Study title:
A placebo-controlled randomized withdrawal evaluation of the efficacy and safety of Baclofen ER GRS capsules in subjects with spasticity due to mltiple scerosis

Protocol number:
CLR_09_21 dated 24 Feb 2012

NCT number: NCT01457352

PROTOCOL
A PLACEBO-CONTROLLED RANDOMIZED WITHDRAWAL EVALUATION OF THE EFFICACY AND SAFETY OF BACLOFEN ER CAPSULES (GRS) IN SUBJECTS WITH SPASTICITY DUE TO MULTIPLE SCLEROSIS

Protocol No. : CLR_09_21

Version No./Date : 07/ 24 Feb 2012

Amendment No./Date : 0

Investigational Product : **Test:** [redacted]
Reference: [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.

PROTOCOL SYNOPSIS

Title: A Placebo-Controlled Randomized Withdrawal Evaluation of the Efficacy and Safety of Baclofen ER Capsules (GRS) in Subjects with Spasticity Due to Multiple Sclerosis

Study Design: This 21-week study will be performed in three parts:

[redacted] (Part 1): Open-label, run-in [redacted]

[redacted] (Part 2): Open-label part in which subjects are converted to the corresponding dose of [redacted]

[redacted] (Part 3): Double-blind [redacted])

A [redacted] Subjects will be encouraged to come for one additional unscheduled visit during this interval in order to [redacted].

The schedule of assessments is provided in Table 1.

Objectives:

Primary Objectives:
The primary objectives are to compare the continued treatment with [redacted]

- Demonstrating efficacy [redacted]
- Indirectly demonstrating [redacted]
- Determining the safety [redacted]

Secondary Objectives:
To determine effects on other corollary measures of spasticity such as:

- Subject's assessment of spasticity severity

Exploratory Objectives:
The following will be explored:

- [redacted]
- [redacted]
- [redacted]
- Effect of concomitant medication use and disease characteristics on [redacted]

Primary Efficacy Outcome: The primary efficacy outcome is the proportion of subjects who become a treatment failure during double-blind randomized withdrawal (Part 3). Each subject's response 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

[1] A change from 1 to 1+ and 1+ to 2 will be counted as a 1-unit change

	The modified Ashworth score will be assessed at each clinic visit, recorded for each of the 12 movements evaluated. The Baseline score against which worsening will be determined [redacted] For the primary efficacy analysis, subjects who provide modified Ashworth and CGIC scores at Visit 11 and meet the treatment failure criterion at Visit 11, or who have met the treatment failure criterion at any prior visit [redacted]) will be classified as being treatment failures. All other subjects will be classified as not being treatment failures.
Secondary Efficacy Outcomes:	Subject Global Impression of Severity (SGIS)
Safety Assessments:	• Treatment Emergent Adverse Events • Daytime sedation • Vital Signs (seated blood pressure and pulse) • Clinical laboratory tests • 12 Lead ECG • Physical examination and neurological evaluation • Columbia – Suicide Severity Rating Scale
Treatments:	• [redacted] • [redacted] • [redacted]
Study Population:	Subjects aged 18 years and above with spasticity due to multiple sclerosis with acceptable symptom control [redacted].
Number of Subjects:	Approximately 300 subjects will be enrolled to ensure that at least 240 subjects are randomized at the beginning of [redacted].
Number of Centers:	Up to 35 centers
Setting:	Out-patient clinics
Statistical Methods:	**Efficacy Analyses:** The primary efficacy analysis will be performed on an intent-to-treat (ITT) population, defined as all subjects who were randomized to double-blind study drug at Visit 7 and subsequently received at least one dose of study medication. [redacted]). A per protocol (PP) population may also be analyzed (if it differs from the ITT population overall by more than 10% in sample size), defined as all ITT population subjects who had at least one on-treatment assessment in Part 3, and did not have any major protocol violation (such as poor compliance). [redacted]

[redacted].

Sensitivity analyses of the primary endpoint will be performed. These will include [redacted] n.

The secondary efficacy outcome is Subject Global Impression of Severity (SGIS). The change in the SGIS from Visit 7 (reference) to Visit 11 will be analyzed using the Mantel-Haenszel test stratified by stabilized dose level. [redacted].

[redacted].

Safety Analyses:
The incidence of treatment-emergent AEs (TEAEs) and SAEs will be summarized for the open-label [redacted] dose conversion / fixed dose phases [redacted], and also by treatment group during the randomized withdrawal phase (Part 3). A TEAE is defined as any event with an onset after the first dose received in a given study phase or that was pre-existing but worsened in severity or increased in treatment attribution; for the randomized withdrawal part, emergent events will be summarized by randomized double-blind treatment group. Adverse events reported as pre-existing prior to run-in [redacted] treatment or that emerge during the [redacted] treatment phase will be considered pre-treatment adverse events. The incidence of TEAEs will be presented by system organ classification and preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA®), by causality, by severity, and by action taken. Analyses of subjects grouped by demographic, baseline disease characteristics, and concomitant medication use will also be undertaken.

[redacted].

Prior and concomitant medications will be coded using WHODRUG and will be summarized using counts and percentages. Possible anti-spasticity medications will be identified during blinded data review; these will be summarized separately.

Vital sign measurements (sitting systolic and diastolic blood pressures and resting pulse) and clinical laboratory testing results at each visit will be summarized using descriptive statistics. Criteria for possibly clinically significant changes will be established *a priori*. Summary of vital signs and laboratory measurements with clinically significant changes will be provided.

ECG interval data and ventricular rate will be summarized at each time point, both as absolute values and as change from Visit 2. Criteria for possibly significant values and changes will be established *a priori*.

Physical examination and neurological evaluation findings will be summarized. These will be reviewed for any emergent abnormalities that could be attributed to the new dosage form.

Columbia – Suicide Severity Rating Scale (C-SSRS) will be used to assess suicidality.

Subject listings will be provided for all safety parameters as well as recently and concurrently used medications.

