footer**

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

Program: PGNAME.sas; Creation Date and Time: DDMMMYYYY HH:MM
Data Cutoff: DDMMMYY:HH:MM:SS – Listing Generated MMM DD, YYYY

where PGNAME = SAS program name.

7.4 Statistical Conventions

7.4.1 **Statistics Reported**

- Unless otherwise specified, the mean and median will be displayed to one more decimal place than the original value and the standard deviation to two more decimal places, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx
  Mean and Median: xx.x
  SD: xx.xx
  Minimum and maximum: xx

- Descriptive statistics in this template include: **Mean, Median, Standard Deviation (SD), Minimum, Maximum, and N**. In addition, 95% CI will be presented when appropriate.

- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 2 decimal places in all tables/listings/figures, with the exception of adverse events,

which will be rounded to 1 decimal place. Rounding will take place after all calculations have been performed.

- Population summaries that include p-values will report the p-value to four decimal places with a leading zero (0.0001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not as 0.0000.

- Use of N versus n:
  N = total number of subjects or subjects in the population.
  n = total number of subjects or subjects in the specific category.

7.4.2 SAS Procedure Output

If appropriate, SAS procedure output may be formatted and saved as source for references and will be included in Appendix.

7.4.3 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- Percent of events should be left blank (including the parentheses) if the number of events is zero.
- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.
- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.

7.4.4 Subject Data Listings

In general, individual subject data listings should include all subjects with data. However, if a subject data listing includes only subjects who met a certain condition, and there were no subjects who met that condition, then a “message” will appear indicating that no subjects met the condition for inclusion in that listing.

8. REFERENCES

.

ICH E3 (1995): Structure and Content of Clinical Study Reports. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E6 (1996): Guideline for Good Clinical Practice. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E9 (1998): Statistical Principles for Clinical Trials. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

MedDRA Version 15.0 (Mar 2012). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

SAS® for Windows® Version 9.3. SAS Inc. Cary, North Carolina USA.

WHO Drug Dictionary (WHO-DD) (Mar 2012). World Health Organization (WHO) Uppsala Monitoring Center (UMC).

9. APPENDICES

Appendix 1: Subject Diary

Sample Subject Diary (Protocol CLR_11_04)

Subject No./Initials:_____ Dates: _____to_____

Instructions:

- Complete this diary if you missed your dose or if you have had any recent illnesses or changes in your condition

[redacted]

Date (mm/dd/yyyy)	Event (Check Box)	Specify Reason For Missed Dose	Comments For An Event Other Than a Missed Dose
	☐ Missed dose ☐ Side effects and symptoms ☐ Other (specify in Comments)		
	☐ Missed dose ☐ Side effects and symptoms ☐ Other (specify in Comments)		
	☐ Missed dose ☐ Side effects and symptoms ☐ Other (specify in Comments)		
	☐ Missed dose ☐ Side effects and symptoms ☐ Other (specify in Comments)		

Appendix 2: Planned Tables, Listings, and Figures

Table 14.1.1.1	Screen Failure Summary
Table 14.1.1.2	Protocol Deviations – Safety Population
Table 14.1.2	Subject Disposition – Safety Population
Table 14.1.3	Demographics – Safety Population
Table 14.1.4	Medical History – Safety Population
Table 14.1.5.1	Prior Medications – Safety Population
Table 14.1.5.2.1	Concomitant Medications – Safety Population
Table 14.1.5.2.2	Concomitant Medications – Anti-Spasticity - Safety Population
Table 14.1.5.2.3	Concomitant Medications – Neurological - Safety Population
Table 14.1.5.3	Physical Therapy Regimens – Safety Population
Table 14.1.6	Physical Examination Results – Safety Population
Table 14.1.7	Neurological Examination Results – Safety Population
Table 14.1.8.1.1	Exposure Duration – Safety Population
Table 14.1.8.1.2	Summary of Dosing by Dose Level and Visit – Safety Population
Table 14.1.8.1.3	Shift Table of Dosing by Dose Level and Visit – Safety Population
Table 14.1.8.2.1	Compliance – Safety Population
Table 14.1.8.2.2	Compliance as Assessed by Subject Diary – Safety Population
Table 14.3.1.1	Overview of Treatment-Emergent Adverse Events – Safety Population
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population
Table 14.3.1.3	Treatment-Emergent Adverse Events by Preferred Term – Safety Population
Table 14.3.1.4	Treatment-Emergent Adverse Events by System Organ Classand Preferred Term by Sex – Safety Population

