Statistical analysis plan Verison 9.0, 21 Sep 2017

Title of the study: A placebo-controlled randomized withdrawal evaluation of the efficacy and safety of Baclofen ER capsules (GRS) in subjects with spasticity due to multiple sclerosis

NCT number: NCT01457352

Statistical Analysis Plan

Study Title:	A Placebo-Controlled Randomized Withdrawal Evaluation of the Efficacy and Safety of in Subjects with Spasticity Due to Multiple Sclerosis
Protocol Number:	CLR_09_21
Amendment	Version 07 Amendment 04 16 Dec 2016
Sponsor:	Sun Pharma Advanced Research Company Ltd., [redacted]
Sponsor Contact:	
CRO:	
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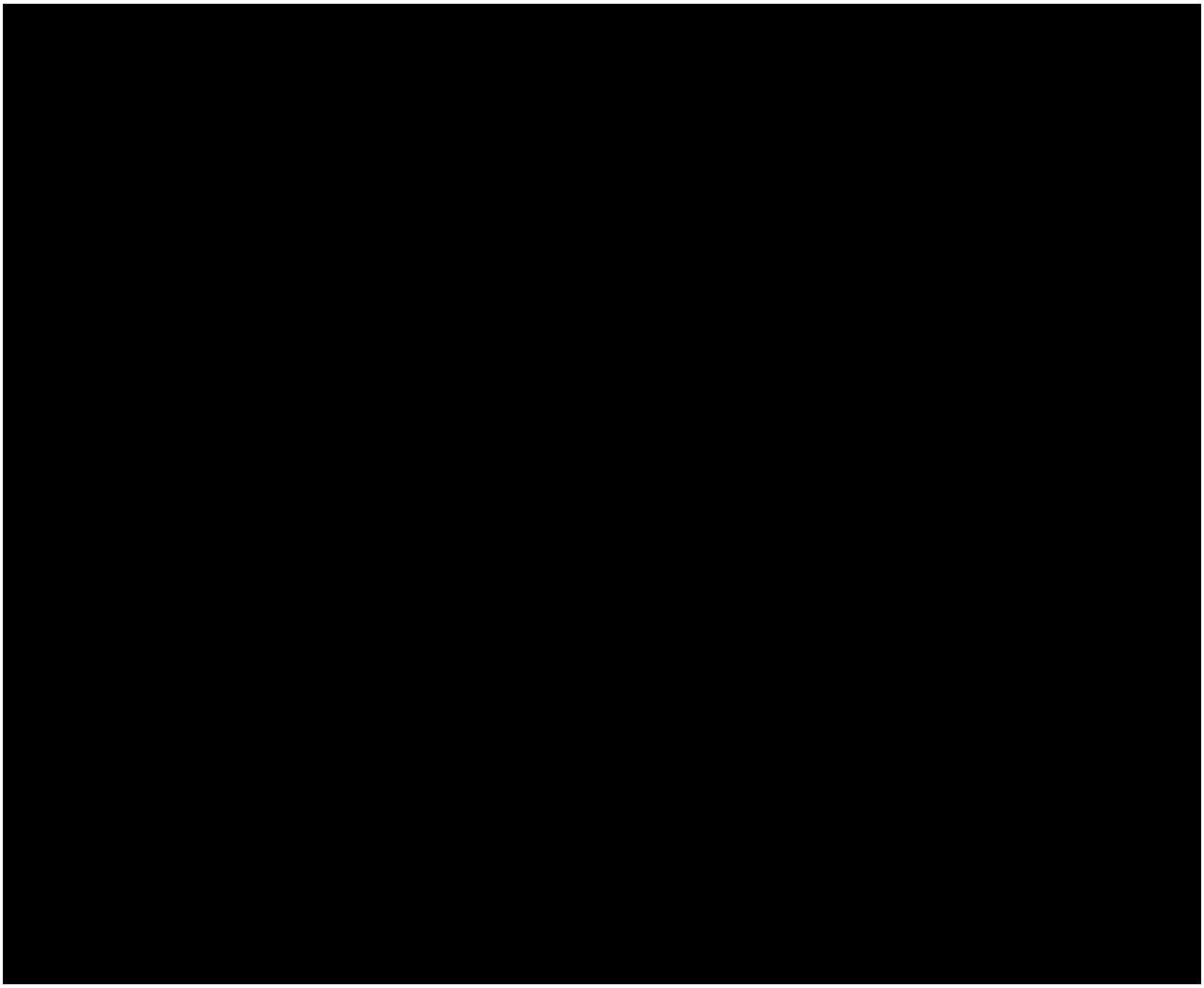
Signatory Page

This Statistical Analysis Plan was reviewed and approved by:



REVISION HISTORY

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1. LIST OF ABBREVIATIONS AND ACRONYMS

