APPLIED BIOLOGY

CLINICAL STUDY PROTOCOL

Study to Investigate the Effect of RJ-101 in Breast Cancer Survivors

[redacted]

[redacted]

PROTOCOL NAME:
Clinical Study: Study to Investigate the Effect of AB-101 in Breast Cancer Survivors

PROTOCOL IDENTIFYING NUMBER:
RJ-101-RCT-001

PROTOCOL VERSION DATE:
September 07, 2017

GENERAL INFORMATION

Name and address of the sponsor of the study:
Applied Biology, Inc.
17780 Fitch
Irvine, CA 92614
USA

Name and address of the person authorized to sign the protocol and amendments:
[redacted]

Name and address of study monitor:
[redacted]

Name, title, address and telephone number(s) of the medical expert for the trial:
Michael Krychman, MD
1501 Superior Ave.
Newport Beach, CA 92663
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[redacted]

Name and title of the investigator(s) and sub-investigators responsible for the trial with address and phone number(s):

Principal Investigator
Michael Krychman, MD

Site Supervisor
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Investigator Assistant
Monica Neagle

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1501 Superior Ave.
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Name and addresses of the clinical laboratories and/or other institutions involved in the trial:

Stability Testing:
Micro Quality Labs Inc.
3200 N. San Fernando Blvd.
Burbank, CA 91504
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GMP Manufacturing Facility:
[redacted]

[redacted]

Protocol signature page
Investigator's Agreement

Clinical Study: Study to Investigate the Effect of RJ-101 in Breast Cancer Surviors

[redacted]

By my signature below I agree to conduct this clinical study in accordance with the protocol, Good Clinical Practice, the Declaration of Helsinki, government regulations and state/local customs or laws, including those applying to institutional/ethics review and informed consent. I have read the protocol. I agree to ensure the confidentiality of my subjects; however, I agree to make available to the CROs, the Sponsor of this clinical study, relevant regulatory authorities, my subjects' medical records. I am aware of my responsibilities as investigator as provided to me by the CROs.

Name	**Signature**	**Date**
Michael Krychman, MD (Principal Investigator)		

[redacted]

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List of Abbreviations

CRO	Clinical Research Organization
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
PRO	Patient Reported Outcome
FSFI	Female Sexual Function Index
DSDS	Decreased Sexual Desire Screener
FSDS-R	Female Sexual Distress Scale (Revised)
FOD	Female Orgasmic Disorder
HSDD	Hypoactive Sexual Desire Disorder
FSAD	Female Sexual Arousal Disorder
FSIAD	Female Sexual Interest/Arousal Disorder
FSD	Female Sexual Dysfunction
OTC	Over The Counter
SAR	Sexual Activity Record
NAC	Nipple Areola Complex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
API	Active Pharmaceutical Ingredient

1. Background

1. Overview

[redacted]

63,410 new cases of non-invasive (in-situ) breast cancer

[redacted]

[redacted]

[redacted]

1.1. Investigational Drug

Drug name: Phenylephrine HCl (CAS# 61-76-7)

Drug formulation(s):

[redacted]

[redacted]

1.2. Preclinical Data

[redacted]

1.2.1. Preclinical Safety Data

[redacted]

[redacted]

[redacted]

[redacted]

1.2.2 Preclinical Efficacy Data

[redacted]

[redacted]

[redacted]

[redacted]

1.2.3 Clinical Safety and Efficacy Data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.4 Other Data

[redacted]

[redacted]

1.3. Risks/Benefits

Benefit(s) of the Proposed Clinical Study

Approximately, 80% of breast cancer survivors will suffer from a permanent reduction in nipple sensitivity and associated decrease in sexual quality of life. Currently, there are no

[redacted]

treatments for restoring nipple sensitivity to improve sexual quality of life. It would thus be of great clinical benefit to post breast surgery patients if a safe and effective topical treatment for this condition can be developed.

Risk(s) of the Proposed Clinical Study
As with all medical interventions, the use of topical phenylephrine hydrochloride solution carries a risk. The main risk maybe the onset of a hypertensive crisis.

