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 protocol: 17 Dec 2015

NCT number: NCT01797185

PROTOCOL
A CLINICAL EVALUATION OF THE SAFETY OF [redacted] WHEN ADMINISTERED [redacted] TO SUBJECTS [redacted] DUE TO MULTIPLE SCLEROSIS (MS): AN OPEN LABEL, LONG TERM, SAFETY TRIAL

[redacted]

Protocol No.	:	CLR_11_04
Version No./Date	:	01, 14 February 2012
Amendment No./Date	:	02, 17 December 2015
Investigational Product	:	[redacted]
Study Phase:	:	3
Sponsor:	:	Sun Pharma Advanced Research Company Ltd. 17/B, Mahal Industrial Estate, Mahakali Caves Road, Andheri (E), Mumbai 400 093, India.

1. SYNOPSIS

Name of Sponsor: Sun Pharma Advanced Research Company Ltd.	
Name of Investigational Product: [redacted]	
Name of active ingredient [redacted]	
Title of trial: A Clinical Evaluation of the Safety of [redacted] When Administered [redacted] to Subjects with Spasticity due to Multiple Sclerosis (MS): An Open Label, Long Term, Safety Trial	
Trial centers: Approximately 35-40 centers	
Trial period: The trial will continue until up to approximately 250 subjects have completed at least 26 weeks of treatment, of which 200 subjects have completed at least 1 year of treatment.	**Phase of Development:** 3
Objectives: To investigate the long term safety of [redacted] when administered [redacted] in subjects with MS aged 18 years and above.	
Methodology: This is a multicenter, open-label, safety trial in subjects with spasticity due to MS. Approximately 550 potential subjects will be screened to yield up to approximately 350 subjects enrolled from 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 will have completed at least 1 year of treatment. [redacted] Subjects who enroll in this trial and participated in the double-blind phase of study CRL_09_21 will temporarily receive blinded study medication during the first 4 weeks which will be dispensed using an electronic drug-dispensing system (IVRS/IWRS). All subjects will undergo safety assessments at Screening (Visit 1), Baseline (Visit 2), Week 4 (Visit 3), Week 12 (Visit 4), Week 26 (Visit 5) and all follow-up visits conducted every three months.	
Number of subjects planned: Approximately 550 potential subjects will be screened to yield 350 subjects 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 100 subjects will have completed at least 1 year of treatment.	
Diagnosis and inclusion/exclusion criteria: The trial will enroll male and female subjects, at least 18 years of age, with spasticity due to MS, who meet all eligibility criteria.	

Inclusion criteria:

1. Willingness to participate *and* give written informed consent
2. Men and women ≥ 18 years of age
3. Sexually active women who are of child bearing potential will practice an acceptable method of birth control for the duration of the trial as judged by the investigator. Examples of acceptable contraception are: condoms, foams, jellies, diaphragm, intrauterine device, oral or long-acting injected contraceptives, bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or having a partner who is incapable of initiating conception. The practice of contraception must have started at least 3 months prior to trial entry.
4. If female, negative pregnancy test result at Screening
5. Diagnosed with MS and a known history of spasticity
6. Completed the double-blind randomized withdrawal phase (Part 3) of trial CLR_09_21 with no major protocol violation

Exclusion Criteria:

Subjects will be excluded from the trial if any of the following exclusion criteria apply prior to enrollment:

1. History of hypersensitivity to [redacted]
2. History of alcohol abuse or use of recreational drugs within 12 months prior to Visit 1
3. History of chronic use of concomitant medications in neurologic or psychiatric illness which would affect the assessment of the safety of the trial medication
4. If the investigator feels that participation in this study is not in the best interest of the subject

Investigational product, dosage and mode of administration, and batch number:

[redacted]

Subjects enrolled following the completion of protocol CLR_09_21 will receive [redacted] as follows:

- Subjects who were randomized to [redacted] in the double-blind part of study CLR_09_21 (Part 3) will continue to receive the same dose of [redacted] as they received in study CLR_09_21.
- Subjects who were randomized to [redacted] in the double-blind part of study CLR_09_21 (Part 3), will receive [redacted] the dose of [redacted] that they received in open-label fixed dose phase (Part 2) of study CLR_09_21.

Subjects enrolled in this study who participated in the double-blind phase of study CLR_09_21 will temporarily receive blinded study medication in the first 4 weeks dispensed according to the IVRS/IWRS.

Duration of treatment: Subjects will continue to receive treatment for the length of the trial.

Criteria for evaluation:

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

Safety: The following safety parameters will be evaluated:

- Treatment Emergent AEs and concomitant medication assessments
- Vital signs (seated blood pressure and pulse)
- Clinical laboratory tests
- 12 lead electrocardiogram (ECG)
- Physical examination and neurological evaluation
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical methods:

Descriptive statistics, including the numbers, means, standard deviations, medians, minimums, maximums and 95% confidence intervals for continuous variables and the numbers and percentages for categorical variables, will be provided. Listings of individual subject's data will also be produced.

[redacted]

Subset analysis will be stratified by concomitant anti-spasticity and MS medication used [redacted] if the percentage of subjects in these stratification groups is ≥10% of the total number of subjects enrolled.