AE	**A**dverse **E**vent
ALT (SGPT)	**Al**anine amino**t**ransferase (**S**erum **G**lutamate **P**yruvic **T**ransaminase)
ANCOVA	**An**alysis of **Cova**riance
AST (SGOT)	**As**partate amino**t**ransferase (**S**erum **G**lutamate **O**xaloacetate **T**ransaminase)
BUN	**B**lood **U**rea **N**itrogen
C-CASA	**C**olumbia **C**lassification **A**lgorithm of **S**uicide **A**ssessment
CGIC	**C**linician **G**lobal **I**mpression of **C**hange
CI	**C**onfidence **I**nterval
CMH	**C**ochran **M**antel-**H**aenszel
CRO	**C**ontact **R**esearch **O**rganization
CSR	**C**linical **S**tudy **R**eport
C-SSRS	**C**olumbia – **S**uicide **S**everity **R**ating **S**cale
ECG	**E**lectrocardiogram
eCRF	**e**lectronic **C**ase **R**ecord **F**orm/ **e**lectronic **C**ase **R**eport **F**orm
EDSS	**E**xpanded **D**isability **S**tatus **S**cale
e.g.	For example
ITT	**I**ntent-**T**o-**T**reat
IVRS	**I**nteractive **V**oice **R**esponse **S**ystem
IWRS	**I**nteractive **W**eb **R**esponse **S**ystem
MedDRA	**Med**ical **D**ictionary for **R**egulatory **A**ctivities
mg	**Mi**lli**g**ram
mL	**Mi**lli**l**iter
MS	**M**ultiple **S**clerosis
SGIS	**S**ubject **G**lobal **I**mpression of **S**everity
PP	**P**er **P**rotocol
SAE	**S**erious **A**dverse **E**vent
SAP	**S**tatistical **A**nalysis **P**lan
SD	**S**tandard **D**eviation
SPARC Ltd.	**S**un **P**harma **A**dvanced **R**esearch **C**ompany **Limited**
TEAE	**T**reatment **E**mergent **A**dverse **E**vent

ULN	**U**pper **L**imit of **N**ormal
VAS	**V**isual **A**nalogue **S**cale
WBC	**W**hite **B**lood **C**ell

2. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for the analysis of data from Study CLR_09_21, "A Placebo-Controlled Randomized Withdrawal Evaluation of the Efficacy and Safety of in Subjects with Spasticity Due to Multiple Sclerosis."

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 7.0 Amendent 04, 16 Dec 2016
- Electronic Case Report Form (eCRF), 09 Mar 2012

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.

[redacted] 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

3.1.1 Primary Objectives

The primary objectives are to compare the continued treatment [redacted] *versus* down-titration to placebo [redacted]

- Demonstrating efficacy of [redacted] in the treatment of spasticity
- Indirectly demonstrating
- Determining the safety profile

3.1.2 Secondary Objectives

To determine effects on another corollary measure of spasticity such as:

- Subject's assessment of spasticity severity

3.1.3 Exoploratory Objectives

[redacted]

3.2 Study Design

The study is a [redacted] multicenter, out-patient trial in subjects with spasticity due to MS (Multiple Sclerosis). The study will be performed in three parts: a 1-week open-label phase (Part 1) [redacted] a 16-week open-label phase (Part 2) [redacted] and a 4-week, double-blind, placebo-controlled, randomized withdrawal phase (Part 3). Subjects will be informed that at some time during the study, they may receive placebo, however, they will not be informed at which visit this will commence. An overview scheme of the study and the schedule of events are presented in Section 3.2.3.

Approximately 300 subjects will be enrolled to ensure that at least 240 subjects are randomized in Part 3. Subjects will be screened for eligibility within 14 days of the initial visit by medical history, recent and concomitant medication use, physical and neurological examination, 12-lead ECG, clinical laboratory testing, and assigned a subject number. Following provision of informed consent and successful screening, eligible

subjects will be enrolled in the study (Visit 1). Once on study, subjects will be seen in the clinic at the end of the 7-day (Visit 2), at which point they will be converted to . They will be seen in the clinic every 2 weeks [redacted]

. [redacted] subjects are to remain on a fixed dose for an additional 12 weeks; [redacted]

At the beginning of Week 18 (Visit 7), subjects who have remained on a fixed dose of for 12 to 16 weeks, without further need for adjustment in medication, will be randomly assigned to either remain on in the same dose or placebo for an additional 4 weeks.

The final scheduled study visit is Visit 11,

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Subjects will be evaluated for efficacy as briefly described below. The efficacy instruments and assessments are further described in Section 6.2.

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  Right and left hip flexion and abduction, knee flexion and extension, and ankle dorsiflexion and plantar flexion will be assessed using the modified Ashworth Scale, 6-point version (inclusive of 1+), rated from 0 to 4, for a total of 12 movements being evaluated. This same individual will query the subject for any changes in physiotherapy regimen. The modified Ashworth Scale assessment is further discussed in Section 6.2.1.
- Clinician Global Impression of Change (CGIC) will be assessed by the Treating Physician, [redacted]

[redacted] the CGIC will be assessed at Visits 4 and 7 [redacted] and at Visits 8,9, 10 and 11 [redacted]

- The Subject Global Impression of Severity (SGIS) [redacted] will be assessed atVisits 4, 7, 8, 9, 10, and 11. [redacted]

During the course of the study, subjects will be monitored for adverse events and vital signs (seated blood pressure, pulse, respiration, and body temperature) measured at each clinic visit. Suicidality will be assessed at every visit using the Columbia – Suicide Severity Rating Scale (C-SSRS). Clinical laboratory testing will be repeated at the end of the open-label phase, after all subjects have received a fixed-dose [redacted], and if needed, at Visit 11 (Week 22) or early termination. ECGs will be recorded at screening, after subjects have completed the run-in (Visit 2), after subjects have received for 6 weeks (Visit 4), after subjects have received for 18 weeks (Visit 7), and if needed, at Week 22 (Visit 11) or early termination. Physical and neurological evaluation will be performed at screening and if needed, at Week 22 (Visit 11) or early termination.