Table 1: STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

Visit	Screening (-14 days)	[redacted]Run-In	Open-Label[redacted]						Double-Blind, Placebo-Controlled Down-Titration			
						Baseline						
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Week		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Informed consent	×											
Demographics	×											
Medical and medication history	×	×										
Physical examination[6]	×											×[2]
Neurological examination[7]	×											×[2]
Vital sign measurements[8]	×	×	×	×	×	×	×	×	×	×	×	×
[redacted]		x										
Clinical laboratory testing[9]	×							×				×[2]
Urine pregnancy test[10]	×							×				×[2]
ECG	×[11]		×[12]		x[12]			×[12]				×[2, 12]
Dispense Medication		×	×	×	×	×	×	×				
[redacted]		×										
[redacted]			×	×								
[redacted]					×	×	×					
Randomization								×				
[redacted]								×	×	×	×	
Modified Ashworth Score	×	×	×	×	×	×	×	×	×	×	×	×
Clinician Global Impression of Change (CGIC)					×			×	×	×	×	×
Subject Global Impression of Severity (SGIS)					×			×	×	×	×	×
Adverse events assessment	×	×	×	×	×	×	×	×	×	×	×	×
C-SSRS Assessment	×	×	×	×	×	×	×	×	×	×	×	×
Dispense and Collect Diary		×[3]	×	×	×	×	×	×	×	×	×	×[4]
Check compliance			×	×	×	×	×	×	×	×	×	×
Concomitant medications	×	×	×	×	×	×	×	×	×	×	×	×
Pharmacokinetic blood sampling	×				×[5]	×[5]	×[5]	×[5]				

[1] [redacted]
[2] Tests and measurements to be performed if needed
[3] Dispense diary only
[4] Collect diary only

[5] Subjects will be encouraged to come for one additional unscheduled visit between [redacted]
[6] The complete examination will consist of evaluation of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, lymph nodes, abdomen, and extremities
[7] 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).
[8] Resting pulse and blood pressure measurement (sitting)
[redacted]
Urinalysis: Dipstick for pH, specific gravity, Microscopic examination of the sediment
[10] Urine pregnancy test (for women)
[11] Done only one time
[12] Done in triplicates at two minutes intervals

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LIST OF ABBREVIATIONS

Abbreviation	Expanded Form
ADR	**A**dverse **D**rug **R**eaction
AE	**A**dverse **E**vent
ALT (SGPT)	**A**lanine amino**t**ransferase (**S**erum **G**lutamate **P**yruvic **T**ransaminase)
ANCOVA	**A**nalysis of **Cova**riance
AST (SGOT)	**A**spartate amino**t**ransferase (**S**erum **G**lutamate **O**xaloacetate **T**ransaminase)
BUN	**B**lood **U**rea **N**itrogen
°C	**D**egree (**C**elsius)
C-CASA	**C**olumbia **C**lassification **A**lgorithm of **S**uicide **A**ssessment
[redacted]	[redacted]
CI	**C**onfidence **I**nterval
CNS	**C**entral **N**ervous **S**ystem
CRF	**C**ase **R**ecord **F**orm/ **C**ase **R**eport **F**orm
CRO	**C**ontact **R**esearch **O**rganization
C-SSRS	**C**olumbia – **S**uicide **S**everity **R**ating **S**cale
DCF	**D**ata **C**larification **F**orm
DCGI	**D**rugs **C**ontroller **G**eneral of **I**ndia
EC	**E**thics **C**ommittee
ECG	**E**lectro-**C**ardiogram
[redacted]	[redacted]
e.g.	For example
[redacted]	[redacted]
GABA	**G**amma- **A**mino-**B**utyric **A**cid
GCP	**G**ood **C**linical **P**ractice
GGT	**G**amma **G**lutamyl **T**ranspeptidase
GLUC	**G**lucose
GMP	**G**ood **M**anufacturing **P**ractice
GRS	**G**astro-**R**etentive **S**ystem
Hb	**H**emoglobin
HDPE	**H**igh **D**ensity **P**oly-**E**thylene
HIV	**H**uman **I**mmunodeficiency **V**irus
IB	**I**nvestigator's **B**rochure
ICH	**I**nternational **C**onference on **H**armonization
IEC	**I**ndependent **E**thics **C**ommittee
IP	**I**nvestigational **P**roduct
[redacted]	[redacted]
IRB	**I**nstitutional **R**eview **B**oard
ITT	**I**ntention-**T**o-**T**reat
IUD	**I**ntra-**U**terine **D**evice
IVRS	**I**nteractive **V**oice **R**esponse **S**ystem
IWRS	**I**nteractive **W**eb **R**esponse **S**ystem
LOCF	**L**ast **O**bservation **C**arried **F**orward
MAOI	**M**ono**a**mine **O**xidase **I**nhibitor
mg	**M**illi**g**ram
min	**M**inute
mL	**M**illi**l**iter
MS	**M**ultiple **S**clerosis
nSAE	**N**on-**S**erious **A**dverse **E**vent
OD	**O**nce **D**aily (every 24 hours)
SGIS	**S**ubject **G**lobal **I**mpression of **S**everity
PI	**P**rincipal **I**nvestigator
PP	**P**er **P**rotocol
QC	**Q**uality **C**heck

R&D	**R**esearch and **D**evelopment
SAE	**S**erious **A**dverse **E**vent
SAP	**S**tatistical **A**nalysis **P**lan
SOPs	**S**tandard **O**perating **P**rocedures
SPARC Ltd.	**S**un **P**harma **A**dvanced **R**esearch **C**ompany **L**imited
SUSAR	**S**uspected **U**nexpected **S**erious **A**dverse **R**eaction
TEAE	**T**reatment **E**mergent **A**dverse **E**vent
[redacted]	[redacted]
UTI	**U**rinary **T**ract **I**nfection
ULN	**U**pper **L**imit of **N**ormal
VAS	**V**isual **A**nalogue **S**cale
WBC	**W**hite **B**lood **C**ell

1 GENERAL INFORMATION

1.1 Protocol Details

Protocol Title	:	A Placebo-Controlled Randomized Withdrawal Evaluation of the Efficacy and Safety of Baclofen ER Capsules (GRS) in Subjects with Spasticity Due to Multiple Sclerosis
Protocol Number	:	CLR_09_21
Version No./ Date	:	07 / 24 Feb 2012
Amendment No./ Date	:	0

1.2 Sponsor and Contract Research Organization (CRO) Details

Sponsor

Name	:	Sun Pharma Advanced Research Company Ltd.
Address	:	17-B Mahal Industrial Estate, Mahakali Caves Road, Andheri (E), Mumbai – 400 093 India
Phone	:	+91 22 66455645
Fax	:	+91 22 66455685

CRO

Name	:	[redacted]
Address	:	
Phone	:	
Fax	:	

1.3 Person(s) Authorized to Sign the Protocol for the Sponsor

Name	:	[redacted]
Title	:	
Address	:	
Phone	:	
Fax	:	
Mobile	:	

[redacted]

08 MAR 2012

Date (dd mmm yyyy)

1.4 Sponsor's Medical Expert for the Study

Name	:	[redacted]
Title	:	
Address	:	
Phone	:	
Fax	:	
Mobile	:	

1.5 Investigator Responsible for Conducting the Study and Study Site(s)

Name	:
Title	:
Address	:
Phone	:
Fax	:
Mobile	:

Signature

Date (dd mmm yyyy)

2 BACKGROUND INFORMATION

[redacted]

2.1 Investigational Product

2.1.1 Name and Description

[redacted]

[redacted]The terms study drug, study medication, study treatment have been used interchangeably throughout the document to denote investigational product.