1.4. Trial Conduct

This study will be conducted in compliance with the protocol approved by the IRB, and according to Good Clinical Practice standards. The interventional phenylephrine drug will be manufactured and packaged at the GMP facility listed in this protocol. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

1.5. Population

The subjects will be premenopausal female breast cancer survivors (first diagnosed with stage I or II) ages 18 to 50 of any ethnicity.

This is a single-center pilot study. The subjects will be recruited as following:

1. Subjects are prior breast cancer patients of the PI
2. Subjects are referred from an oncologist to the PI
3. Subjects are referred form an OBGYN to the PI

1.6. Literature

We provide the following references of peer reviewed published studies as support of our study:

[redacted]

[redacted]

Arch Fr Pediatr.

[redacted]

[redacted]

2. Trial Objective(s)

To provide a preliminary assessment of the efficacy of the investigational drug in alleviating the symptoms of nipple neuropathy (i.e., increase nipple sensitivity) and improving the sexual quality of life of breast cancer survivors.

3. Trial Design

3.1 Primary Study Endpoints/Secondary Endpoints

Primary Outcome Measures:

1. Delayed orgasm (CTCAE v4.0) [baseline, week 4, week 8]
2. Vaginal dryness (CTCAE v4.0) [baseline, week 4, week 8].

[redacted]

3.2 Study Design/Type

This study is a single blinded (only the subjects will be blinded) placebo controlled study. The study will have 2 arms:

Arm 1: Subjects applying the interventional drug (approximately 1 hour prior to sexual activity).

Arm 2: Subjects applying a placebo (approximately 1 hour prior to sexual activity).

Study Environment:

This is a single-center pilot study to be conducted at the PI's medical office listed above (the "site"). There will be one PI. The study to be conducted will be approved by the IRB. All data collection will be performed at the site.

During the study, subjects will apply at home the assigned topical intervention approximately 1 hour prior to sexual activity.

Study Design:

Study Phase I: Enrollment and Safety Evaluation (first site visit):

1. Each potential subject will visit the site for initial screening.
2. The PI will screen each potential subject for the exclusion and inclusion criteria.
3. The PI will review each potential subject's medical and cardiac history.
4. The PI will measure and record the blood pressure and heart rate of the potential subject.
5. The subject will be administered a rapid OTC urine pregnancy test (e.p.t – Insight Pharmaceuticals, Trevose, PA, USA or equivalent).
6. If the PI determines that the subject qualifies for the study, the PI will present the subject with the Informed Consent Form.
7. The subject will complete and sign the Informed Consent Form.
8. The subject will be assigned a subject study number. The first subject will be assigned the number 001 and each subject thereafter will be assigned a consecutive number i.e., 002, 003, etc.
9. The subject will be assigned an Arm of the study in accordance with Section 3.3.

10. Each subject will be provided with a private examination room. The room temperature will be 23° C.

11. The PI's assistant (female) will be the only person present in the room with the subject.

12. The PI's assistant will record in the appropriate CRFs the blood pressure, heart rate, and patient reported nipple sensitivity of each subject at baseline.

13. If the subject reports a baseline nipple sensitivity >5 (Likert scale), the subject participation in the study will be discontinued.

14. The PI's assistant will demonstrate the application of the intervention on a silicone breast model (3B SKINlike™ silicone women breast silicone). The subject will need to apply the intervention (a pre-wetted single use gauze) to the nipple areola complex as proximal as possible to the nipple starting from the nipple and continuing in circular motion working to the periphery of the areola. The intervention (pre-wetted single use gauze) will be disposed after application to both nipples.

15. The PI's assistant will supply each subject the assigned intervention (based on the arm the subject was assigned in Study Phase I) in the form of pre-wetted single use gauze.

16. The PI's assistant will leave the room and allow the subject to self-apply to each nipple and areola (in accordance with step 14) the interventional treatment. After the subject has applied the interventional treatment and the area of application has dried (approximately 5 minutes), the subject will dress and wait for the PI's assistant.