At the final visit [redacted] clinical laboratory testing, ECG measurement, and physical and neurological evaluation will be performed if needed. Any treatment-emergent abnormalities shall continue to be evaluated with testing as needed to follow resolution.

Subjects will be instructed that even though they may have extra medication, they should return to the clinic for their visits according to the schedule of events.

Subjects who enter the double-blind randomized withdrawal phase (Part 3) will be offered the opportunity to participate in a separate open-label trial [redacted]

3.2.1 **Sample Size Considerations**

Approximately 300 subjects will be enrolled to ensure that at least 240 subjects are randomized at the beginning of Week 14 (Visit 7).

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3.2.2 **Randomization**

Subjects who finish Visit 7 (at the beginning of Week 18) will be randomized to double-blind treatment

3.2.3 Study Assessments Schedules

Study schema and assessments are described in detail in the protocol, and summarized below in Table 1 and Table 2.

Table 1: Schema of Study Visits and Corresponding Study Week and Day

Part 1	**Part 2**																				
Open-label																	**Part 3**				
																	Double-Blind				
(1 week)	**(4 weeks)**					**(12 weeks)**											**Placebo-controlled, Down-titration Phase (4 weeks)**				
Visit Number																					
1	2	(T)	3	(T)	4	(T)		5	(T)		6	(T)		7	8	9	10	11			
Beginning of Study Week																					
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	--
Corresponding Study Day																					
1	8	15	22	29	36				64				92				120	127	134	141	148

Table 2. Study Design and Schedule of Assessments

Visit	Screening (-14 days)	(Part 1)	Open-Label (Part 2)								Double-Blind, Placebo-Controlled Down-Titration (Part 3)			
			Stabilized on baclofen ER (GRS)					Baseline						
Week		Visit 1	Visit 2		Visit 3		Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Day														
Informed consent	X													
Demographics	X													
Medical and medication history	X	X												
Physical examination[6]	X													X[2]
Neurological examination[7]	X													X[2]
Vital sign measurements[8]	X	X	X		X		X	X	X	X	X	X	X	X
	X	X												
Clinical laboratory testing[9]	X									X				X[2]
Urine pregnancy test[10]	X									X				X[2]
ECG	X[11]		X[12]				X[12]			X[12]				X[2,12]
Dispense Medication		X	X		X		X	X	X	X				
		X												
			X		X									
							X	X	X					
Randomization										X				
Down-titration / placebo										X	X	X	X	
Unscheduled Visit as needed					X		X	X	X	X				
Telephone call				X		X								
Modified Ashworth Score	X	X	X		X		X	X	X	X	X	X	X	X
							X			X	X	X	X	X
							X			X	X	X	X	X
Adverse events	X	X	X		X		X	X	X	X	X	X	X	X

assessment														
C-SSRS Assessment	X	X	X		X		X	X	X	X	X	X	X	X
Dispense and Collect Diary		X[3]	X		X		X	X	X	X	X	X	X	X[4]
Check compliance			X		X		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X		X		X	X	X	X	X	X	X	X
	X						X[5]	X[5]	X[5]	X[5]				

Urine pregnancy test for women

4. STUDY ENDPOINTS AND DEFINITIONS

4.1 Primary Efficacy Endpoint

The primary efficacy variable is the proportion of subjects who become a treatment failure during the double-blind randomized withdrawal part (Part 3). A subject's response status will be determined after database lock, but prior to unblinding the data. A subject who meets the following criterion will be considered a treatment failure:

- A CGIC of ≥ 5 ("minimally worse" to "very much worse") and at least one movement with a ≥ 1 unit increase 1 in modified Ashworth score from Baseline

Derivation of the primary endpoint is outlined in Section 6.2.1.3.

4.2 Secondary Efficacy Endpoints

- The secondary efficacy variable is the difference between treatment groups in Subject Global Impression of Severity (SGIS) scores at Visit 11. If Visit 11 is missing, the last available SGIS will be used.

4.3 Additional Efficacy Endpoints

4.4 Exploratory Endpoints

Exploratory efficacy endpoints include:

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4.5 Safety Endpoints

- Adverse Events
- Vital signs – resting pulse, sitting systolic and diastolic blood pressure, respiration, and body temperature
- Clinical laboratory tests
- 12 lead electrocardiogram (ECG)
- Neurological examinations
- Suicidality assessments
- Exposure and compliance
-
- Physical examinations

4.6 Study Definitions

4.6.1 Study Day

For purposes of describing days on study drug in data listings, data will be assigned a study day, relative to the start [redacted] at Visit 2, according to the following rules (this numbering of days differs from the Study Days as described in the protocol):

For events that occurred after Visit 2:

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

For events prior to Visit 2:

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.