[redacted]

[redacted]

2.1.2 Clinical Data to Date for [redacted]

[redacted]

[redacted]

[redacted]

2.2 Summary of the Known and Potential Risks and Benefits, If Any, to Human Subjects

[redacted]

The most common adverse effects are [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3 Description of the Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

[redacted]

[redacted]

2.4 Compliance Statement for Study Conduct in Accordance with Protocol, GCP and Applicable Regulatory Requirements

The study protocol, amendments to the protocol (if applicable), the IB (Investigator"s Brochure), subject recruitment procedures (*e.g.*, advertisements), and the subjects' information and informed consent form as well as consent form updates (if applicable) will be submitted to the IRB/IEC, which is constituted according to local law to obtain approval before initiation of the study and as applicable thereafter.

The study will only be initiated after receipt of the approval from the IRB/IEC. The Investigator will report promptly to the IRB/IEC new information that may adversely affect the safety of the subjects or the conduct of the study.

The Investigator will follow the protocol in conformity with Good Clinical Practice (GCP) described in Guideline E6 of the ICH and applicable regulatory requirements.

Before admission into the study, the written informed consent form must be signed and personally dated by the subject and by the Investigator or designee who conducted the informed consent discussion. In obtaining and documenting informed consents, the Investigator must comply with the applicable regulatory requirement(s), and must adhere to GCP.

The Investigator must inform the subject of all pertinent aspects of the study including the written information approved/favorably assessed by the IRB.

2.5 Description of the Study Population

Subjects 18 years of age and older, with an established diagnosis of Multiple Sclerosis, [redacted]

2.6 References to Literature and Data that are Relevant to the Study

1. [redacted]

3 STUDY OBJECTIVES AND PURPOSE

3.1 Primary Objectives

The primary objectives are to compare the continued treatment with [redacted] for the purposes of:

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

3.2 Secondary Objectives

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

- Subject"s assessment [redacted]

3.3 Exploratory Objectives

The following will be explored:

- [redacted]
- [redacted]
- [redacted]
- Effect of concomitant medication use and disease characteristics [redacted]

4 STUDY DESIGN

4.1 Description of Type and Design of Study

The study is a 21-week (exclusive of screening) multicenter, out-patient trial in subjects with spasticity due to MS that is [redacted]. The study will be performed in three parts: a [redacted] (Part 1) in which subjects receive [redacted] a [redacted] Part 2) in which subjects are, [redacted] and a 4-week, double-blind, placebo-controlled, [redacted] (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 is presented below.

Schema of Study Visits and Corresponding Study Week and Day

Part 1	Part 2																Part 3				
	Open-label																Double-Blind				
[redacted]	C[redacted]					[redacted]											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

[redacted]

Approximately 300 subjects will be enrolled to ensure that at least 240 subjects are randomized in Part 3; [redacted]e. 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. Upon successful screening and provision of informed consent, 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 [redacted] run-in (Visit 2), at which point they will be converted to [redacted] (described in Section 4.3.1). They will be seen in the clinic every 2 weeks during the [redacted]; subjects are to be contacted by telephone during the intervening weeks [redacted]). As described in Section 4.3.1, dose adjustments will be allowed during this 4-week phase; dose adjustments may only be made at a clinic visit, including at an unscheduled meeting if needed. [redacted]

At the beginning of [redacted] (Visit 7), subjects who have remained on a fixed dose of [redacted], without further need for adjustment in medication, will be randomly assigned to either remain on [redacted] In subjects [redacted] All subjects will be seen in the clinic every week (see Table 1) or sooner, if required. [redacted] The final scheduled study visit is [redacted] Subjects will be encouraged to continue study participation to the end of the trial. In subjects [redacted]

Subjects will be instructed to take study drug at the same time of day, 30 minutes following the evening meal. Throughout the study, clinic visits should be timed to occur at approximately the same time of day relative to dosing. Clinic conditions, *e.g.*, ambient temperature and lighting, should be kept as consistent as possible. Similarly, concomitant physiotherapy should also not change during the course of the study.

Subjects will be evaluated for efficacy as briefly described below. The efficacy instruments and assessments are further described in Section 8.1.

- [redacted]. 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, [redacted] The modified Ashworth Scale assessment is further

discussed in Section 8.1.1.1.

- Clinician Global Impression of Change (CGIC) will be assessed by the Treating Physician, *i.e.*, an evaluator other than the one performing the Ashworth assessment; the CGIC will be [redacted]
- The Subject Global Impression of Severity (SGIS) over[redacted].

In addition, subjects will fill out a daily diary throughout the study assessing the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

During the course of the study, subjects will be monitored for adverse events and vital signs (seated blood pressure and pulse) measured at each clinic visit. Suicidality will be assessed at every visit using C-SSRS. Clinical laboratory testing will be repeated at the end of the open-label phase, [redacted] after all subjects have received [redacted], and if needed, a [redacted]. ECGs will be recorded at screening, after subjects have completed the 1-week Baclofen IR run-in (Visit 2), after subjects have received [redacted] for 4 weeks (Visit 4), after subjects have received [redacted] 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 included in Section 4.4.

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

4.2 Measures Taken To Avoid Bias

4.2.1 Subject Number

At Screening, after signing informed consent form, each subject will be allotted a unique 6-digit number. This number will be noted on the electronic case report form (eCRF).

[redacted]

4.2.2 Randomization

Subjects who finish [redacted] will be randomized to double-blind treatment such that they continue on their [redacted]. A computer generated material list will be produced by [redacted]

4.2.3 Blinding

For blinding purposes, each capsule will be white in color. [redacted]

4.3 Study Medication, Dose, Dosage Regimen, Dosage Form, Packaging, and Labeling

The study drug Baclofen ER Capsules (GRS) and placebo are manufactured by [redacted] The dimensions are approximately 9 mm × 24 mm. The batch numbers including the certificate of analysis and stability documentation will be maintained in the study master file.

4.3.1 Dosage Regimen

- [redacted]
  Subjects will receive [redacted] in the same dose and schedule prior to study participation

- [redacted].
  - [redacted]:

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

  - [redacted]

Subjects will be allowed [redacted], [redacted]

For purposes of determining how subjects are converted, the [redacted] Whenever a dose [redacted]

*

- Subjects will continue on , such that total exposure to . If a dose adjustment is required during this phase either due to poor tolerance or worsening spasticity, the subject will be discontinued; such a subject will not be offered participation in the separate open-label study of

- Subjects will be randomly assigned to remain on their fixed

[redacted]

4.3.2 Dispensing (Labeling and Packaging) and Compliance

[redacted]ill be performed by [redacted] respectively. Details of packaging are briefly described here and will be elaborated on in a separate packaging and distribution protocol. Drug will be [redacted]

The [redacted]

The [redacted]

The study medication will be [redacted]

[redacted] All [redacted]

[redacted]

[redacted]
Caution: New Drug – Limited by Federal (United States) Law to Investigational Use

The study medication number for the double-blind period (Part 3) will be according to the [redacted].