17. 15 minutes following the application of the interventional treatment in step 16, the PI's assistant will measure and record in the appropriate CRF the blood pressure and heart rate of each subject.

18. 30 minutes following the application of the interventional treatment in step 16, the PI's assistant will measure and record in the appropriate CRFs the blood pressure and heart rate of each subject.

19. 60 minutes following the application of the interventional treatment in step 16, the PI's assistant will measure and record in the appropriate CRFs the blood pressure, heart rate and patient reported nipple sensitivity.

20. The PI's assistant will ask the subject if they have experienced any adverse events (e.g., pain or irritation) following the application of the interventional treatment.

21. All information will be recorded in the appropriate CRFs.

22. If the subject was assigned to Arm 1 (interventional drug) and the subject did not report an increase >=2 from baseline in nipple sensitivity (Likert scale), the subject participation in the study will be discontinued.

Study Phase II: PRO (first site visit continued):

1. Each subject will be supplied a private room to complete the PRO forms (according to section 5.1).

2. The PI will provide each subject with a 4-week (12 single use pre-wetted gauze pads) supply of the investigational treatment i.e., drug or placebo based on the arm assignment in Study Phase I.

3. The subject will be instructed to apply, at home (in accordance with Step 16, Study Phase I), the assigned intervention treatment approximately 1 hour prior to sexual activity.

4. All information will be recorded in the appropriate CRFs.

Study Phase III (week 4, second site visit):

1. The PI will assess each subject for adverse events in accordance with section 6.1

2. Each subject will be supplied a private room to complete the PRO forms (according to section 5.1).

3. The PI will provide each subject with a 4-week (12 single use pre-wetted gauze pads) supply of the investigational treatment i.e., drug or placebo based on the arm assignment in Study Phase I.

4. The subject will be instructed to apply, at home (in accordance with Step 16, Study Phase I), the assigned intervention approximately 1 hour prior to sexual activity.

5. All information will be recorded in the appropriate CRFs.

Study Phase IV (week 8, third site visit):

1. The PI will assess each subject for adverse events in accordance with section 6.1.

2. Each subject will be supplied a private room to complete the PRO forms (according to section 5.1).

3. The PI will collect and dispose of any remaining interventional treatment dispensed during Study Phase II and III.

4. All information will be recorded in the appropriate CRFs.

After Study Follow-up:

30 days after the completion of the study, the PI's assistant, will monitor the subjects via a phone call for adverse events as well as ask the subjects for a self assessment of the study's impact on sexual function.

3.3 Randomization

Subjects will be randomized into 1 of 2 arms. Each subject will receive an interventional treatment.

Arm 1: Active drug (Phenylephrine HCl solution)
Arm 2: Placebo (solution vehicle only)

During the enrollment phase (first site visit), each subject will be assigned a subject study number. The first subject will be assigned the number 001 and each subject thereafter will be assigned a consecutive number i.e., 002, 003, etc. The randomization plan is based on a 3:1 ratio of active drug vs. placebo. Since the study is single-blinded study i.e., subjects will be blinded to the intervention, but not the PI, we designed the following randomization schedule:

Subjects 001-010 will be assigned to Arm 1
Subjects 011-013 will be assigned Arm 2
Subjects 014-025 will be assigned to Arm 1
Subjects 026-030 will be assigned to Arm 2

3.4 Records

Each subject will be assigned a number. The numbers will be consecutive starting at 001 and be used in conjunction with the subject's initials.

A record will be created for each subject. Each record will contain a medical history, and the PI's assessment of the subject documented in the appropriate CRF.

The subjects' records will be stored and handled in the same manner as the PI's other clinical study subjects' records are stored i.e., in a locked research storage area.

The PRO data will be stored with each subject's clinical study records. No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

3.5 Duration

The duration of the study is 8 weeks. There will be no follow-up treatment.

3.6 Discontinuation

In the event that a subject reports an adverse effect or does not adhere to the treatment regimen, the PI will discontinue the study for that particular subject.