4.6.2 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

5. STATISTICAL ANALYSIS GENERAL CONSIDERATIONS

5.1 Analysis Populations

Safety Population:

The safety population will be all subjects who received at least one dose of . Subjects who discontinue having received only (in Part 1) and are not available for evaluation at Visit 2 will not be included in the safety population. The Safety Population for Part 3 will be based on only those Safety subjects who received a dose of randomized study drug at Visit 7.

Intent-to-Treat (ITT) Population:

The ITT population will be defined as all subjects who are randomized to double-blind study drug at Visit 7 and subsequently received at least one dose of study medication, and have one subsequent modified Ashworth and CGIC score at the same assement.

Per Protocol (PP) Population:

The per protocol (PP) population will be defined as all subjects who are randomized to double- blind study drug at Visit 7, subsequently receive at least one dose of study medication, have at least one subsequent modified Ashworth and CGIC score at the same assement, and do not have any important protocol deviations. Protocol deviaitions will be reviewed and subjects with important/not important violations will be identified prior to unblinding the clinical database.

In addition, concomitant medications will be reviewed for anti-spasticity medication use, its dose, and the timing relative to the in-clinic assessment. Adverse events will be reviewed in a similar fashion for confounding medical conditions. Finally, confounding due to changes in physiotherapy regimen will be assessed. In-clinic Ashworth assessments that are judged to be potentially confounded will be flagged. The analysis of the PP population will exclude such potentially confounded assessments.

Analyses of the primary efficacy endpoint will be repeated using the PP population if it differs in size from the ITT population in total number by more than 10% overall.

5.2 *P*-Values

Unless stated otherwise, all significance tests will be two-sided with statistical significance (alpha, α) assessed at the 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. For intention–to-treat (ITT) efficacy data, multiple sensitivity analyses will be completed. Further details about sensitivity analyses can be found in Section 6.2.1.6.

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

An interim analysis will not be performed.

5.5 Blinded Review of Data

The checking and assessment of data to revisit the proposed methods of statistical analysis for the purpose of finalizing the planned analysis prior to the breaking of the blind will be conducted by The following lists some of the aspects of the blinded data review that would be considered:

- Checking of data for important/not important protocol deviations;
- Precise determination of analysis populations (intent-to-treat, per-protocol, and safety), especially which subjects will be included and which will be excluded from these populations;
- Handling of missing data;
- Outlier identification in the data and specific decisions taken on how these will be handled;
- Reviewing and identifying concomitantly used medications that have potential anti-spasticity or neurological effects;
- Reviewing and identifying changes in physiotherapy regimens;
- Reviewing and identifying adverse events for potential confounding of modified Ashworth scores.

The blinded data review will be discussed with SPARC Ltd. and will be documented in agreed and signed meeting minutes.

5.6 Final Reporting and Analysis

The randomization code will be broken at the end of the trial when all subjects have completed the study and only after all data have been entered into the database, cleaned, anti-spasticity medication use identified, and the database locked. Prior to the final unblinding, a review to identify the Per Protocol population will be undertaken. After database lock, the results will be analyzed and unblinded to the CRO statistician, programmer, and Sponsor.

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;
- Treatment Failures have been identified; and
- Protocol deviations have been identified.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the CSR.

5.7 Multi-center Studies

There are expected to be approximately 75 study sites in this study. Due to the large number of study sites and the small numbers of subjects per site, the analysis of efficacy endpoints will not include adjustments for study site.

6. STATISTICAL ANALYSIS METHODOLOGY

All data collected for this study will be presented in summary tables, figures, and listings (TFLs) as indicated in Appendix 1 of this SAP. Shells for TFLs 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 TFLs 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), median, 95% confidence interval, 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. Unless otherwise noted, all percentages will be presented to one decimal place.

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 final study disposition of each subject will be captured in the eCRF. For those subjects who do not complete the study as planned, all potential reasons for discontinuation should be provided, with one indicated as primary. The reasons for discontinuation will be categorized as described below and the following descriptive summaries of study disposition will be provided.

- Number of subjects who were enrolled in each phase of the study (Part 1, Part 2, Part 3):
  - Part 1: Received at Visit 1
  - Part 2: Received at Visit 2 (Safety Population)
  - Part 3:
    - Randomized at Visit 7
    - Dispensed Blinded Study Drug at Visit 7 (Safety Population Part 3) by treatment group and overall
    - Intent-to-Treat Population by treatment group and overall
    - Per Protocol Population by treatment group and overall
- Number and proportion of subjects (overall for Parts 1 and 2 and by treatment group and overall for Part 3) who discontinued each phase of the study.
- Number and proportion of subjects (overall for Parts 1 and 2 and by treatment group and overall for Part3) who dropped-out for each of the following categories (based on primary reason and also based on all reasons) for why a subject may be prematurely discontinued from the study.

- Withdrew Consent
- Adverse Event
- MS-related Disease Progression
-

- Required Dose Change Between Visit 4 and Visit 11
- Major Protocol Deviation
- Lost to Follow-up
- Worsening of Clinical Condition or Loss of Efficacy
- Withdrew, Per Sponsor
- Withdrew, Per Investigator
- Other

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 by the categories above. A CONSORT figure will summarize subject disposition.