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	-	X	X	X	X
Concomitant medication and physical therapy assessments	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X
Dispense study medication	X	X	X	X	X	X
Collect study medication	-	X	X	X	X	X
Dispense / collect subject diaries	X	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.

[c]These visits will be scheduled 90 (± 5) days following the previous visit.

[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

2. TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

	Definition
AE	Adverse event
AUC	Area under the concentration-time curve
BUN	Blood urea nitrogen
C_{max}	Peak plasma concentration
C_{min}	Trough plasma concentration
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CNS	Central nervous system
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IRB	Institutional Review Board
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter
MS	Multiple sclerosis
ng	Nanogram(s)
PI	Principal Investigator
QC	Quality control
RBC	Red blood cell
SAE	Serious adverse event
SOP	Standard operating procedures
SPARC	Sun Pharma Advanced Research Company
T_{max}	Time to peak concentration
WBC	White blood cell

4. GENERAL INFORMATION

4.1. Protocol Details

Protocol Title:	A Clinical Evaluation of Safety of [redacted] when Administered [redacted] in Subjects with Spasticity due to MS: An Open Label Safety Trial
Protocol Number:	CLR_11_04
Version No./ Date:	01/ 14 Feb 2012
Amendment No./ Date:	02/ 17 Dec 2015

4.2. Sponsor and Contract Research Organization (CRO) Details

Sponsor:

Name:	Sun Pharma Advanced Research Company Ltd.
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]

CRO:

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

4.3. Person(s) Authorized to Sign the Protocol for the Sponsor

[redacted]

Signature Date

4.4. Sponsor's Medical Expert for the Trial

[redacted]

Signature Date

4.5. Investigator's Agreement

As the Investigator of this clinical trial, I confirm that I have read and understood the protocol. I agree to suitably brief my team and supervise the conduct of this clinical trial in conformity with the Good Clinical Practice guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use as well as the relevant laws, rules and regulations currently in force in my state and country.

Investigator's Printed Name : _____

Title : _____

_____ _____

Signature Date (dd mmm yyyy)

5. INTRODUCTION

This protocol describes a clinical study designed to investigate the long term safety of [redacted] when administered [redacted] in subjects with spasticity due to multiple sclerosis (MS).

This clinical trial will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

5.1. Background

MS is the most common neurological disease of young adults. MS is characterized by the appearance of scattered plaques of demyelinated axons in the central nervous system (CNS). The Multiple Sclerosis Association of America estimates that there are approximately 400,000 individuals in the United States diagnosed with MS and about 10,000 new cases per year. As reviewed by Paisley et al, spasticity is a major contributor to disability in MS.[1] It is estimated that between 40 and 75% of all subjects are affected. The survey by the MS Society[1] reported fatigue, spasticity (stiffness, spasms, or both), and problems with balance as the most commonly experienced symptoms. Overall, 64% of respondents reported muscle stiffness, 51% muscle spasms, and 74% reported stiffness, spasms, or both. Spasticity consists of an abnormal, velocity-dependent increase in the phasic and muscle tonic stretch reflexes, due to an abnormal integration of the nervous system motor responses to sensory input.

[redacted]

[redacted]

5.2.1. Nonclinical Studies

A comprehensive battery of nonclinical studies has been performed with [redacted]. [redacted]. Please refer to the Investigator's Brochure[3] for a complete summary of nonclinical data for [redacted].

[redacted]

[redacted]

[redacted]

5.3. Trial Rationale

Study CLR_11_04, Version 01 was an extension of trial CLR_09_21,[6] which is being conducted to demonstrate the efficacy and safety of [redacted] for the treatment of spasticity due to MS [redacted] Safety data will be collected for at least 26 weeks to examine the continued long-term safety of [redacted]

All subjects will immediately or within 4 weeks of study entry, receive [redacted] at a dose titrated to achieve acceptable control of their spasticity symptoms, [redacted]

6. TRIAL OBJECTIVE AND PURPOSE

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

7. TRIAL DESIGN

7.1. Type and Design of Trial

This is a multicenter, open-label, safety study in subjects with spasticity due to MS. Approximately 550 potential subjects will be screened to yield 350 subjects 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 100 subjects will have completed at least 1 year of treatment.

Subjects enrolled in clinical trial CLR_09_21 who completed the double-blind randomized withdrawal phase (Part 3) of that trial will be eligible to participate in this trial.

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

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.

7.2. Trial Endpoints

The trial endpoints to be evaluated are safety parameters including vital signs, clinical laboratory results, 12-lead electrocardiogram (ECG), physical examination and neurological examination results, and treatment emergent adverse events (AEs).

7.3. Subject Number

Subjects enrolling CLR_11_04 will retain the same subject number as was assigned to them in the CLR_09_21 trial.

The subject number will uniquely identify each enrolled subject. The subject number will appear on all study documents relating to that subject and will be cross-referenced by the subject's initials and age.

8. SUBJECT POPULATION

8.1. Number of Subjects

Approximately 550 potential subjects will be screened to yield 350 subjects 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 100 subjects will have completed at least 1 year of treatment.

