~Sun Pharma Advanced Research Company, LTD~

[redacted]

A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Trial to [redacted] in Subjects with Spasticity due to Multiple Sclerosis (MS)

[redacted]

Statistical Analysis Plan

Version *1.0*

Prepared by:

[redacted]

Approved by

[redacted]

[redacted]

[redacted]

REVISION HISTORY

Version No.	Version Date	Description of Modifications
0.1	22Jul2014	[redacted]
0.2	28Apr2017	[redacted]
0.3	22May2017	[redacted]
1.0	31May2017	[redacted]

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse event
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
CS	Clinically significant
[redacted]	[redacted]
ECG	Electrocardiogram
[redacted]	[redacted]
ITT	Intent-to-treat
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NCS	Not clinical significant
NE	Not estimable
PT	Preferred term
[redacted]	[redacted]
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGIS	Subject's Global Impression of Severity
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

1. Introduction

The purpose of the Statistical Analysis Plan is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose:

- To prospectively (a priori) outline the types of analyses and data presentations that will address the study objectives outlined in the protocol.
- To explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of statistical analysis in the pharmaceutical industry.

2. Objectives

The objective of this trial is [redacted] in alleviating spasticity [redacted].

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a double-blind, [redacted] a single [redacted], in subjects with spasticity due to MS. [redacted].

Upon completion of informed consent, at the start of [redacted]. Safety and efficacy assessments will be performed according to the schedule of events in Section 11.5. [redacted]

[redacted] following the completion of exit assessments.

3.2. Study Endpoints

3.2.1. Efficacy Endpoints

Primary Efficacy Endpoint:

[redacted] Total Modified Ashworth Score over time [redacted]. The primary efficacy endpoint of the study [redacted] Total Modified Ashworth Scores [redacted] assessed on Days 23 and 24.

Secondary Efficacy Endpoints:

- [redacted] spasm frequency
- [redacted] nighttime awakening score
- [redacted] Clinical Global Impression of Change (CGIC) score on [redacted]
- [redacted] Subject's Global Impression of Severity (SGIS) [redacted]

3.2.2. Safety Endpoints

- Adverse events (AEs)
- Vital signs
- 12-lead electrocardiogram (ECG)
- Laboratory tests

- Columbia Suicide Severity Rating Scale (C-SSRS)

4. General Statistical Considerations

In general, continuous variables will be summarized with descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum, and 95% CI) and categorical variables will be summarized with count and percentage, unless otherwise specified. If there is only one observation, the standard deviation will be displayed as NE (Not Estimable). The p-values will be two-sided and rounded to four decimal places, and a significance level of alpha (α) = 0.05 will be used to reject the null hypothesis. Baseline will be defined as the last pre-dose non-missing measurement, unless specified otherwise.

4.1. Sample Size

[redacted]

[redacted] 31 evaluable subjects in each treatment group is required to provide 90% power, assuming a common standard deviation [redacted]. To account for the drop-out rate of 30%, approximately 135 subjects will be randomized in this trial.

4.2. Randomization, Stratification, and Blinding

Eligible subjects will be randomized to receive [redacted].

[redacted] as required for regulatory reporting

purposes. [redacted]

4.3. Analysis Sets

Two analysis sets will be used in this study:

- [redacted]The Intent-to-Treat (ITT) population consists of all subjects who are randomized to a treatment, who receive [redacted]. Subjects in this population will be analyzed according to the treatment they were randomized to, regardless of any dosing error. [redacted]

- [redacted].

5. Subject Disposition

5.1. Disposition

Subject disposition will be listed and summarized for all enrolled subjects, by dose group and overall. The number and percentage of subjects who were screened, were randomized, and who are in the ITT and Safety populations will be summarized. The number and percent of subjects who completed and who discontinued the study will be summarized. The reasons for study discontinuation will be summarized for the categories below:

- Adverse Event
- Major Protocol Violation
- Lost to Follow-Up
- Worsening of Condition

- Other Reasons

5.2. Protocol Deviations

Protocol violations (i.e., divergences from the inclusion and exclusion criteria, received excluded concomitant medications, received wrong treatment or incorrect dose, and those who developed withdrawal criteria but were not withdrawn) and deviations (i.e., non-adherence to trial procedures or schedule) will be recorded on the CRF and tracked in a deviation log. Protocol violations will be summarized in a table for the ITT population, by dose group and overall. Protocol violations and deviations will be displayed in a listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

Subject demographics, including age, [redacted] sex, race and ethnicity, will be summarized with descriptive statistics for the ITT and Safety populations, by dose group and overall. Listings of individual subjects' data will also be produced.