6.1.2 **Demographics**

Descriptive summaries of the Safety Population will be prepared for the demographic and baseline (Screening) parameters listed below. Categorical variables will be described with counts and percentages and continuous variables with mean and 95% confidence interval (CI). These variables will also be summarized for the ITT population (and also for the PP population if it differs from the ITT population by more than 10% in overall sample size).

- Age (years)
- Age Group (<65 vs. ≥65)
- Gender
- Race/ethnicity
-
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
-

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 an important protocol deviation as described below:

> Important Protocol Deviation: A 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 the 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 violations during Part 3 will be summarized by treatment group for the ITT population, and all protocol violations and deviations will be listed.

6.1.4 Medical and Surgical History

Medical history at Visit 1 (prior conditions and present conditions) will be coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA®) and tabulated by system organ class and preferred term. A by subject listing will also be created.

6.1.5 Multiple Sclerosis History

Multiple sclerosis history at screening will be summarized by MS type, MS duration (years), course severity, symptoms/signs symmetrical, time since last relapse (months), for the ITT and Safety Populations. This information will also be presented in a data listing.

6.1.6 Spasticity History

Spasticity history at Screening will be summarized by duration of spasticity (years), daily frequency before treatment, for the ITT and Safety Populations. This information will also be presented in a data listing.

6.1.7 Concomitant Medications

Prior and concomitant medications will be coded using the most current version available of the World Health Organization Drug Dictionary (WHODRUG) March 2012. These will be summarized based on Anatomical Therapeutic Chemical (ATC) classification level 3 and Preferred Name, using incidence and percentage.

Neurological and anti- spasticity concomitant medications, identified during blinded data review, will be summarized separately overall for Part 2 and by treatment group and overall for Part 3 using counts and percentages and will be listed for all subjects.

Medications used only during Screening and/or the run-in treatment (i.e., discontinued prior to the first dose of will be considered Prior Medications. These will be summarized separately.

A Concomitant Medication is defined as a medication that was started prior to the first dose of and that continued for at least 1 day following the start of or that was started after the start of

.

Concomitant medications will be summarized separately for Parts 2 and 3. Concomitant status will be re-confirmed for Part 3.

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 the last 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. Prior medications used within 30 days of Screening will be provided in a separate listing.

6.1.8 **Exposure and Compliance**

Exposure data at each visit starting with Visit 1 will be summarized for the Safety Population for Parts 1 and 2, and for Part 3, separately. Specifically, the numbers of subjects for each dose level will be summarized with counts and percentages, and descriptive summaries (mean, 95% confidence interval, median, mode, and standard deviation) of dose at each visit will be provided. The number of tablets of exposure will be calculated for each visit and will also be summarized, where the exposure is calculated as (number of tablets dispensed – number of tablets returned). Exposure duration for each visit will also be summaried, where duration is calculated as ((last dose date – first dose date) + 1). For Safety Population Part 3, summaries will be included of down-titration exposure in the placebo randomized group.

[redacted]

Study medication will be dispensed by the site personnel with the amount dispensed and the amount returned documented in the eCRF. Treatment 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. 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%.

Individual subject listings of dosing will be prepared, based on dispense dates and subject diary data. A separate listing of drug accountability will be prepared.

6.2 Efficacy Analysis

6.2.1 Primary Efficacy Analysis

6.2.1.1 *Modified Ashworth Score*

The first and best known scale for measuring the degree of spasticity was the Ashworth scale, first developed in 1964 for use in a multiple sclerosis therapeutic trial. Spasticity accounts for much of the disability affecting lower limbs. Modified Ashworth score for the 12 movements of the lower extremities that will be measured will be evaluated as one of the primary efficacy parameters. The Ashworth assessment is the current standard for clinical assessment of lower extremity spasticity and the most commonly used tool to evaluate the efficacy of pharmacologic and rehabilitation interventions for treatment of spasticity.

The 6-point modified Ashworth scale scores are presented below:

Score	:	Analysis Value	:	Degree of Muscle Tone
0	:	0	:	No increase in tone
1	:	1	:	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance at the end of the range of movement when the affected part(s) is moved in flexion or extension
1+	:	2	:	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement
2	:	3	:	More marked increase in muscle tone through most of the range of movement, but affected part(s) easily moved
3	:	4	:	Considerable increase in muscle tone, passive movement difficult
4	:	5	:	Affected part(s) rigid in flexion or extension

*note: A change from 1 to 1+ and from 1+ to 2 will each be counted as a 1-point change

For the purposes of summaries and analyses, the analysis value above will be presented.

6.2.1.2 *Clinical Global Impressions of Change (CGIC)*

CGIC will be assessed at Visits 4, 7, 8, 9, 10, and 11.