8.2. Inclusion Criteria

Subjects are required to give written consent to participate in the trial. They will be informed that their primary medical practitioner and physiotherapist may be contacted to inform them of the trial and its conditions. Subjects must meet all entry criteria listed below.

1. Willingness to participate *and* give written informed consent
2. Men and women ≥ 18 years of age
3. Sexually active women who are of child bearing potential will practice an acceptable method of birth control for the duration of the trial as judged by the investigator. Examples of acceptable contraception are: condoms, foams, jellies, diaphragm, intrauterine device, oral or long acting injected contraceptives, bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or having a partner who is incapable of initiating conception. The practice of contraception must have started at least 3 months prior to trial entry.
4. If female, negative pregnancy test result at Screening
5. Diagnosed with MS and a known history of spasticity
6. Completed the double-blind randomized withdrawal phase (Part 3) of trial CLR_09_21 with no major protocol violation

8.3. Exclusion Criteria

Subjects will be excluded from the trial if any of the following exclusion criteria apply prior to enrollment:

[redacted]

2. History of alcohol abuse or use of recreational drugs within 12 months prior to Visit 1
3. History of chronic use of concomitant medications in neurologic or psychiatric illness which would affect the assessment of the safety of the trial medication
4. If the investigator feels that participation in this study is not in the best interest of the subject.

8.4. Withdrawal Criteria

The subject will receive oral and written information about the trial, which includes information about the right to withdraw from the trial at any time without prejudice to future treatment. In this case, the subject must immediately contact the investigator and inform the investigator that he/she is leaving the trial. The subject will be encouraged to provide the reason for wishing to withdraw. The subject must return the trial drug as well as undergo early study termination procedures.

The investigator must withdraw a subject from the trial in the following cases:

- Occurrence of an AE which does not justify a continuation of the trial in that subject

- Major protocol violation which jeopardizes the interpretation of that subject's data

The following are additional justifiable reasons for removing a subject from the trial:

- Subject experiences intolerable spasticity
- Subject has a treatment related SAE
- Subject becomes pregnant during the trial
- If, in the investigator's opinion, continuation in the trial would be detrimental to the subject's well being

9. TREATMENT OF SUBJECTS

9.1. Trial Medications

The study drug, [redacted] is manufactured by SPARC Ltd., India. [redacted]

The batch numbers including the certificate of analysis and stability documentation will be maintained in the trial master file.

9.2. Treatment Doses

[redacted]

[redacted] Subjects are to maintain a Subject Diary (Appendix 1) to record missed doses and other events or issues. The clinic will review the diaries with the subjects during the subsequent visits.

9.2.1. Trial 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 for the first 4 weeks of the study. [redacted] Blinded study medication for subjects in the first month of study CLR_11_04 will

ensure that the blind in study CLR_09_21 is preserved. [redacted]

9.3. Concomitant Medications

All concomitant treatments must be appropriately recorded and described in the electronic case report form (eCRF).

9.4. Study Drug Administration

Subjects will be instructed to take study medication at the same time of day [redacted]

9.5. Treatment Compliance

Treatment compliance will be measured on the basis of a capsule count by the investigator or his/her 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."

Subject Diary (Appendix 1):

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 actual 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.

9.6. Withdrawal From the Study

9.6.1. Premature Discontinuation of Subject in the Trial

The investigator will make every effort to keep each subject in the study. However, should a subject be removed from the study or elect to decline further study participation, the information will be recorded on the appropriate page in the eCRF, and the primary reason for discontinuation will be selected: 1) adverse event; 2) major protocol violation; 3) lost to follow-up; 4) worsening of clinical condition or loss of efficacy; or 5) other (for which the reason should be clearly stated).

As far as possible, all assessments and procedures scheduled for the end-of-trial visit must be performed on all subjects who receive trial medication but do not complete the trial according to protocol. The subject must return all unused investigational products.

Subjects who are withdrawn from the trial due to AEs will be treated according to established acceptable medical practice and will be followed for outcome. All pertinent information concerning the outcome of such treatment will be entered in the eCRF.

The investigator will make every effort to contact subjects lost to follow-up.

9.6.2. Discontinuation of the Trial

SPARC Ltd. may discontinue the trial at any time, for ethical, scientific, or business reasons. The investigator is entitled at any time to stop his or her participation in the trial due to medical reasons. In such a case, he/she should consult SPARC Ltd. at the earliest opportunity.

If the study is prematurely terminated or suspended, the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the regulatory authorities will be informed promptly and will be provided with the reasons for the termination or suspension by the investigator and SPARC Ltd., respectively.

10. SEQUENCE OF PROCEDURES

Table 1 summarizes all visits and study procedures by time point.

Visits will be scheduled on: Days -14 (Week -2), 1 (Week 1), 28 (Week 4), 84 (Week 12), 182 (Week 26), and at 3 month interval visits.

10.1. General Conduct of the Trial

Written informed consent will be obtained for this trial by the Principal Investigator (PI) or his/her designee from all subjects before the performance of any protocol-specific procedure.