Individually, each wallet will have the following information in case it gets separated from the kit:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

A starter supply of each dose level will be available for the start of the study at each study site. The [redacted].

Upon receipt of the study medication supplies, an inventory must be performed and a [redacted].

4.3.3 [redacted]

[redacted]

4.3.4 Study Medication Numbering

[redacted]

4.4 [redacted]

[redacted]

4.4.1 [redacted]

- Informed consent
- Demographic details
- Medical and medication history
- Physical examination
- Neurological examination
- 'Resting pulse and blood pressure measurement (sitting)
- ECG
- Clinical laboratory testing
- Urine pregnancy test
- Modified Ashworth score
- Adverse events assessment
- [redacted]
- Concomitant medication record and description of current physiotherapy regimen
- Blood sample for baclofen plasma concentrations

4.4.2 Study Part 1 [redacted]

4.4.2.1 Visit 1 [redacted]

- Medical and Medication history
- 'Resting pulse and blood pressure measurement (sitting)
- [redacted]
- [redacted]
- Dispense subject diary
- Modified Ashworth score
- Adverse events assessment
- [redacted]
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.3 [redacted]

4.4.3.1 [redacted]

4.4.3.1.1 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- ECG
- [redacted]
- Collect and dispense subject diary
- Modified Ashworth score
- Adverse events assessment
- [redacted]
- [redacted]
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.3.1.2 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- [redacted]
- Collect and dispense subject diary
- Modified Ashworth score
- Adverse events assessment
- C-SSRS
- Assess Baclofen ER Capsules (GRS) compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.3.1.3 [redacted]

- Ask subject/ caregiver [redacted]. If subject/ caregiver reports [redacted] The visit will be recorded as un-scheduled visit.
- If subject/ caregiver reports acceptable control of spasticity, and tolerable side effects a reminder for next scheduled visit will be given.

4.4.3.1.4 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- [redacted]
- Review subject diary
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]***Stabilize on GRS***

4.4.3.2.1 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- ECG
- Dispense [redacted]
- Collect and dispense subject diary
- Modified Ashworth score
- CGIC relative to previous IR treatment and SGIS over prior week
- Adverse events assessments
- [redacted]
- Assess [redacted]
- Concomitant medication record and whether or not there is a change in physiotherapy regimen
- Blood sample for baclofen plasma concentrations

4.4.3.2.2 Visit 5 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- Dispense [redacted]
- Collect and dispense subject diary
- Modified Ashworth score
- Adverse events assessment
- [redacted]
- Assess [redacted] compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen
- Blood sample for baclofen plasma concentrations

4.4.3.2.3 [redacted]

- 'Resting pulse and blood pressure measurement (sitting)
- Dispense [redacted]
- Collect and dispense subject diary
- [redacted]
- Adverse events assessments
- [redacted]
- Assess [redacted]
- Concomitant medication record and whether or not there is a change in physiotherapy regimen
- Blood sample for baclofen plasma concentrations

4.4.3.2.4 [redacted]

If the unscheduled visit is [redacted]. If an unscheduled visit is required for another reason (other than blood collection for plasma baclofen concentration), the following evaluations should be done.

- 'Resting pulse and blood pressure measurement (sitting)
- Collect and dispense subject diary
- Modified Ashworth score
- Adverse events assessment
- C-SSRS
- Assess double-blind medication compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen
- [redacted]

[redacted]

4.4.4 Study Part 3 (4-week, double-blind, placebo-controlled):

4.4.4.1 Visit 7 (Week 18, Day 120 ± 1 day)

- 'Resting pulse and blood pressure measurement (sitting)
- ECG
- Clinical laboratory testing
- Urine Pregnancy Test
- Randomization to [redacted]
- Dispense double-blind medication pack for 28 (+4) days

- Collect and dispense subject diary
- Modified Ashworth score
- CGIC relative [redacted] and SGIS over prior week
- Adverse events assessment
- C-SSRS
- Assess Baclofen ER Capsules (GRS) compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen
- [redacted]

4.4.4.2 Visit 8 (Week 19, Day 127 ± 1 day)

- 'Resting pulse and blood pressure measurement (sitting)
- Collect and dispense subject diary
- Modified Ashworth score
- CGIC [redacted] and SGIS over prior week
- Adverse events assessment
- C-SSRS
- Assess double-blind medication compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.4.3 Visit 9 (Week 20, Day 134 ± 1 day)

- 'Resting pulse and blood pressure measurement (sitting)
- Collect and dispense subject diary
- Modified Ashworth score
- CGIC [redacted] and SGIS over prior week
- Adverse events assessment
- C-SSRS
- Assess double-blind medication compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.4.4 Visit 10 (Week 21, Day 141 ± 1 day)

- 'Resting pulse and blood pressure measurement (sitting)
- Collect and dispense subject diary
- Modified Ashworth score
- CGIC [redacted] and SGIS over prior week
- Adverse events assessment
- C-SSRS
- Assess double-blind medication compliance

- Concomitant medication record and whether or not there is a change in physiotherapy regimen

4.4.4.5 [redacted]

- Physical examination (as needed to follow adverse events to resolution)
- Neurological examination (as needed to follow adverse events to resolution)
- 'Resting pulse and blood pressure measurement (sitting)
- Clinical laboratory testing (as needed to follow adverse events to resolution)
- Urine pregnancy test (as needed)
- ECG (as needed to follow adverse events to resolution)
- Collect subject diary
- Modified Ashworth score
- CGIC [redacted] and SGIS over prior week
- Adverse events assessment
- C-SSRS
- Assess double-blind medication compliance
- Concomitant medication record and whether or not there is a change in physiotherapy regimen

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Approximately 300 subjects with known history of [redacted] due to multiple sclerosis, treated with a stable dose of [redacted] are to be enrolled. Subjects are required to consent to participate in the study. They will be informed that their primary medical practitioner and physiotherapist may be contacted to inform them of the study and its conditions. Subjects must fulfill inclusion/exclusion criteria as listed below.