Table 14.3.1.5	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Age (<65 Years and ≥65 Years) – Safety Population
Table 14.3.1.6	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Race – Safety Population
Table 14.3.1.7.1	Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term by Medications Present in 20% or More of Overall Subjects at Visit 1 – Safety Population
Table 14.3.1.7.2	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term by Medical Conditions Present in 20% or More of Overall at Visit 1 – Safety Population
Table 14.3.1.7.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by MS-Related Medications Taken by ≥ 10% of All Subjects at Visit 1 - Safety Population
Table 14.3.1.8	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
Table 14.3.1.9.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Highest Relationship – Safety Population
Table 14.3.1.9.2	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term – Safety Population
Table 14.3.1.9.3	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
Table 14.3.1.10	Treatment-Emergent Adverse Events Resulting in Discontinuation from the Study by System Organ Classand Preferred Term – Safety Population
Table 14.3.1.11	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Dose at Time of Event – Safety Population
Table 14.3.1.12	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Time of Onset Windows – Safety Population
Table 14.3.2.1	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Safety Population, Overall and by Safety Group
Table 14.3.2.2	Treatment-Emergent Fatal Serious Adverse Events by System Organ Class and Preferred Term – Safety Population
Table 14.3.2.3	Treatment-Related Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term and Severity – Safety Population
Table 14.3.4.1.1	Vital Sign Results – Safety Population
Table 14.3.4.1.2	Number and Percentage of Subjects with a Possibly Clinically Significant (PCS) Post-Baseline Vital Sign Result, by Visit and Overall – Safety Population
Table 14.3.4.2.1	Hematology Assessments – Safety Population
Table 14.3.4.2.2	Hematology Shift Table – Safety Population
Table 14.3.4.2.3	Number and Percentage of Subjects with a Possibly Clinically Significant (PCS) Post-Baseline Hematology Result, by Visit and Overall – Safety Population
Table 14.3.4.3.1	Serum Chemistry Assessments – Safety Population
Table 14.3.4.3.2	Serum Chemistry Shift Table – Safety Population
Table 14.3.4.3.3	Number and Percentage of Subjects with a Possibly Clinically Significant (PCS) Post-Baseline Serum Chemistry Result, by Visit and Overall – Safety Population
Table 14.3.4.4	Electrocardiogram (ECG) Results – Safety Population
Table 14.3.4.5.1	Columbia Suicide Severity Rating Scale (C-SSRS) Results: Suicidal Ideation and Suicidal Behavior – Safety Population
Table 14.3.4.5.2	Columbia-Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation and Behavior Overall During Trial – Safety Population
Figure 14.1.2.1	Subject Disposition – Safety Population
Figure 14.3.4.5.1.1	Columbia Suicide Severity Rating Scale (C-SSRS): Suicidal Ideation and Behavior Histogram – Safety Population
Listing 16.2.1.1	Subject Eligibility – Inclusion/Exclusion Criteria

Listing 16.2.1.2	Subject Disposition
Listing 16.2.1.3	Identification of Analysis Sets
Listing 16.2.2	Protocol Deviations
Listing 16.2.4.1	Demographics
Listing 16.2.4.2.1	Medical History
Listing 16.2.4.2.2	Surgical History
Listing 16.2.4.2.3	Spasticity and MS History
Listing 16.2.4.2.4	MS Symptoms Other Than Spasticity
Listing 16.2.4.3.1	Prior and Concomitant Medications
Listing 16.2.4.3.2	Neurological Concomitant Medications
Listing 16.2.4.3.3	Anti-Spasticity Concomitant Medications
Listing 16.2.4.3.4	Medications Used within 30 Days Prior to Screening
Listing 16.2.4.3.5	Physiotherapy Regimen
Listing 16.2.4.4	Baclofen History
Listing 16.2.5.1.1	Dose Administration
Listing 16.2.5.1.2	Dose Change, Sleep and Meal Information
Listing 16.2.5.2	Subject Diary
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Serious Adverse Events
Listing 16.2.8.1	Chemistry Laboratory Results
Listing 16.2.8.2	Hematology Laboratory Results
Listing 16.2.8.3	Urine Pregnancy Test Results
Listing 16.2.9	Vital Signs
Listing 16.2.10.1	Categorical 12-Lead ECG
Listing 16.2.10.2	Continuous 12-Lead ECG
Listing 16.2.11	Physical Examination
Listing 16.2.12	Neurological Examination
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]