10.2. Screening (Visit 1, Day -14 to Day -1/Week -2)

All potential subjects who have not completed CLR_09_21 will complete all CLR_11_04 assessments during the Screening Visit.

[redacted]

- Written informed consent will be obtained
- Medical history and demographic information will be obtained
- A physical examination will be performed
- A neurological examination will be performed
- A urine pregnancy test will be performed (if applicable)
- Vital Signs (sitting), after resting for 5 minutes, will be obtained
- Clinical laboratory testing will be performed including hematology (red blood cell [RBC] count, hemoglobin, total and differential white blood cell [WBC] count, platelet count), and serum chemistry including sodium, potassium, chloride, blood urea nitrogen [BUN], and creatinine
- A 12-lead ECG will be performed in triplicate
- [redacted]
- Concomitant medication and physical therapy will be recorded
- Study medication and diary will be dispensed. Study medication will be dispensed via IVRS/IWRS
- The next trial visit will be scheduled

10.3. Baseline (Visit 2, Day 1/Week 1)

During this visit, the investigator will review all entry criteria, making certain that the potential subject meets all criteria. In addition, the following procedures will be performed:

- AEs will be recorded for all subjects Concomitant medications will be recorded
- Study medication and Subject diary collected and reviewed from previous visit for compliance
- Study medication and diary will be dispensed via IVRS/IWRS
- The next trial visit will be scheduled

10.4. Visits 3 (Day 28 ± 5 days/Week 4) and 4 (Day 84 ± 5 days/Week 12)

- Vital Signs (sitting), after resting for 5 minutes, will be obtained
- A 12-lead ECG will be performed in triplicate
- [redacted]
- Concomitant medication and physical therapy will be recorded
- AEs will be recorded
- A urine pregnancy test will be performed
- Study medication and Subject diary collected and reviewed from previous visit for compliance
- Study medication and subject diary will be dispensed
- The next trial visit will be scheduled

10.5. Visit 5 (Day 182 ± 5 days/Week 26), or Premature Termination

- Physical and neurologic examinations will be performed during Visit 5, but will be performed as needed during the Premature Termination visit to follow the resolution of any adverse events
- A urine pregnancy test will be performed
- Vital Signs (sitting), after resting for 5 minutes, will be obtained
- Clinical laboratory testing will be performed including hematology (RBC count, hemoglobin, total and differential WBC count, platelet count), and serum chemistry including sodium, potassium, chloride, BUN, and creatinine
- A 12-lead ECG will be performed in triplicate. 12-lead ECG should be performed at the Premature Termination visit, as needed, in order to follow adverse events to resolution.
- C-SSRS assessment will be performed
- Concomitant medication and physical therapy will be recorded
- AEs will be recorded
- Study medication and Subject diary collected and reviewed from previous visit for compliance
- Study medication and subject diary will be dispensed
- The next trial visit will be scheduled

10.6. Visits Every 3 Months after Visit 5 (90 ± 5 days following Visit 5 and all subsequent visits)

- Concomitant medication and physical therapy will be recorded
- AEs will be recorded
- A urine pregnancy test will be performed
- C-SSRS assessment will be performed
- Study medication and Subject diary will be dispensed (for subjects continuing on treatment only)

- Study medication and Subject diary collected and reviewed from previous visit for compliance
- The next trial visit will be scheduled

10.7. Unscheduled Visits

- Concomitant medication and physical therapy will be recorded
- AEs will be recorded
- Study drug dose may be adjusted per Sections 9.2.2 and 9.2.3
- Study medication collected and reviewed for compliance
- Study medication will be dispensed as required
- The next trial visit will be scheduled

11. PROCOTOL PROCEDURES

11.1. Enrollment

Enrolment should only occur once subject eligibility is confirmed. Each successive subject will be assigned a unique identification number.

11.2. Assessment of Efficacy

This is a safety trial and efficacy will not be assessed.

11.3. Assessment of Safety

The PI and/or the study staff will monitor the subjects throughout the trial period.

The following safety assessments will be made:

- AEs
- Vital signs (seated blood pressure and pulse)
- Clinical laboratory tests
- 12 lead ECG in triplicate
- Physical examination and neurological evaluation
- C-SSRS

11.3.1. Adverse Events

An AE is any untoward medical occurrence during treatment with a pharmaceutical product in a subject that does not necessarily have a causal relationship with the treatment being administered. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An untoward medical event occurring prior to the start of study treatment does not meet the above mentioned definition of an AE. Nevertheless, pre-dosing medical history and physical examination anomalies must be documented in the appropriate section of the eCRF. Each subject will be queried for the occurrence of baseline medical anomalies or conditions prior to study drug administration. Included will be an assessment of their grade (mild, moderate, or severe). These events will be reported under medical history or physical examination. During and following a subject's participation in this trial, the investigator must ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values, related to the trial. The subject will be treated and/or followed up until the symptom(s) returns to normal or stabilizes, as judged by the PI. For data management purposes, for subjects completing the study, follow-up information on AE will be terminated at 30 days from the time of onset of the adverse event.