The 7-point scale for CGIC is presented below:

Scale	:	**Overall impression**
0	:	Not assessed
1	:	Very much improved
2	:	Much improved
3	:	Minimally improved
4	:	No change
5	:	Minimally worse
6	:	Much worse
7	:	Very much worse

6.2.1.3 ***Derivation of Primary Endpoint***

The primary efficacy variable is the proportion of subjects who become a Treatment Failure during the double-blind randomized withdrawal part (Part 3). Using the primary efficacy variable, the CRO will perform a determination of failures (the blinded failure analysis). A subject's response status will be determined after database lock, but prior to unblinding the data. A subject who meets the following criterion will be considered a treatment failure:

- A CGIC of ≥ 5 ("minimally worse" to "very much worse") and at least one movement with a ≥ 1 unit increase in MAS from Baseline (A change from 1 to 1+ and 1+ to 2 will be counted as a 1-unit change)

The MAS at a given visit will be recorded for each of the 12 movements measured. [redacted]

For the Treatment Failure analysis, subjects who provide MAS and CGIC scores at Visit 11 and meet the treatment failure criterion at Visit 11, [redacted]

All other subjects will be classified as not being Treatment Failures.

6.2.1.4 *Null Hypothesis of the Primary Effiacy Analysis*

The null hypothesis is that there is no difference in the failure rates between [redacted] groups. The alternative hypothesis is that there is a difference in the failure rates between the [redacted] groups.

6.2.1.5 *Primary Efficacy Analysis*

The primary efficacy analysis will be performed using the intent-to-treat (ITT) population.

[redacted] The primary efficacy analysis will be carried out using a two-sided test at the alpha=0.05 level of significance.

. Alternate approaches to handling missing data are discussed in Section 6.2.1.6.

6.2.1.6 *Sensitivity Analysis of the Primary Efficacy Analysis*

Several sensitivity analyses of the impact of missing data on the primary efficacy endpoint will be performed. First, the primary efficacy analysis will be repeated in the PP population if it differs in size from the ITT population by more than 10% overall. In addition, the primary efficacy analysis will also be performed (using the ITT population) with different assumptions regarding the response status of a subject with missing data.

[redacted]

6.2.2 Secondary Efficacy Analyses

6.2.2.1 *Subject Global Impression of Severity (SGIS)*

Subjects will be asked to rate their overall impression of severity at Visits 4, 7, 8, 9, 10, and 11. At each of these visits, the subject is to be asked "Overall, how would you rate the severity of your spasticity over the past week?"

The 7-point scale for SGIS is presented below:

Scale		**Overall impression**
0	:	Not assessed
1	:	Normal, no spasticity
2	:	Borderline spasticity
3	:	Mild spasticity
4	:	Moderate spasticity
5	:	Marked spasticity
6	:	Severe spasticity
7	:	Worst spasticity imaginable

6.2.2.2 ***Secondary Analysis of SGIS***

The difference between treatment groups in SGIS scores at Visit 11 will be analyzed [redacted]

If Visit 11 is missing, the last available SGIS will be used.

6.2.3 Additional Efficacy Analyses

The exploratory analyses described below will be performed on the ITT population.

6.2.4.5 Time Since Last Dose

Because the timing of post-dose of assessments is a factor potentially related to efficacy, time from prior dose to modified Ashworth assessment will be summarized descriptively for each visit in Part 3 (Visits 8, 9, 10, 11), by treatment group. [redacted]

[redacted]

6.2.4.6 Subgroup Analyses

Exploratory analyses will be performed to investigate the effect of different subgroups on the primary outcome treatment failure analysis. [redacted]

[redacted]

[redacted]

6.3 Safety Analysis

6.3.1 Adverse Events

All adverse events will be coded using version 15.0 of MedDRA, which will be noted in the CSR.

Adverse events reported as pre-existing at the start of the run-in [redacted] or that emerge during the [redacted] treatment phase will be considered pre-treatment adverse events; these will be flagged in a listing.

A treatment-emergent adverse experience (TEAE) is defined as any event that only occurred after administration or that existed before drug administration but increased in severity or treatment attribution.

The duration of an AE will be calculated as:

Duration = (AE End Date – AE Onset Date) + 1

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.

The incidence of TEAEs and serious adverse events (SAEs) will be summarized [redacted]

An overall summary of TEAEs will include:

- 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

The incidence of TEAEs will be presented by system organ classification and preferred terms, by highest relationship, by treatment-related status (possibly, probably, certainly), by highest severity, by descending order of frequency of preferred terms, by dose at earliest onset for all possible dose groups, and by discontinuation status.

In addition, separate summaries of TEAEs will be prepared with subjects categorized by sex, age (below 65 years of age and 65 years of age and older), race, and renal impairment category (see Section 6.1.2).

The effects of concomitant medications and/or medical conditions present at screening 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 categorized accordingly and the incidence of TEAEs in each part summarized. Additional drugs or diagnoses of interest may be identified during the blinded data review.

The incidence of treatment-emergent serious adverse events (SAEs) will be presented by system organ classification and preferred terms, by treatment-related status (possibly, probably, certainly), and for those that are fatal.

Adverse events will be listed for all subjects, including verbatim and coded terms.

6.3.2 **Clinical Laboratory Tests**

The following tests will be performed at Screening and Visit 7 (end of open-label fixed dose phase or upon early discontinuation):

Hematology:

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

Serum chemistry (Full Panel):

- Sodium
- Potassium
- Chloride
- CO_2
- Glucose (random)
- BUN
- Creatinine
- Calcium
- ALT
- AST
- Alkaline phosphatase
- Total bilirubin
- Total protein
- Albumin

Urinalysis:

- Dipstick for pH, specific gravity
- Microscopic examination of the sediment
- Urine pregnancy test (for women) to be performed at Screening, Visit 4 (Week 6), and Visit 7 (Week 14)

Scheduled laboratory testing will be performed at a central laboratory using sex- and age-appropriate normal ranges. Laboratory tests may also be repeated between scheduled visits at the discretion of the Investigator. In addition, repeat testing should be performed at the end of the study to follow any clinically significant abnormality to resolution/stabilization.