1. Men and women age 18 years and older
2. Women of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) [such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), oral or long acting injected contraceptives, bilateral tubal ligation or vasectomized partner] for at least 3 months prior to study entry OR postmenopausal for at least 1 year OR surgically sterile (bilateral oophorectomy or hysterectomy)
3. If female, negative pregnancy test
4. [redacted]

7. Has an ECG that is not clinically significantly, abnormal and a blood pressure <160/95 mmHg (systolic/diastolic) at screening, measured in the sitting position after approximately 5 minutes of quiet rest
8. If the subject has a history of or presence of clinically significant liver disease, diabetes mellitus, hypertension or heart disease, the subject must be on a stable treatment regimen for a minimum of 3 months prior to Screening Visit
9. Able and willing to comply with the protocol, including availability for all scheduled clinic visits
10. Willingness and giving of written informed consent

5.2 Subject Exclusion Criteria

1. [redacted]
[redacted]
3. Concomitant neurologic conditions causing spasticity (*e.g.*, stroke, cerebral palsy, traumatic brain injury) or rigidity (*e.g.*, Parkinson's disease, contractures that confound assessment of spasticity)
4. Advanced arthritis or any other cause of clinically significant limitation of passive range of motion around any of the joints being assessed in this study
5. Any medical condition, including psychiatric disease or epilepsy, which would interfere with the interpretation of the study results, the conduct of the study, or the safety of the subject
6. [redacted]
7. History of alcohol abuse or use of recreational drugs within 12 months prior to the Screening Visit
8. [redacted]
[redacted]
11. Unable to comply with study procedures in the opinion of the investigator
12. [redacted]
13. Has had major surgery within 3 months prior to Screening visit that may affect spasticity assessments such as abdominal surgery, back surgery, or lower leg or knee surgeries

5.3 Subject Withdrawal Criteria

The subject will receive oral and written information about the study, 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 state that he/she is leaving the study. The subject will be encouraged to provide the reason for wishing to withdraw. The subject must return the study drug as well as undergo final study visit procedures.

The Investigator must withdraw a subject from the study in the following cases:

- [redacted]
- [redacted]

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

- There is need for further Baclofen ER Capsules (GRS) dose change after the first 4 weeks
- Subject experiences intolerable spasticity
- Subject has a treatment related serious adverse event (SAE)
- Subject gets pregnant during the study
- If, in the Investigator"s opinion, continuation in the study would be detrimental to the subject"s well-being

6 TREATMENT OF SUBJECTS

6.1 Study Medication(s) including Name(s), Dose(s), Dosing Schedule(s), Route(s), Treatment Period(s), Follow-up Period(s)

Study Medication For	:	**Part 1 (1-week open-label)**
Study Medication	:	[redacted]
Formulation	:	Tablet
Dose strength in mg	:	[redacted]
Dosing schedule	:	[redacted]
Route of administration	:	Oral
Treatment period	:	1 week

Study Medication For	:	**Part 2 (16-week open-label)**
Study Medication	:	[redacted]
Formulation	:	[redacted]
Dose strength in mg	:	[redacted]
Dosing schedule	:	[redacted]l
Route of administration	:	Oral
Treatment period	:	16 weeks

Study Medication For	:	**Part 3 (4-week double-blind, placebo-controlled)**
Study Medication	:	[redacted]
Formulation	:	[redacted]
Dose strength in mg	:	[redacted]
Dosing schedule	:	[redacted]
Route of administration	:	Oral
Treatment period	:	4 weeks
Follow-up	:	Until end of study part 3 or until resolution of adverse event, whichever is later

Subjects will be instructed that [redacted].

6.2 Medication(s)/Treatment(s) Permitted and Not Permitted Before and/or During the Study

All subjects will be questioned about the use of any pre-study and concomitant medication. All concomitant treatments must be appropriately recorded and described in the eCRF.

6.2.1 Medication(s) Permitted

Medications permitted would be other than those mentioned in Section 6.2.2, after consulting with the Investigator. These will be recorded as concomitant medications.

6.2.1.1 [redacted]

[redacted].

This list of medications includes the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

As antacids may affect the release of baclofen from the GRS capsule by the same mechanism, it is recommended that subjects refrain from taking antacids within 2 hours before or after taking study medication.

6.2.2 Concomitant Medication Restriction

6.2.2.1 [redacted]

[redacted]

[redacted]

During the blinded review (to be explained in detail in the statistical analysis plan (SAP)) prior to database lock and unblinding, concomitantly used medications will be reviewed and any that have potential anti-spasticity effects will be identified. The dose and time of use relative to the efficacy [redacted] list of medications that affect spasticity includes (but is not limited to) the following:

- Benzodiazepines
- Anti-spasticity medications: Tizanidine, fampridine/ dalfampridine
- Muscle relaxants: Cyclobenzaprine, metaxalone, dantrolene, mephenesin, carisoprodol, methocarbamol, meprobamate, chlorzoxazone and chlormezanone
- GABAergic drugs: Progabide, gabapentin
- Others (as identified by blinded data review)

6.2.3 Dietary Restrictions

An effort will be made to minimize variability of spasticity by advising stable caffeine and nicotine consumption, minimization of alcohol consumption, timing of study medication, and permitted prescription medication during the study period.

6.3 Procedure(s) for Monitoring Subject Compliance

Study medication will be dispensed by the site personnel. This will be documented in the eCRF. Thus, it is expected that compliance will be accurately documented for each subject.

Treatment compliance will be measured on the basis of a capsule count by the Investigator or designee for Visits 2 through 11. Subjects will be instructed to bring the study medication (with the capsules that remain) with him/her at 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 same within the next 3 days, failing which it will be recorded as not available.

6.4 Accountability Procedures for the Investigational Product

A distributor will ship the medication to the study sites according to country specific laws and regulations, and the procedures will be described in Study Drug Accountability Document. Both the distributor and the Investigator must keep record of all drugs received, used, and returned. When the study 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 study, 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 study drug.

6.5 Maintenance of Study Treatment Randomization Codes and Procedures for Breaking Codes

The randomization codes and blinding codes will be maintained by the statistician at the IVRS/IWRS. The randomization numbers and blinding codes generated will not be disclosed to any individual associated with reviewing the study documents.

The IVRS/IWRS will hold the only set of treatment codes and unblind individual subjects as required for regulatory reporting purposes. However, the Investigator, Sponsor, and study team will be kept blinded to treatment allocation. The treatment codes will be stored in a secure environment within the IVRS/IWRS and accessible only to the statistician.

The treatment code may be broken on an individual basis, in case of an SAE for which the Investigator must know the study agent identity to initiate appropriate treatment. The Investigator will be supplied with necessary information to break the study blind on an individual subject basis. If the study blind is broken, the Investigator must inform the medical monitor or designee and report the reason for unblinding. Date, time, and reason, together with the Investigator"s signature, must be recorded. The site will contact the designated personnel from the IVRS/IWRS in case the treatment code needs to be broken.