11.3.2. Serious Adverse Events

An SAE or serious adverse drug reaction is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
  Or
- Is a congenital anomaly/birth defect

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3.3. Pregnancy

A urine pregnancy test will be performed at Visit 1 and at all post-baseline visits. Subjects with a positive test will be excluded from further participation in the trial and the pregnancy will be monitored by the clinic to term. Sexually active women of child-bearing potential will be instructed to practice an acceptable method of birth control for the duration of the trial as stated in the entry criteria. However, if a subject becomes pregnant during the trial, the pregnancy will

be recorded as a significant medical event. The pregnancy will be followed until its outcome, and the outcome will be reported as a significant medical event.

11.4. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

11.4.1. Eliciting, Documentation and Reporting of Adverse Events, Intercurrent Illnesses, and Subject Diaries

Information on AEs will be derived by questioning the subjects in general and unbiased terms (eg, "How do you feel?" or "How have you been feeling since the last study visit?"), by subjects' spontaneous reports, or by observation. The subject diaries will also be reviewed with the subject for the presence of potential AEs.

AEs will be documented on the source document. The AE will be entered to the AE eCRF pages. The following information will be given for each AE: description of the AE, start date, stop date, severity, action taken, outcome, seriousness, and relationship to the trial medication.

11.4.1.1. Rating of Adverse Events

The following system will be used to assess treatment relationship as well as intensity of the AEs.

Table 2: Criteria to Rate Treatment Relationship of Adverse Events

TERM	DEFINITION*	CLARIFICATION
Unrelated	Those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, *etc*.)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (Improbable temporal relationship) from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could also be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug.
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required tofulfil this definition.	1. It follows a reasonable temporal sequence from administration of the drug. 2. It could not be readily explained (unlikely) by the patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. 4. No rechallenge information is available or possible.
Certainly	A clinical event, including laboratory test abnormality,	1. It follows a plausible time sequence to drug intake, this means that there

TERM	DEFINITION*	CLARIFICATION
	occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.	is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically; eg pharmacokinetics and type of reaction. 2. It could not be explained by patient's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions (i.e. no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. *This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive rechallenge observation).* 5. It reappears upon readministration of the drug (only if ethically correct ie, in case of non-serious, and easily treatable adverse events).

- *http://www.who-umc.org/Graphics/24734.pdf (as accessed on 19-Nov-2011).

The intensity of an adverse event is characterized as:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE, which prevents normal daily activities.

11.4.1.2. Documentation and Reporting of Immediately Reportable Adverse Events

The subject will be examined for any new medical conditions, worsening of the pre-existing ones, or change in the frequency of pre-existing medical condition. Any clinically significant change in pre-existing conditions, new conditions, or change in the frequency of pre-existing conditions post study drug dosing should be entered on the AE page of the eCRF and any medication given in response to the condition should be listed on the concomitant medication page.

All SAEs, whether or not considered attributable to the study drug, must be reported, in the eCRF and on a separate SAE Report Form according to the following procedures. As much information as possible should be supplied at the time of the initial report with at least the following information:

- Name, address, and telephone number of the reporting investigator
- Investigational product(s)
- Protocol number
- Subject identification number, initials, sex and date of birth

- Description of the AE, reason for serious status, measures taken and outcome (if resolved)
- Likelihood of drug causation of the adverse event assessed by the investigator.

All SAE Reports must be reported to the Clinical Drug Safety Department of the CRO. Copies will be then forwarded to the Sponsor and the Sponsor's Designee for Regulatory Reporting within 24 hours of receipt.

Reports will be addressed to:

[redacted]

The investigator will report all SAEs to the IRB/IEC within 7 working days of the investigator becoming aware of the event. The investigator will inform the IRB/IEC about any SAE occurring during the course of this trial that could adversely affect the safety of the subjects or the performance of the trial.

Any unexpected and study drug-related SAE, which is reported during the course of this study, will be expeditiously reported by the Sponsor or designee to the appropriate regulatory agencies as described in the relevant ICH (E6; Guideline for Good Clinical Practice) and FDA (Safety Reporting Requirements for INDs and BA/BE Studies) guidance documents. The reporting of any unexpected and drug-related SAE will be immediately shared with all participating investigators in the [redacted] program, as mandated in the referenced regulatory guidance documents. All SAEs must be reported, whether or not considered attributable to the study drug on a separate SAE Report Form. The information in the SAE Form will comprise of at least the data described above.

11.4.1.3. Follow-Up of Subjects after Adverse Events (Serious and Non-Serious)

11.4.1.3.1. Unresolved Events

If an AE/SAE is present when the subject has completed the main trial period, the course of the event post-study must be followed as previously described.

11.4.1.4. Post-trial Events

Any AE/SAE that occurs within 30 days after the end of the trial should be reported. Such events will be included in the safety analysis of the trial.

AEs continuing after end-of-trial will be followed up by telephone or with visits at the discretion of the investigator. Any AE which remains unresolved after completion of the trial requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found.