6.2. MS Medical History

The MS medical history at screening will be summarized by [redacted] ITT and Safety Populations, by dose group and overall. This information will also be presented in a data listing.

[redacted] history will also be created.

6.4. Inclusion and Exclusion Criteria

All inclusion/exclusion information on enrolled subjects will be included in a by-patient listing. The listing will include a flag indicating whether all criteria were satisfied. For subjects who did not satisfy the criteria, the criteria number will be listed with the deviation

7. Treatments and Medications

7.1. Prior and Concomitant Medications

A medication will be categorized as prior medication if the medication end date is before the first dose date. A medication will be categorized as a concomitant medication if the medication end date is after the first dose date or is ongoing at study completion. If the start or end date of a medications is missing, it will be imputed as described in Appendix 11.4. All prior and concomitant medications will be coded to Anatomical Therapeutic Chemical (ATC) Class 3 and Preferred Name according to the latest version of the World Health Organization Drug Dictionary (WHODD).

The number and percentage of subjects in the Safety population taking prior or concomitant medications will be summarized by ATC class and Preferred Name in two separate tables, by dose group and overall. In addition, the prior medications for MS and spasticity, and the medications subjects washed out from in order to enter the study, as well as neurological and anti-spasticity concomitant medications, and concomitant medications present at Day 23 check-in will be summarized separately. Antispasticity and neurological medications will be identified via a Medial Monitor review of coded terms prior to database lock. Subject listings of prior and concomitant medications will be provided. The medications taken within 30 days prior to the screening visit will be listed in a separate listing.

7.2. Study Treatments

[redacted] Duration of exposure will be summarized descriptively using number, mean, standard deviaion, median, minimum and maximum at [redacted], by dose group and overall. Counts and percentages will be provided for subjects exposed for [redacted]

Study treatment compliance rate will be calculated as the ratio of the total number of tablets taken to the total number of tablets assigned, where the total number of tablets taken is ([redacted]). [redacted]. A subject listing of study treatment compliance will be provided.

8. Efficacy Analysis

This is a pharmacodynamic study. Analysis of the primary pharmacodynamic endpoint, the Modified Ashworth Score, is described in Section 8.1. Analyses for the secondary endpoints, spasm frequency, nighttime awakening due to spasms, CGIC and SGIS are described in Sections 8.2. The primary and secondary efficacy analyses will be based on the ITT population.

8.1. Primary Efficacy Analysis

[redacted] the duration of effect, p-values will be used as a guide; a hierarchical approach to the analysis of time points will be used as described below. For these reasons, the p-values will not be adjusted for the multiple comparisons performed.

The baseline total Modified Ashworth Score is defined as the total score at [redacted]. Statistical significance of [redacted] total Modified Ashworth Score will be assessed. At each time point, the change from baseline will be computed. A hierarchical testing procedure will be used to assess duration of effect separately for each dose level. [redacted] total Modified Ashworth Score as a covariate, and the interaction between treatment group and baseline Modified Ashworth Score. [redacted]

[redacted]. This procedure will be continued until reaching a time point at which the difference between active and placebo is statistically significant.

[redacted], the corresponding standard error (SE), 95% Confidence Interval (CI), and the p-value representing the significance of treatment effect will be displayed for each timepoint in a separate table. The observed score and change from baseline will be displayed in separate boxplots by time points.

8.2. Secondary Efficacy Analyses

[redacted]. For the spasm frequency and nighttime awakening score, baseline is the measurement taken at the screening visit.

8.2.1. Spasm Frequency

The [redacted] baseline spasm [redacted] will be summarized by visit. Statistical significance of treatment difference [redacted]

[redacted], 95% CI, and the p-value representing the significance of treatment effect will be displayed in a table. The change from baseline in spasm frequency will be displayed in histograms for each treatment group by visit. The actual score will be listed in a data listing.