Clinical laboratory testing (hematology, chemistry, and urinalysis) results at each visit (Screening and Visit 7) and its change from Screening (for all continuous clinical laboratory parameters) will be summarized using descriptive statistics (n, mean, 95% confidence interval, standard deviation, minimum, median, and maximum) using Conventional units. Where applicable (e.g., red blood cell indices), results will be presented separately for men and women. 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. Summaries will be based on values obtained from the central laboratory only and appropriate visit windows for categorizing results will be established prior to database lock and unblinding.

When more than one laboratory value is available within a given visit window, the latest value will be used for tabulation purposes.

Criteria for possibly significant changes have been established for selected parameters, tabulated below. The numbers and percentage of subjects meeting these criteria will be summarized.

PCS Hematology Values:

Parameter	PCS values	
	S.I. Units	Conventional Units
White blood cells (WBC)	≤ 2.8 or $\geq 16 \times 10^9$/L	≤ 2.8 or $\geq 16 \times 10^3$/L
Lymphocytes	≤ 0.5 or $\geq 4.5 \times 10^9$/L	≤ 0.5 or $\geq 4.5 \times 10^3$/L
Monocytes	$\geq 1.5 \times 10^9$/L	$\geq 1.5 \times 10^3$/L
Neutrophils	$\leq 1.0 \times 10^9$/L	$\leq 1.0 \times 10^3$/L
Eosinophils	$\geq 0.7 \times 10^9$/L	$\geq 0.7 \times 10^3$/L
Basophils	$\geq 0.4 \times 10^9$/L	$\geq 0.4 \times 10^3$/L
Red blood cells (RBC)	M: $\leq 2.5 \times 10^{12}$/L F: $\leq 2.0 \times 10^{12}$/L	M: $\leq 2.5 \times 10^6$/mm^3 F: $\leq 2.0 \times 10^6$/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: $\leq 37\%$ F: $\leq 32\%$
Platelet count	≤ 75 or $\geq 700 \times 10^9$/L	≤ 75 or $\geq 700 \times 10^3$/L

S.I. = International System of Units

PCS Blood Chemistry Parameters

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

Clinical laboratory results will be listed for all subjects, inclusive of flags for whether or not the value is outside laboratory normal range, considered significant by the Investigator, or meet the pre-specified criteria for being possibly clinically significant. Normal ranges will be noted in the listing. Values outside laboratory normal ranges as well as those considered clinically significant by the Investigator will be flagged as L (low) and H (high).

6.3.3 **Vital Signs**

Sitting diastolic and systolic blood pressures, resting pulse measurements, respiration, and body temperature (°C) at each visit will be summarized using descriptive statistics (n, mean, 95% confidence interval, standard deviation, median, minimum, and maximum) for measurements during the open-label phase and also by treatment groups during the randomized double-blind withdrawal phase. 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. Appropriate visit windows for categorizing results will be established prior to database lock and unblinding.

For summary purposes, if more than one vital sign measurement is available for an analysis visit, then the latest value of each parameter will be used.

Values considered possibly clinically significant by the Investigator are to be flagged. Criteria for possibly significant changes are presented in the table below. Number and percentages of subjects with values of clinical significance will be summarized for each study Part; in Part 3, summaries will be by treatment group.

PCS Values for Vital Signs

Parameter	PCS Criteria
Systolic Blood Pressure	≤ 90 mmHg and a decrease of ≥ 30 mmHg from baseline* or ≥ 180 mmHg and an increase of ≥ 40 mmHg from baseline
Diastolic Blood Pressure	≤ 55 mmHg and a decrease of ≥ 20 mmHg from baseline or ≥ 90 mmHg and an increase of ≥ 30 mmHg from baseline
Pulse	≤ 50 bpm and a decrease of ≥ 30 bpm from baseline or ≥ 120 bpm and an increase of ≥ 30 bpm from baseline

6.3.4 **12-Lead ECG**

Electrocardiograms will be performed at Screening, Visits 2, 4, 7, and 11. Only one assessment will be made at Screening, while assessments will be made in triplicate at later visits. All triplicate results will be averaged for summary and analysis purposes. Parameters to be summarized include: 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 2 (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.

ECG results will be summarized by treatment group and visit. Descriptive statistics will include mean, 95% confidence interval, standard deviation, median, minimum, and maximum. Continuous ECG parameters will be summarized as change from Baseline (Visit 2). 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. Clinical interpretations will also be summarized by visit and treatment group. Any ECG abnormalities, based on clinical interpretation, will be listed.

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 Exam**

Complete physical examination is to be performed at Screening and, as needed in response to changes in medical history, at the final study visit (Visit 11, or earlier in the event of premature termination). The complete examination will consist of evaluation of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, lymph nodes, abdomen, and extremities. Brief, targeted physical examinations are to be performed at other visits as necessary in response to clinically significant adverse events.