11.4.2. Vital Sign Measurement

Vital signs will be measured at Visits 1, 3, 4, and 5. Measurements will be made with the subject in a seated position (after resting for at least 5 minutes). Vital sign results will be evaluated against pre-specified criteria for clinically significant changes.

11.4.3. Clinical Laboratory Testing

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:
    - Sodium
    - Potassium
    - Chloride
    - BUN
    - Creatinine

Results for clinical laboratory parameters will be evaluated for clinically significant values according to pre-specified criteria. Laboratory tests may also be repeated between scheduled Screening Visits and Visit 5 at the discretion of the investigator.

11.4.4. 12-Lead ECG

ECG will be performed at Visit 1 (Week -2), Visit 3 (Week 4), Visit 4 (Week 12), Visit 5 (Week 26), and during the premature termination visit (if applicable).

ECG measurements will be collected in triplicate 2 minutes apart and read at the site. The following intervals will be collected: PR interval, QRS, and ventricular rate; the presence of T-waves will be noted.

A clinically significant change in any post-dosing ECG will be reported as an AE.

11.4.5. Physical and Neurological Examinations; Physical Therapy Assessments

Complete physical and neurological examinations are to be performed at Visit 1 (Week -2), Visit 5 (Week 26), and the Premature Termination Visit (as needed during the Premature Termination visit to follow the resolution of any adverse events).

The complete physical 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 AEs.

The neurological 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).

Concurrent physical therapy will be assessed at every visit.

11.4.6. Columbia Suicide Severity Rating Scale (C-SSRS)

[redacted]

12. STATISTICAL PLAN

12.1. Sample Size

Approximately 550 potential subjects will be screened to yield 350 subjects 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 100 subjects will have completed at least 1 year of treatment.

12.2. Definitions

12.2.1. Safety Population

The safety population will be all subjects who received at least one dose of [redacted] and have subsequent contact with the clinic.

12.2.2. Observational Period

At the time of the NDA submission, an interim report will be prepared and timed such that it will include at least 350 subjects enrolled in approximately 35-40 centers, in order to obtain safety data from up to approximately 250 subjects who have completed at least 26 weeks of treatment and at least 100 subjects will have completed at least 1 year of treatment. [redacted].

12.3. Statistical Analysis

12.3.1. Demographics and Background Characteristics

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, will be provided. Listings of individual subject's data will also be produced.

- Age (years)
- Sex
- Race/ethnicity
- Renal function (blood urea nitrogen and serum creatinine)
- Duration of MS
- Type of MS

Medical history at Screening Visit (prior conditions and present conditions) will be tabulated by body system, both with a summary of incidence by diagnosis and the numbers and proportions with any abnormality. A by-subject listing will be created.

12.3.2. Trial Disposition and Dosing

The following descriptive summaries of trial disposition and dosing will be provided.

12.3.2.1. Subject Disposition Criteria

- 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 (Section 9.6.1):
    - 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.

12.3.2.2. Dosing

Dosing data at each visit will be summarized. Specifically, the numbers of subjects for each dose level and descriptive summaries (mean, median, and standard deviation) of dose at each visit will be provided. Individual subject listings will be prepared.

For [redacted], the starting dose, titration frequency, and maintenance dose will be noted and presented using descriptive statistics

12.3.3. Analysis of Safety Variables

12.3.3.1. Adverse Events

All AEs will be coded in a standardized manner for regulatory activities. All AEs will be coded by system organ classification and preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA®). A AE is defined as: any new event that occurred after [redacted] administration, 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.

Medical history and physical examination anomalies that existed prior to Visit 1 will be considered baseline, abnormal, medical conditions, and will be described in the medical history or physical examination CRFs. These will be summarized separately.

The incidence of AEs and SAEs will be summarized by relationship to the trial treatment, by severity, and by action taken. In addition, separate summaries will be prepared with subjects categorized by sex, age (below 65 years of age and 65 years of age and older), and race.

The effects of concomitant 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 categorized accordingly and the incidence of AEs in each part summarized.

12.3.3.2. Vital Signs

Vital sign measurements Visits 1, 3, 4, and 5 will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Similarly, change from Visit 1 at each visit will be summarized using descriptive statistics.

Values considered clinically significant by the investigator are to be flagged. Criteria for possibly significant changes will be established a priori. Number and percentages of subjects with values of clinical significance will be summarized.

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.

12.3.3.3. Clinical Laboratory Tests

Clinical laboratory testing (hematology and chemistry) results at Visit 1 relative to Visit 5 (Week 26) will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum). Change from Visit 1 to Visit 5 will also be summarized.

Values outside the laboratory normal range as well as those considered clinically significant by the investigator 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 will be established a priori for selected parameters. The numbers and percentages of subjects meeting these criteria will be summarized.

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.

12.3.3.4. 12-Lead ECG

Any ECG abnormalities, based on clinical interpretation, will be listed and reviewed for any emergent abnormalities that could be attributed to the new dosage form. Proportion of subjects with change from baseline will be summarized.

12.3.3.5. Physical and Neurological Examinations

Descriptive statistics will be provided, by treatment group, for proportions of subjects with abnormalities on physical and neurological examinations. 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.