8.2.2. Night Time Awakening Score

The nighttime awakening score will be summarized in the same way as spasm frequency. [redacted]. The observed scores will be listed in a data listing. The change from baseline in nighttime awakening score will be displayed in histograms for each treatment group by visit.

8.2.3. CGIC

The CGIC at [redacted].

8.2.4. SGIS

The SGIS will be summarized in the same way as the CGIC for the categorical outcomes [redacted].

9. Safety Analysis

Safety evaluations will be based on the incidence, severity, and causality of AEs, vital signs, Columbia-Suicide Severity Rating Scale C-SSRS, electrocardiogram (ECG), and clinical laboratory results. The safety analysis for female subjects will also include urine pregnancy results. All safety analyses will be conducted on the Safety population.

9.1. Adverse Events

Treatment-emergent adverse events (TEAEs) will be used for summary and analysis purposes. A TEAE is defined as: any new event that occurred [redacted], a condition that existed before drug administration but increased in severity, or a condition that existed prior to drug treatment but increased in frequency of occurrence. A treatment-emergent serious adverse event (SAE) is defined as any treatment-emergent event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. TEAEs will be recorded [redacted] will be coded to System Organ Class (SOC) and Preferred Terms (PTs) using the latest version of of MedDRA®.

A treatment-related AE is an event that is considered possibly or probably related to study drug, in the judgment of the investigator. If the AE start date is missing, it will be imputed as described in Appendix 11.4.

The following summaries of AEs by SOC and PT will be provided:

- Overall TEAE summary, including:
    - Incidence of subjects with one or more TEAE
    - Incidence of TEAEs by highest relationship
    - Incidence of TEAEs by highest severity
    - Incidence of TEAEs by action taken
    - Incidence of TEAEs by outcome
    - Incidence of treatment-emergent SAEs

- TEAEs by SOC and PT
- TEAEs by descending order of frequency of PTs
- TEAEs by SOC and PT and highest relationship to treatment
- Treatment-related TEAEs by SOC and PT
- TEAEs by SOC and PT and highest severity
- Treatment-related TEAEs by SOC and PT and highest severity
- TEAEs by SOC and PT and sex
- TEAEs by SOC and PT and age group
- TEAEs by SOC and PT and race
- TEAEs by SOC and PT and frequently used concomitant medications (i.e., medications used by 20% or more of the subjects overall)
- TEAEs by SOC and PT and concomitant medications present on [redacted]
- TEAEs leading to treatment discontinuation by SOC and PT
- SAEs by SOC and PT
- Fatal SAEs by SOC and PT
- Treatment-related SAEs by SOC and PT

At each level of summarization, a subject will be counted only once for each AE he/she experiences within that level. For the summary by relationship, if a subject has more than one AE on different levels, the most related AE will be counted. For the summary by severity, if a subject has more than one AE on different levels, the most severe AE will be summarized in the table. All summaries by SOC/PT will be presented in the descending order of frequency in the total column (i.e., all treatment groups combined). Data listings will be provided for all AEs, SAEs, and AEs leading to study drug discontinuation.

9.2. Clinical Laboratory Evaluations

Clinical laboratory tests performed at screening and Day 24 include the following:

Hematology:

- Red blood cell indices, including RBC count and hemoglobin
- Total WBC count
- Differential WBC count
- Platelet count

Serum chemistry:

- Sodium
- Potassium
- Chloride
- BUN
- Creatinine

A central laboratory will be used for chemistry and hematology testing. Values outside the laboratory normal ranges (see Appendix 11.6) as well as those considered clinically significant by the investigator are to be flagged as L (low) or H (high). Chemistry and hematology results will be displayed in separate data listings with abnormal values flagged. The numerical results of laboratory tests will be summarized separately for Chemistry and Hematology, including observed values, change from baseline, and shift from baseline for the L/H/Normal flags. For change from baseline summaries at [redacted] only subjects with data present at both screening [redacted] will be summarized. Due to subject dropout, this will generally reflect a smaller sample than at screening. Therefore, at [redacted] an additional baseline mean and standard deviation summary will be provided for those subjects present. The investigators will assign a rating of not clinically significant (NCS) or clinically significant (CS) to all laboratory values. The CS clarification requires reporting of the laboratory event as an AE. Clinically significant results will be flagged in data listings.