3.7 Product Accountability

The interventional treatment i.e., active drug (phenylephrine pre-wetted gauze) and placebo (vehicle only pre-wetted gauze) will be dispensed to subjects for the duration of the study

only. Each subject will receive an interventional treatment based on her assigned arm, i.e., 1 or 2.

The interventional treatment (placebo and active) will be stored at the site in the same manner other prescription drugs are stored at the site.

Records of dispensation will be recorded in the appropriate CRF.

3.8 Data Identification

The subject records kept by the PI will be stored and handled in the same manner as the PI's other clinical research subject records. Only authorized personnel named in this study, or medical professional retained by the sponsor in case of an adverse event, will have access to the subject records.

No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

4. Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

- Female breast cancer survivor
- Age: 18 to 50 (pre-menopausal)
- First diagnosed with Stage I or II breast cancer
- Have had breast surgery: nipple sparring mastectomy or lumpectomy
- At least 3 years post surgery
- Nipple neuropathy post breast surgery (change in Likert scale >= 3 between pre and post surgery)
- Baseline nipple sensitivity <=5 (Likert scale)
- QoL-BC (>=7)
- Delayed orgasm (CTCAE v4.0) Grade 2
- Sexually active within the last 30 days
- Willing to engage in sexual activity at least once a month during the duration of the study
- Willing to use an adequate method of birth control
- Able to comply with the study requirements for 8 consecutive weeks
- Able to give informed consent

4.2 Exclusion Criteria

- Previous adverse event to phenylephrine (oral, nasal, topical, or ocular) or drugs in this class
- Currently pregnant
- Nursing within the last 6 months

- History of cardiovascular or cerebrovascular disease, e.g., heart attack, disease of the arteries of the heart, partial heart block, rapid ventricular heartbeat, slow heartbeat, chronic heart failure, severe hardening of the arteries, blood clot in an artery
- Actively being treated for breast cancer
- Changes in chronic medication for oncology, cardiology, or endocrinology in past 12 months
- Uncontrolled or severe hypertension
- Decreased oxygen in the tissues or blood
- Active inflammation of the liver
- Acute inflammation of the pancreas
- Overactive thyroid gland
- Acidosis
- Diabetes
- Spinal cord injury
- Surgical post menopause
- Nipple dermatitis
- Regional complex pain syndrome
- Use of any hypertensive drugs
- Use of MAO inhibitors
- Subjects assigned to interventional drug arm and failed to report an increase >=2 from baseline in nipple sensitivity (likert scale) during phase I
- In partners: sexual dysfunction or erectile dysfunction
- Currently enrolled in any other medical study or has been enrolled in any medical study in the past 30 daysUnable to provide consent or make allotted clinical visits

4.3 Subject Withdrawal

Subjects may withdraw at any time for any reason. In the event the principal investigator or the site monitor believes a subject is at risk of injury, the subject will be withdrawn from the study and:

(a) If the subject has not completed at least 4 weeks of the study, the data will be discarded

(b) The subject may be replaced with another subject

(c) The PI or his designee will follow-up with the subject within 1 week

(d) The information will be recorded in the appropriate CRF

4.4 Treatment of Subjects

During the study, subjects will apply, in a private room at the site, the interventional treatment i.e., active drug or placebo. They will be provided with adequate undergarment coverings to ensure privacy and discretion during the treatment process.

During the study, subjects will apply at home the assigned interventional treatment

approximately 1 hour prior to sexual activity.

4.5 Medication

No drug interactions of clinical importance have been identified with topical phenylephrine. Source: DrugBank Interactions (http://www.drugbank.ca/drugs/DB00388)

4.6 Monitoring for Subject Compliance

Every 2 weeks, The PI or his designee will monitor the subjects via a phone call or email to assure compliance with the treatment and assess any adverse events.

At each site visit, the PI or the PI's assistant will assess each subject's compliance with the treatment and any adverse events.

The information will be recorded in the appropriate CRF.