12.3.3.6. Suicidality Assessment using C-SSRS

[redacted] No inferential testing is planned. Results of the C-SSRS and the C-CASA categorization will be listed for each subject.

12.3.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHODRUG and will be summarized using counts and percentages.

Neurological and anti-spasticity concomitant medications will be summarized separately using counts and percentages and will be listed for all subjects.

All recently used (within 30 days prior to Visit 1) concomitant medications will be listed for all subjects.

Changes in physical therapy regimens (screening through final visit) will be assessed.

12.3.5. Subset Analysis

Subset analysis will be planned depending on concomitant [redacted] medication used, [redacted] of the total number of subjects enrolled.

12.3.6. Interim analysis

For regulatory purposes, interim reports of safety data accrued will be prepared annually following the statistical analysis described in the Section 13.3.

12.4. Procedure for Amendments to Statistical Plan

It is intended that all statistical analyses specified in this protocol will be performed. However, it is conceivable that due to the study observations, some scheduled analyses may not be performed. In addition, trial observations or analysis results may suggest the need for additional statistical analyses of the collected trial data. In either case, deviations (subtractions or additions) from the planned statistical analysis will be fully described in the final clinical trial report.

13. TRIAL DRUG MANAGEMENT

13.1. Packaging and Labeling

Packaging and central distribution will be performed by [redacted]

[redacted]

All used and unused supplies will be retrieved from the investigators at the end of the trial.

All study medication labeling will contain all information required for compliance with regulatory requirements. The storage conditions for the trial medication will be described on the medication label.

13.2. Blinding

[redacted]

13.3. Storage

All trial mediation will be stored in a securely locked cabinet, [redacted] and protected from light and moisture. Access should be strictly limited to the investigators and their designees. Neither the investigators nor any designees may provide [redacted] to any subject not participating in this protocol.

13.4. Administration

See Section 9.2 of the protocol for details.

13.5. Accountability

[redacted]

When the trial is completed, all unused investigational products must be returned to the Sponsor unless the Sponsor has approved other arrangements. Any destruction of investigational products must be performed in accordance with the documented approved procedure from the Sponsor.

At the completion of the trial, there will be a final accountability of drug received, drug used, and drug returned/destroyed. This reconciliation will be logged on the cumulative drug accountability form, signed and dated. Any discrepancies must be investigated, resolved, and documented prior to return or destruction of unused trial drug.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Monitoring

On-site monitoring will be performed before, during, and after the trial. The monitor will ensure that the trial is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements. The monitor will check the accuracy and completeness of the eCRF entries, source documents, and other trial-related records against each other. The investigator will provide direct access to source data/documents for trial-related monitoring. It is important that the investigator and/or other staff are available at these visits. The investigator should maintain source documents such as laboratory reports, history and physical examination reports, etc., for possible review.

The monitor will follow written SOPs as well as those procedures that are specified by the CRO for monitoring a specific trial. The monitor will record the date of each visit together with a summary of the status and progress of the trial. Proposed actions will be confirmed with the investigator in writing.

14.2. Documentation at the Trial Site

All data relating to the trial will be documented in the eCRF. This eCRF is developed to record the data requested by the protocol. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRFs.

At the beginning of the trial, a site master file will be established at the investigational site. The investigator will maintain the trial documents as specified in the ICH Guideline of GCP and as required by the applicable regulatory requirements. The investigator will take measures to prevent accidental or premature destruction of these documents.

Prior to the start of the trial, a signature and delegation list will be completed showing the signatures and hand-written initials of all who are authorized to entry data or make corrections in the eCRF.

The investigator will permit trial-related monitoring, audits, and regulatory inspection, providing direct access to source data/documents.

14.3. Subject's Data and Data Protection

To protect the subject's identity, subject initials and a subject number will be assigned by the investigator to each trial subject and used in lieu of the subject's name when the investigator reports AEs and/or other trial-related data. Personal information will be treated as confidential but may need to be reviewed by authorized representatives of the CRO (monitor and auditor) and regulatory authorities. The subject's consent for direct access to his original medical records for data verification purposes has to be obtained prior to a subject's participation in the trial.

The investigator must maintain a list of names and identifying information (eg, initials, date of birth, subject identification code) of all subjects enrolled in the trial. The investigator will keep the subject identification code list in the site master file.

14.4. Data Management and Analysis

Data management based on GCP refers to the activities defined for achieving routines for entering subject information in a database in an efficient and error-free manner.

Data management routines include procedures for handling the eCRFs, database set up and handling, data verification, data validation, database quality control (QC), and documentation of activities performed, including information on discrepancies in the procedure.

Data Manager and Biostatistician from the CRO will perform the data management and analysis.

The initial notification of SAEs will be entered into the CROs safety database for coding, medical evaluation, and notification to the Health Authorities according to national regulatory requirements. Before clean-file, reconciliation will be performed between the two databases for all SAEs.