[redacted]

7 WITHDRAWAL AND REPLACEMENT RULES

7.1 Withdrawal

7.1.1 Premature Discontinuation of Subject in the Study

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 (Final Status) in the eCRF and the [redacted]

As far as possible, all examinations scheduled for the final study visit must be performed on all subjects who receive study drug but do not complete the study according to protocol.

The subject must return all unused investigational products.

Subjects who are withdrawn from the study due to AE will be treated according to established acceptable medical practice and 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.

7.1.2 Early Stopping of the Study

SPARC Ltd. may discontinue the study at any time, for ethical or scientific reasons. The Investigator is entitled at any time to stop his or her participation in the study 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 IRB/IEC and the regulatory authorities will be informed promptly and provided with the reasons for the termination or suspension by the Investigator and SPARC Ltd., respectively.

7.2 Replacement

Data from all enrolled subjects will be reported as outlined in Section 10.3. Specifically, the same subject number will not be re-allotted if a subject withdraws from the study.

8 ASSESMENT OF EFFICACY AND PHARMACOKINETICS

8.1 Description of Efficacy Parameters

Several measures are necessary to complete a thorough [redacted]

8.1.1 Primary Efficacy Parameter(s)

8.1.1.1 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.

At each scheduled visit for [redacted]

[redacted]

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

Score	:	Degree of Muscle Tone
0	:	No increase in tone
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+	:	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	:	More marked increase in muscle tone through most of the range of movement, but affected part(s) easily moved
3	:	Considerable increase in muscle tone, passive movement difficult
4	:	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

8.1.1.2 Clinical Global Impression of Change (CGIC)

CGIC will be assessed at Visits 4, 7, 8, 9, 10 and 11. [redacted] as indicated below:

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

[redacted]

[redacted] :

[redacted]

[redacted]

8.1.2 Secondary Efficacy Parameter(s)

8.1.2.1 Subject's Global Impression of Severity (SGIS)

Subjects will be asked to rate their overall impression of severity at [redacted] At each of these visits, the subject [redacted].

[redacted]

[redacted]

8.1.3 Exploratory Parameters

8.1.3.1 Nighttime Awakening and Sleep Time

[redacted]

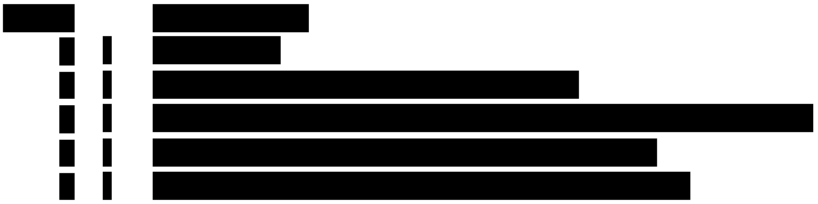
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

8.1.3.2 Spasm Frequency

[redacted]



8.2 Methods and Timing for Assessing and Recording Efficacy Parameters

Spasticity will be assessed at every visit using the . Assessment at Visits 2 through Visit 11 will be performed in the clinic. The subject and his/her caregiver will be instructed about visit schedules . Throughout the study during both the fixed dose phase (Part 2) and 4-week double blind phase (Part 3) assessments are to occur .

Assessors in the study team (doctors/ physiotherapists/ occupational therapists/ nurses across primary and secondary care) at all sites will be trained on scoring to achieve uniformity in assessments. Attempts will be made to assign the same assessor to an individual study subject for the duration of the study.
Scores for each movement assessed will be recorded in the source documents and entered in the eCRF. Determination of treatment response and derivation of means and averages will be performed at the time of statistical analysis (see Section 10). Statistical analysis of the efficacy parameters will be performed after data-lock according to the statistical analysis plan.

8.3

8.3.1

.

All blood samples will be collected . The blood samples will be collected .

8.3.2 [redacted]

8.3.2.1 [redacted]

[redacted]

8.3.2.2 [redacted]

[redacted]

8.3.3 [redacted]

[redacted]

[redacted]

[redacted].

9 ASSESSMENT OF SAFETY

The Principal Investigator (PI), including the study staff, will monitor the subjects throughout the study period. The staff will be available for subject queries during the regular business hours and *via* an answering service. The PI or qualified medical designee will be on-site and/or available by cell phone throughout the study.

9.1 Description of Safety Parameters

The following safety parameters will be assessed during the study:

- Treatment emergent adverse events
- Daytime sedation
- Vital Signs (seated blood pressure and pulse)
- Clinical laboratory tests
- 12 Lead ECG
- Physical examination
- Neurological evaluation

- C-SSRS Suicidality Assessment

9.1.1 Adverse Event

An AE is any untoward medical occurrence during treatment with a pharmaceutical product in a subject that does not necessarily have a 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.

Untoward medical experience occurring during medication-free pre-treatment periods does not meet the above-mentioned definition of an AE. Nevertheless, they have to be documented in the same way as AE. Each subject will be queried generally for the occurrence of adverse experiences prior to study drug administration and throughout the subject‟s participation in the study. During and following a subject's participation in this study, the Investigator has to ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values, related to the study. The subject will be treated and/or followed up until the symptom(s) returns to normal or stabilizes, as judged by the PI.

9.1.2 Serious Adverse Event

A 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.

9.1.3 Pregnancy

A urine pregnancy test will be performed at screening and subjects with a positive test will be excluded from study. Women of child-bearing potential will be instructed to practice an acceptable method of birth control for the duration of the study. A follow-up urine pregnancy screen will be conducted at Visit 7. However, if subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and procedure for expedited reporting (Section 9.2.1) will be followed. The pregnancy will be followed until its outcome, and the outcome will be reported as a significant medical event and procedure for expedited reporting (Section 9.2.1) will be followed.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Eliciting, Documentation and Reporting of Adverse Events and Intercurrent Illnesses

Information on AEs will be derived by questioning the subjects in general terms (*e.g.*, "How do you feel?" or "How have you been feeling since the last questioning?" respectively), by subjects' spontaneous reports, or by observation.

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, pattern (continuous/intermittent), action taken, outcome, seriousness, and causality assessment.

9.2.1.1 Rating of Adverse Events

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

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 to fulfil 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.
Certain	A clinical event, including laboratory test abnormality,	1. It follows a plausible time sequence to drug intake ,this means that there is a positive argument in sufficient detail to support the view that the drug

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 causally involved, pharmacologically or pathologically e.g. 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 on readministration of the drug (only if ethically correct i.e. 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 severity 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.

9.2.1.2 Documentation and Reporting of Immediately Reportable Adverse Events

Subject will be examined for any new medical conditions or worsening of the pre-existing ones. Any change in pre-existing conditions or new conditions must be entered on the AE page of the eCRF and any medication given on the concomitant medication pages.