Descriptive statistics will be provided for proportions of subjects with abnormalities on physical examination. Physical 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 **Neurological Examinations**

Neurological examination sufficient to establish the EDSS score is to be performed at Screening. The examination is to consist of an evaluation of mental status; corneal reflexes; extra-ocular movements; facial sensation (light touch); facial strength; palatal movement; tongue movements; neck extension; neck flexion; head turning; respiration; forced vital capacity; tendon reflexes of the right and left biceps, triceps, supinator, quadriceps, and ankle (scored as 0=absent, 1=reduced, 2 =normal, 3=increased, 4=clonus); and plantar stimulation (scored as 0=no movement or flexor; 1=extensor). Targeted examination is to be repeated, as needed in response to changes in medical history, at the final study visit (Visit 11, or earlier in the event of premature termination).

Descriptive statistics will be provided for proportions of subjects with abnormalities on neurological examination. Neurological examination findings will be listed. These will be reviewed for any emergent abnormalities that could be attributed to the new dosage form.

6.3.7 **Suicidality Assessments using C-SSRS**

The Columbia Suicide Severity Rating Scale (C-SSRS) is used to assess [redacted] suicidal ideations and behaviors at Baseline, with monitoring prospectively thereafter at every subsequent visit. [redacted]

Frequencies of suicidal ideation and suicidal behavior at Baseline and during the trial (since last visit version) will be summarized.

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 Clinical Data Management System (CDMS) database. Further all tables, figures, and listings (TFLs) will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data stored in CDMS.

7.1 Programming Specifications for TFLs

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

7.2 Formatting Conventions

The following formatting conventions will be used to output TFLs:

- TFLs 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, figure, or listing) will have the following header:

Sun Pharma Advanced Research Company Ltd.
Protocol CLR_09_21 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/Figures/Listings 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., ITT Subjects from Study Site 1, Per-Protocol 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 first time in the whole set of TFLs 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 TFLs.
- 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 – ADaM 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), Q1, Q3, and N**. In addition, 95% CI will be presented when appropriate.

- Unless specified in the actual TFL shells for a study, all percentages will be rounded to 2 decimal places in all tables/figures/listings, 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

9.1 Planned Tables, Listings, and Figures

Tables and Figures:

Table 14.1.1.1	Screen Failure Summary (All Subjects)
Table 14.1.1.2	Subject Disposition (All Subjects)
Table 14.1.2	Protocol Deviations Part 3 (ITT Population)
Table 14.1.3.1	Demographics and Baseline Characteristics (ITT Population)
Table 14.1.3.2	Demographics and Baseline Characteristics in Part 2 (Safety Population)
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Table 14.1.4	Medical History (Safety Population)
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Table 14.1.10.2.2	Dosing Compliance Part 3 (Safety Population)
Table 14.2.1	Treatment Failure Rates (ITT Population)
Table 14.2.2	Subject Global Impression of Severity (ITT Population)
[redacted]	[redacted]
Table 14.2.5	Treatment Failure Rates by Gender (ITT Population)
Table 14.2.6	Treatment Failure Rates by Race (ITT Population)
Table 14.2.7	Treatment Failure Rates by Age Group (<65 or ≥65) (ITT Population)

[redacted]	[redacted]
Table 14.2.20	Time To Dropout in Part 3 (ITT Population)
Table 14.3.1.1.1	Overview of Adverse Events in Part 2 (Safety Population)
Table 14.3.1.1.2	Incidence of Treatment-Emergent Adverse Events in Part 2 (Safety Population)
Table 14.3.1.1.3	Incidence of Treatment-Emergent Adverse Events by Descending Order of Frequency of Preferred Terms in Part 2 (Safety Population)
Table 14.3.1.1.4	Incidence of Treatment-Emergent Adverse Events by Maximum Severity in Part 2 (Safety Population)
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Table 14.3.1.1.6	Incidence of Treatment-Related Treatment-Emergent Adverse Events by Highest Relationship in Part 2 (Safety Population)
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Table 14.3.1.1.13	Incidence of Treatment-Emergent Adverse Events by Renal Function in Part 2 (Safety Population)
Table 14.3.1.1.14	Incidence of Treatment-Emergent Adverse Events by Dose at Earliest Onset in Part 2 (Safety Population)
Table 14.3.1.2.1	Overview of Adverse Events by Treatment Group in Part 3 (Safety Population)
Table 14.3.1.2.2	Incidence of Treatment-Emergent Adverse Events by Treatment Group in Part 3 (Safety Population)
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Table 14.3.1.2.5	Incidence of Treatment-Emergent Adverse Events by Highest Relationship by Treatment Group in Part 3 (Safety Population)
Table 14.3.1.2.6	Incidence of Treatment-Related Treatment-Emergent Adverse Events by Highest Relationship by Treatment Group in Part 3 (Safety Population)
Table 14.3.1.2.7	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation by Treatment Group in Part 3 (Safety Population)
Table 14.3.1.2.8	Incidence of Treatment-Emergent Adverse Events by Gender by Treatment Group in Part 3 (Safety Population)
Table 14.3.1.2.9	Incidence of Treatment-Emergent Adverse Events by Age Group by Treatment Group in Part 3 (Safety Population)
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[redacted]	[redacted]

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

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