All data will be entered into the Oracle Clinical RDC system by site personnel. All data will undergo 100% source verification at the interim site visits by the monitor. In addition all data will undergo electronic edit checks and validation. Discrepant data will require resolution by the site personnel. The data will require Principal Investigator electronic signature at predetermined time points and at the end of each trial book. When the data for a subject are declared clean (all data entered, verified, validated and resolved) the case book will be frozen. At the close of the trial, after all data has been transmitted to the statistician for final analysis; the Sponsor will authorize final database lock.

The QC of data will be performed to ensure that data entry and verification have been performed correctly in accordance to predefined instructions.

When the data have been entered, verified, and validated, the database will be locked for the analysis to start (Clean File).

14.5. Amendments to the Protocol

The investigator will not implement any deviation from, or changes to the protocol without agreement by Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazards to trial subject or when the changes involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change in telephone numbers).

All changes or deviations of the trial must be confirmed in writing. Changes resulting in amendments will be made jointly between the CRO, the Sponsor and investigators. Amendments will be signed off in the same way as the protocol.

14.5.1. Emergencies

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the following person immediately by telephone at:

[redacted]

Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the trial. The eCRFs will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

14.5.2. Protocol Violations/ Deviations

Protocol violations may be defined as divergences from the inclusion and exclusion criteria, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the trial. A subject may, but is not required, to be withdrawn if it is discovered that he/she committed a protocol violation during the course of the trial. Protocol waivers will be allowed on a case-by-case basis by the Sponsor's project manager and the waiver will be documented.

A protocol deviation may be defined as an occurrence when there is non-adherence to trial procedures or schedules as specified by the protocol that does not involve inclusion/exclusion criteria or the primary endpoint and that does not place the subject at any added risk or affect the

data quality or trial outcome. Examples of "deviations" may include common out-of-window visits, a missed procedure, etc. A subject may not have to withdraw if the deviation is discovered during the course of the trial; this decision will be made by the investigator in conjunction with the Sponsor.

Protocol violations and deviations will be recorded on the appropriate eCRF page and tracked in a protocol violation and deviation log. The Medical monitor and Sponsor (or designee) should also be made aware of all protocol violations. Protocol violations and deviations must be reported in the final clinical trial report.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator and the trial monitor (or designee) will to ensure that the trial staff receives appropriate training and that any information relevant to the conduct of this trial is forwarded to other staff as appropriate.

Quality assurance and quality control systems are implemented and maintained using written SOPs to ensure that the trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Sponsor or designee at the end of the trial may conduct an internal or external audit. In such an instance, the auditor will be allowed direct access to the source medical records, the eCRFs, and the Site's master file for the trial.

Regulatory authorities worldwide may also audit the investigator during or after the trial. The investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

16. ETHICS

Before initiation of the study, Sponsor will seek permission from the regulatory authorities for conducting the trial. All documents required by the appropriate authorities will be submitted. Any notification/submission will be dated and contain sufficient information to identify the protocol.

16.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This study will be initiated after the protocol is reviewed and approved by the appropriate IRB/IEC. The approval should be kept on file in the site master file with a copy in the Sponsor's file at the CRO.

16.2. Ethical Conduct of the Trial

This study will be carried out in conformity with GCP described in Guideline E6 of the ICH. This trial will also be carried out in conformity with the laws, rules, and regulations prevailing in the state and country of the investigational site.

16.3. Subject Information and Consent

Subjects will be screened and included in the study only after giving them adequate and appropriate information, and obtaining a written informed consent. The subject will be given sufficient time to consider the trial's implications before deciding to participate. The subject will be provided with a copy of the signed informed consent form. The confidentiality of the subject's records will be maintained.

Should there be any amendments to the final protocol, such that would directly affect the subject's participation in the trial, eg, a change in any procedure, the ICF will be amended to incorporate this modification and the subject must agree to sign this amended form indicating that they re-consent to continue their participation in the trial.

The investigator is responsible for obtaining the subject's freely given written consent, including date, and thereafter sign and date the consent form by her/himself before any trial related procedure is performed.

17. DATA HANDLING AND RECORD KEEPING

The investigator must maintain all documentation related to this trial. Essential documents (as defined in the ICH Guideline for GCP) must be retained until at least 5 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Sponsor.

In any case, all trial records such as but not limited to eCRFs, regulatory documents, the subject identification code list, subject files and other source data that support eCRFs must be retained for at least 15 years after the completion or discontinuation of the trial. If the investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred and Sponsor notified in writing.

Sponsor will notify the investigator in writing when the trial-related records are no longer needed.

18. FINANCING AND INSURANCE

The Sponsor is covered by a liability insurance that also covers liability towards subjects in clinical trials. Sponsor is covered by a General and Products liability insurance that includes clinical trials.

19. PUBLICATION POLICY

The CRO and investigators agree to keep strictly confidential all unpublished information and results concerning this trial. Unpublished information must not be published or disclosed without Sponsor's prior written approval. Sponsor reserves all the rights to declare any of its data confidential or of business importance and will provide it only to the regulatory authorities of concern on request/demand.

Publications except for summaries of product characteristics are subject to the written consent of the other party of the contract, which shall not unduly be refused.

20. REFERENCES

[redacted]

21. APPENDIX

Sample Subject Diary (Protocol CLR_11_04)

[redacted]

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