Any unexpected AE that could adversely affect the safety of the subjects or the conduct of the study and any SAE, which occurs during the course of this study, will be reported to the pharmacovigilance department of the CRO within 24 hours of the Investigator becoming aware of the event. Any new information relating to an SAE that subsequently becomes available should also be faxed to the CRO Drug Safety within 24 hours of the Investigator becoming aware of the information.

All SAEs must be reported, whether or not considered attributable to the study drug 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 considered serious, measures taken and outcome (if resolved)
- Likelihood of drug causation of the adverse event assessed by the Investigator.

[redacted]

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

Unresolved events and post-study events will be followed up by telephone or with unscheduled visits at the discretion of the Investigator. These require evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found.

9.2.1.3.1 Unresolved Events

If an AE/SAE is present when the subject has completed the main study period, the course of the event must be followed until final outcome is known.

9.2.1.3.2 Post-study Events

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

9.2.2 [redacted]

[redacted]

[redacted] following will be assessed:

- [redacted]

[redacted]

9.2.3 Concomitant Medication and Physiotherapy Recording

Medications used at study entry (and within the prior 30 days) will be recorded at Screening . Thereafter, concomitant medications used will be recorded at each visit. At Screening , subjects will also be queried about their physiotherapy regimen and the nature and schedule recorded. At subsequent visits, subjects will be questioned by the Ashworth assessor whether or not there has been a change; the nature of any substantive changes is to be described.

9.2.4 Vital Sign Measurement

Blood pressure and pulse will be measured at each clinic visit throughout study participation. Measurements will be made with the subject in a seated position (for at least 5 minutes). Results will be evaluated against pre-specified criteria for clinically significant change.

9.2.5 Clinical Laboratory Testing

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, and Visit 7 (Week 18) and Visit 11

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 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.

9.2.6 12-Lead ECG

ECG measurements will be collected in triplicate 2 minutes apart (except at Screening where only one measurement will be taken) and read by a central reader. The QTc data will be corrected using Fridericia‟s correction and Bazett‟s correction. In addition to the QT interval, the following parameters will be collected: PR interval, QRS, and ventricular rate; the presence of T-waves will be noted.

Clinically significant abnormalities will be reported as AEs.

9.2.7 Physical Examination

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.

9.2.8 Neurological Examination

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).

9.2.9 Columbia – Suicide Severity Rating Scale (C-SSRS)

[redacted]

10 STATISTICAL CONSIDERATIONS

10.1 Primary and Secondary Efficacy Variables

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 [2] in modified Ashworth score from baseline

The modified Ashworth score at a given visit will be recorded for each of the 12 movements measured. The Baseline score against which worsening will be determined is [redacted] during the [redacted]

For the primary efficacy analysis, subjects who provide modified Ashworth and CGIC scores at Visit 11 and meet the treatment failure criterion at Visit 11, [redacted]

The secondary efficacy variable is:

- Subject Global Impression of Severity (SGIS)

10.2 [redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

10.3 Study Populations

10.3.1 Efficacy Populations

10.3.1.1 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.

10.3.1.2 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 on-treatment assessment in Part 3, and do not have any major protocol violation (such as poor compliance). Protocol violations will be reviewed and subjects with major/minor violations will be

identified prior to unblinding the clinical database. Subjects with a major protocol violation will be excluded from the analysis of the PP population.

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. 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; response status will be solely on the basis of the clinician-rated CGIC.

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.

10.3.2 Safety Population

The safety population will be all subjects who received at least one dose of [redacted] and have a subsequent contact. Subjects who discontinue having received only [redacted] and are not available for evaluation in Visit 2 or subjects dispensed [redacted] at Visit 2 but with no subsequent contact will not be included in the safety population.

10.4 Statistical Methods

A detailed statistical analysis plan (SAP) will be written and finalized before the study starts. The plan will follow the outline of the statistical analyses including but not limited to points presented below, but details necessary to complete the statistical analyses will be given.

10.4.1 Demographic and Other Baseline Characteristics

Descriptive summaries of the Safety Population will be prepared for the demographic and baseline (Screening) characteristics listed below. Categorical variables will be described with counts and percentages, ordinal variables with medians and quartiles, and interval variables with mean and 95% confidence interval (CI). [redacted] Descriptive comparisons will be made using the Pearson‟s chi-square test for categorical variables, Mann-Whitney U-test for ordinal variables, and Student‟s two-sample t-test for interval variables.

- Age (years)
- Gender
- Race/ethnicity
- Renal function (as estimated by calculated creatinine clearance)
- [redacted]
- [redacted]
- [redacted]

Medical history at Visit 1 (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.

10.4.2 Study Disposition and Dosing

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

10.4.2.1 Subject Disposition Criteria

- Number of subjects who were enrolled in each phase of the study [redacted]
- Number and proportion of subjects (by treatment group and overall) who discontinued the double-blind phase prior to Visit 11.
- Number and proportion of subjects (by treatment group and overall) who dropped-out for each of the following categories for why a subject may be prematurely discontinued from the study (Section 7.1.1):

    - Dropped-Out Due to Adverse Event: Subjects who are discontinued from the study medication due to the occurrence of an AE will be recorded as dropouts. The AE will be recorded and all subjects irrespective of time of dropout (after Visit 2 and have taken one study dose) will be considered for safety analysis.

    - Dropped-Out Due to Major Protocol Violation: Subjects who are discontinued from the study due to the occurrence of a major protocol violation will be recorded as dropouts. The protocol violation will be recorded and all subjects irrespective of time of dropout (after Visit 2 and have taken one study dose) will be considered for safety analysis.

    - Lost to Follow-Up: Subjects available for evaluation in Visit 2 [redacted], but not evaluated for subsequent visits will be considered as lost to follow-up, [redacted] will be considered for safety analysis.

    - [redacted]

    - Dropped Due to Other Reasons: Subjects who are discontinued from the study due to any other reason will be recorded as dropouts. The reason for discontinuation will be recorded all subjects irrespective of time of dropout (after Visit 2 and have taken one study dose) will be considered for safety analysis.

Subjects who drop out after Visit 1 will not be replaced (Section 7.2).

10.4.2.2 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. [redacted]

10.4.3 Efficacy Analysis

10.4.3.1 Primary Efficacy Analysis

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

A subject will be classified as „treatment failure" if the definition for failure (Section 10.1) is met at any time during the double-blind withdrawal period (Part 3). [redacted]. The primary efficacy analysis will be carried out using a two-sided test at the alpha=0.05 level of significance.

10.4.3.2 Additional Analyses of the Primary Efficacy Outcome

10.4.3.2.1 Sensitivity Analyses

Several sensitivity analyses [redacted] The sensitivity analyses are as follows:

(a) [redacted].