9.3. Vital Sign Measurements

Seated diastolic and systolic blood pressures and resting pulse measurements at baseline and each post-baseline timepoint will be summarized using descriptive statistics. Similarly, change from baseline to [redacted] will also be summarized. Change from baseline summaries will use subjects who have both a baseline and a post-baseline value present and will include an additional baseline mean and standard deviation summary for those subjects present. The change from baseline for vital sign measurements will be shown in a boxplot. The investigators will assign a rating of NCS or CS to all vital sign values. The CS clarification requires reporting of the vital sign value as an AE. Vital sign values will be displayed in a data listing with CS results flagged.

9.4. Physical Examination

Physical examinations will be performed at screening, the beginning of [redacted] and the end of [redacted]. The results will be displayed in a data listing.

9.5. Electrocardiogram

ECG recordings will be collected at screening, [redacted], [redacted], [redacted]. ECG measurements will be collected in triplicate, [redacted] will be calculated for ECG intervals (QT, PR, RR QRS, ventricular rate). The QT interval will be corrected for heart rate using Fridericia's correction (QTcF) and Bazett's correction (QTcB). ECG intervals will be summarized using descriptive statistics. In addition, change from baseline in ECG intervals and shift from baseline in overall ECG interpretation (Normal, Abnormal – NCS, Abnormal – CS) will be provided. Change from baseline summaries will use subjects who have both a baseline and a post-baseline value present and will include an additional baseline mean and standard deviation summary for those subjects present. All ECG results will be displayed in a data listing and the ECG abnormalities will be flagged out.

9.6. C-SSRS Assessments

The C-SSRS is assessed at screening and [redacted] and results will be summarized for the Safety Population. The suicidal ideation and suicidal behavior results will be displayed in a listing. The number and percentage of subjects who answered yes to each of the five categories in suicidal ideation and suicidal behavior will be summarized.

Suicidal ideation score is defined as the maximum suicidal ideation category present for the assessment. [redacted]. The number and percentage of subjects with any decrease in suicidal ideation score [redacted] will be summarized.

Similarly, suicidal behavior score [redacted] will be summarized. [redacted] will be constructed.

9.7. Pregnancy Test

Urine pregnancy test results for female subjects will be displayed in a listing.

9.8. Comments

Comments will be listed with the eCRF section they are associated with noted.

10. References

[redacted].

11. Appendices

11.1. List of Tables

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

11.2. List of Listings

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

11.3. List of Figures

[redacted]

[redacted]

11.5. Schedule of Study Procedures

Activities / Visit Days	[redacted]	[redacted]	Phone call	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent	X																					
Demographics	X																					
Washout[2]	X																					
Medical and medication history	X																					
C-SSRS assessment	X																					X
Urine pregnancy test	X			X																		X
Physical examination	X			X																		X
Clinical laboratory tests[3]	X																					X
12-lead ECG	X	X		X[4]					X											X 5		
Vital sign measurements[6]	X	X		X					X											X		
Randomization		X																				
Study medication [redacted]		X	X	X																		
Dosing under supervision [redacted]						X 7																
Modified Ashworth score		X		X[8]			X				X		X		X	X		X		X		
Clinical Global Impression of Change (CGIC)	X				X																X	
Subject Global Impression of Severity (SGIS)	X				X																X	
AE evaluation				X					X	X											X	X
Record spasm frequency[9]		X		X																	X	
Record nighttime awakening due to spasm score	**X**									X												
Record concomitant medication	X	X		X						X											X	
Meals[10]					X 11a			X 11		X 11		X 11		X 11			X[1] 1f		X 11			

Activities / Visit Days			Phone call																			
								b		c		d		e					g			

[1]Subject will check-out of the clinic following the .
[2]Subjects will be required to be currently receiving prior to enrollment, and

[3]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.
[4]Within 2 hours
[5]23 or 24 hours post-dose
[6]Within 10 minutes of 12-lead ECG
[7]Dosing at time "0
[8]Within 2 hours pre-dose
[9]Spasm frequency assessment

11.6 Lab Normal Ranges

[redacted]				