5 Assessment of Efficacy

5.1 Efficacy Parameters

5.1.1 Phase I Site Visit: Patient Reported Outcomes (PRO)

During the first site visit the following subject reported efficacy parameters will be measured:

Nipple Sensitivity:

Each subject will self-report her nipple sensitivity on a Likert scale of 1 to 10 (1 being insensitive, 10 being extremely sensitive bordering on uncomfortable/pain) at baseline and within 60 minutes following application of the assigned intervention.

5.1.2 Phase II, III, and IV (Week 0-8)

During the first site visit, week 4 site visit, and week 8 site visit, the PI will instruct the subject in the use of standardized patient reported outcomes (PROs). Subjects will be instructed by the PI or the PI's assistant to complete the PRO forms. Each subject will be supplied a private room to complete the PRO forms.

1. **CTCAE v4.0**: Common Terminology Criteria for Adverse Events version 4.0. is a descriptive terminology developed by the National Cancer Institute. It is considered the standard classification for oncological adverse events as well as outcomes of oncological related clinical studies. Two specific questions are related to sexual adverse events in oncology:

Adverse Event	1	2	3	4	5
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					

5.2 Method and Timing

All assessments described in section 5.1 will be recorded on paper forms (CRFs) and stored with each subject's clinical study record.

The nipple sensitivity assessments made at Phase I site visit as described in section 5.1 will be recorded by the PI. This will occur during the Phase I site visit at baseline and 60 minutes following application of the interventional treatment.

PRO assessments (1, 2 and 3) will occur at the first site visit, week 4 site visit, and the final site visit at week 8.

PRO assessment (4) will occur at the final site visit at week 8.

The methods employed for completing assessments are described in section 5.1.

6 Assessment of Safety

6.1 Safety Parameters

Safety will be assessed by summarizing the incidence and type of Adverse Events.

Due to the potential for increasing blood pressure from the systemic absorption of topical phenylephrine the following safety parameters will be assessed:

Cardiac Hemodynamics Assessment:

[redacted]

Subject Self Assessment:

During each site visit, each subject will be asked:

1. Have you had any abnormal symptoms since your last visit? Since starting treatment?

6.2 Method and Timing

At the start of the trial, week 4, and week 8 each subject shall visit the site. During the visit

the PI or his designee will assess each subject for adverse events by oral questioning, blood pressure and heart rate measurement. The assessments, as described in section 6.1, will be recorded by the PI.

The methods employed for completing assessments are described in section 6.1

6.3 Adverse Event Reporting

While we do not anticipate any adverse event from the use of the compounded drug, we will comply with any ethics committee and/or FDA requirements for adverse events reporting.

The following events will be reported within 10 days:

- Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems), which in the opinion of the local investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
- Any serious accidental or unintentional change to the ethics committee approved protocol that involves risk or has the potential to recur.
- Any deviation from the protocol taken without prior ethics committee review to eliminate apparent immediate hazard to a research subject.
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
- Any breach in confidentiality that may involve risk to the subject or others.
- Any complaint from a subject that indicates an unanticipated risk that cannot be resolved by the research staff.
- Any other serious and possibly related event, which in the opinion of the investigator constitutes an unanticipated risk.

In the event of any adverse event during or after the trial we will keep records of such events in the appropriate CRFs, report to the EC/IRB/FDA and any treating physician if necessary.

6.4 Definitions

- **Unanticipated** (unexpected) problems/events are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator's Brochure or *not* part of an underlying disease. **Anticipated** (expected) problems/events do NOT meet the EC's definition of UPIRTSO.
- **Serious** problems/events are those, which in the opinion of the local investigator involve risk to subjects or others. Examples may include death, hospitalization, disability as well as breach of confidentiality. **Non-serious** problems/events do NOT meet the EC's definition of UPIRTSO.
- Problems/events that are unanticipated and serious should be reported to the EC within 10 working days *only* if, in the opinion of the local investigator, they are possibly,

probably or definitely **related** to the research procedures. Those serious, unanticipated problems/events that the local investigator deems unlikely or **not related** do NOT meet the EC's definition of UPIRTSO.