(b) [redacted]

(c) [redacted]

(d) [redacted]

10.4.3.2.2 [redacted]

[redacted]

[redacted]

[redacted]

10.4.3.3 Secondary Variable Analysis

The secondary efficacy outcome is the Subject Global Impression of Severity (SGIS). The change in the SGIS from Visit 7 (reference) to Visit 11 will be analyzed using the Mantel-Haenszel test stratified by stabilized dose level. [redacted]

[redacted]

10.4.3.4 Exploratory Analyses

10.4.3.4.1 [redacted]

[redacted]

[redacted]

10.4.3.4.2 Subgroup Analyses

Exploratory subgroup analyses will be performed to investigate the effect of the drug for different subgroups, [redacted] those who used neurological concomitant medications *versus* those that did not use such medications, and initial severity based on modified Ashworth score.

10.4.3.4.3 Sleep Interference Due to Spasticity

10.4.3.4.3.1 Awakenings Due to Spasticity

[redacted]

[redacted].

[redacted].

10.4.3.4.3.2 Hours of Sleep

[redacted]

[redacted]

10.4.3.4.4 Spasm Frequency

[redacted]

[redacted]el.

The weekly mean of the daily spasm frequency will be computed using the average of the daily results that are obtained during the specified 7-day period. However, the weekly mean will be set to a missing value if a subject provides fewer than 3 days of data during the week.

[redacted]

[redacted]

10.4.5 Safety Analysis

Safety parameters include AEs, daytime sedation, vital signs (resting pulse and sitting systolic and diastolic blood pressures), clinical laboratory tests, 12 lead ECG, physical examinations, neurological examinations and suicidality assessment.

[redacted]

10.4.5.1 Adverse Events

All treatment-emergent adverse events (TEAE) will be coded in a standardized manner for regulatory activities. TEAEs will be coded according to body systems and preferred terms. A

TEAE is defined as any event that only occurred after [redacted] administration or that existed before drug administration but increased in severity or treatment attribution. For the randomized withdrawal phase, emergent events will be determined relative to the double-blind medication.

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 summarized separately.

The incidence of TEAEs and SAEs will be summarized for the [redacted] s (Part 2) and also by treatment group during the double-blind, [redacted] part (Part 3). For each part, the incidence of TEAEs will be presented by system organ classification and preferred terms according to the Medical Dictionary for Regulatory Activities (MedDRA®), by causality, 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 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.

In addition, adverse events will be listed for all subjects, including verbatim and coded terms.

10.4.5.2 [redacted]

[redacted]

10.4.5.3 Vital Signs

Sitting diastolic and systolic blood pressures and resting pulse measurements at each visit will be summarized using descriptive statistics (n, mean, 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.

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 for each part; in Part 3, summaries will be by treatment group.

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.

10.4.5.4 Clinical Laboratory Tests

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, standard deviation, minimum, median, and maximum).

Values outside 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 Screening and Visit 7 will be generated. Criteria for possibly significant changes will be established *a priori* for selected parameters. The numbers and percents 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.

[redacted]

10.4.5.6 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.

[redacted]

10.4.6 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 for each treatment group using counts and percentages and will be listed for all subjects.

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

10.5 Unblinding

Breaking of the blind will occur at completion of the study.

At completion of the study, breaking of the blind will occur once the database has been cleaned and locked. Prior to final database lock, any major protocol violations, including changes in medication use or physiotherapy, and changes in medical condition will be identified. Only at that time will the Sponsor be granted access to the unblinded data.

At all other timepoints, breaking of the blind for any subject is discouraged and should be performed only under medical emergency conditions where the identification of the subject‟s treatment assignment is critical for proper medical care to be administered. In such circumstances, the Investigator must contact the Sponsor‟s Medical Representative (or designee) for permission to unblind. The representative will be available 24 hours a day. If a decision is made to unblind a subject's assignment, the Investigator will call the IVRS/IWRS statistician and request the subject's treatment group. Only the Investigator and the IVRS/IWRS statistician will be unblinded to the subject's treatment group and they will be responsible for documenting the time, date, and reason for code break.

10.6 Level of Significance

All statistical tests will be carried out at the alpha=0.05 level of significance.

10.7 Missing Data

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.

All missing values will be queried and resolved to the best possible extent.

10.8 Procedures for Reporting Protocol Violations/Deviations

Before starting the study, a list of major protocol violations that justify exclusion of subjects from efficacy analysis will be made. Likewise, a list of minor protocol violations/deviations that are tolerable for retaining the subject in the study will be made.

Subjects excluded for analysis for major protocol violations will be listed along with the nature of the violation. Subjects having minor protocol violations/deviations will be listed.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1 Monitoring

On-site monitoring will be performed before, during, and after the study. The monitor will ensure that the study is conducted, recorded and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements. The monitor will check the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The Investigator will provide direct access to source data/documents for study-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 study. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

11.2 Documentation at the Study Site

All data relating to the study 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. Any change or correction to an eCRF will be dated, initialed, and explained (if necessary) and will not obscure the original entry.

At the beginning of the study, a site master file will be established at the investigational site. The Investigator will maintain the study 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 study, 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 study-related monitoring, audits, and regulatory inspection, providing direct access to source data/documents.

11.3 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 study subject and used in lieu of the subject's name when the Investigator reports AEs and/or other study-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 study.

The Investigator must maintain a list of names and identifying information (*e.g.*, initials, date of birth, subject identification code and date of study randomization) of all subjects enrolled in the study. The Investigator will keep the subject identification code list in the site master file.

11.4 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 study book. When the data for a subject is declared clean (all data entered, verified, validated and resolved) the case book will be frozen. At the close of the study, 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).

11.5 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 study subject or when the changes involve only logistical or administrative aspects of the study (*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 Investigator(s). Amendment(s) will be signed off in the same way as the protocol.

11.5.1 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:

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 study. 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.

11.5.2 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 study. 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 study.

A protocol **deviation** may be defined as an occurrence when there is non-adherence to study 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 study 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 study; 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 study report.

12 QUALITY CONTROL AND QUALITY ASSURANCE

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

Quality assurance and quality control systems are implemented and maintained using written SOPs to ensure that the study 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 study 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 study.

13 ETHICS

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

13.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This study will be initiated after the protocol is reviewed and approved by the concerned 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.

13.2 Ethical Conduct of the Study

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

13.3 Subject Information and Consent

Subject 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 study"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 study, *e.g.*, 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 study.

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 study related procedure is performed.

14 DATA HANDLING AND RECORD KEEPING

The Investigator must maintain all documentation relating to this study. Essential documents (as defined in the ICH Guideline of 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 study 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 study. If the Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred and Sponsor notified in writing.

Sponsor will notify the Investigator in writing when the study-related records are no longer needed.

15 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.

16 PUBLICATION POLICY

The CRO and Investigator agree to keep strictly confidential all unpublished information and results concerning this study. 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.