- Follow-up reports on previous events should be reported as UPIRTSOs if the initial event itself met the EC's definition of UPIRTSO **AND** in the local investigator's judgment, this follow-up report adds value to the initial report.
- Reports of off-site events on studies that are now closed at this site should be reported as UPIRTSOs if the event meets the EC's definition of UPIRTSO **AND** in the local investigator's judgment, this event may affect risk to subjects who have completed the study.
- For reports involving blinded study drug, the assessment of relatedness will often be "at least possibly related" as relatedness cannot always be ruled out. If there are numerous reports on the same blinded drug and these reports all meet the 3 criteria for UPIRTSO, they may be reported on one UPIRTSO form with an accompanying table/spreadsheet. A narrative regarding whether risk is altered or subjects should be notified may be provided for each group of similar events.

6.5 Adverse Event Follow-up

Follow-up of 1 month after adverse event via a call to the subject.

7 Statistical Plan

7.1 Statistical Methods

Co-Primary Null Hypothesis 1: the number of subjects reporting grade 1 delayed orgasm (CTCAE v4.0) in the active arm will be smaller or equal to the placebo arm.

Co-Primary Null Hypothesis 2: the number of subjects reporting grade 1 vaginal dryness (CTCAE v4.0) in the active arm will be smaller or equal to the placebo arm.

Statistical Analysis: We intend to use a one-sided paired sample student-t test to analyze the difference between the two arms.

7.2 Subject Population(s) for Analysis

Based on our prior clinical study in breast augmentation subjects, we believe that approximately 40% of women will have an improvement in either delayed orgasm and/or vaginal dryness; therefore, in order to reject the null hypothesis (p=0.05 and 80% power) we will need 28 subjects to complete the study.

We intend to enroll a maximum of 35 subjects to have adequate data for analysis. We estimate that 7 subjects (20% of subjects) may fail to complete the study due to compliance or other unforeseen issues.

[redacted]

* Reference: Rosner B. *Fundamentals of Biostatistics*. 7th ed. Boston, MA: Brooks/Cole; 2011.

7.3 Significance

We plan to reach a statistical significance level of $p<0.05$ and 80% power.

7.4 Termination Criteria

[redacted]

7.5 Accountability Procedure

The data will be analyzed by a bio-statistics expert employed by the sponsor.

7.6 Deviation Reporting

No deviation from the statistical plan will be implemented without the prior review and approval of the ethics committee.

8 Direct Access to Source Data/Documentation

Applied Biology, Inc. will permit trial-related monitoring, audits, IRB/IEC(s) review and regulatory inspection(s) by providing direct access to source data/documentation.

9 Quality Control and Quality Assurance

Due to the short duration of the study, every effort will be made to keep staff assignments consistent throughout the entire study. The PI who assesses the subject at baseline should follow the subject throughout the completion of the study. This will ensure that this study is conducted – and that data is generated, documented (recorded), and reported - in compliance with this protocol, with GCP, and any other applicable regulatory requirements.

10 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and Applied Biology, Inc. research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the ethics committee for formal approval to conduct the study. The decision of the ethics committee concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and provide sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by

the ethics committee. The formal consent of a subject, using the ethics committee approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or a legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

During enrollment, each subject will be assigned a number. The numbers will be consecutive starting at 001.

During enrollment a record will be created for each subject. Each record will contain a medical history, subject's efficacy parameters recorded during each site visit and any adverse events or study related information.

The PRO data will be stored with no subject identifying information. The subjects' records will be stored and handled in the same manner as the PI's patients' records.

The study monitor will keep a separate record at the sponsor's office of each subject's identification number, the corresponding treatment assigned to the subject. The record will not contain any personal information that can be used to identify a subject without access to the subject's record stored at the study site. The PI will not have access to the records located at the sponsor's office.

No other data will be recorded. No personal information will be kept outside the study site.

Data compiled at the end of the study will not include any information that can be used to identify individuals.

The site will keep all subject records for a minimum of 3 years after the completion of the study.

12 Finance and Insurance

[redacted]

[redacted]