The University of Miami Miller School of Medicine
Desai Sethi Urology Institute

Clinical Research Protocol

Title:	**NOVEL TREATMENT FOR ERECTILE DYSFUNCTION COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA (COCKTAIL)**
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Sponsor:	**Emad Ibrahim, MD**
Telephone:	**(305) 243 – 9082**
Fax:	**(305) 243 – 3381**
Email:	**eibrahim@med.miami.edu**

Investigator Signature Page

Title: **NOVEL TREATMENT FOR ERECTILE DYSFUNCTION COMBINING SHOCKWAVE THERAPY AND PLATELET RICH PLASMA (COCKTAIL)**

I have read the enclosed protocol. I will ensure the safety of the study subjects enrolled under my supervision, and will provide the sponsor with complete, accurate, and timely information on this study, as outlined in this Protocol. The signature below constitutes approval of this protocol and the attachments and provides the required assurances that this trial will be conducted according to all stipulations of the protocol, including local legal and regulatory requirements, applicable US federal regulations and (ICF E6) guidelines. I shall hold strictly confidential all information pertaining to the study, and that this confidentiality requirement applies to all study staff at the site(s) and/or under my supervision.

Emad Ibrahim, MD 04/16/2024

Print Name for Principal Investigator Date

_____

Principal Investigator Signature

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List of Abbreviations and Definition of Terms

AE	Adverse Events
BPH	Benign Prostatic Hyperplasia
BRB	Biomedical Research Building
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
ED	Erectile Dysfunction
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction
EDV	End Diastolic Velocity
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ICI	Intracavernosal Injection
IEC	Institutional Ethics Committee
IIEF	International Index of Erectile Function
IIEF-EF	Erectile Function Subdomain Score
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ISCI	Interdisciplinary Stem Cell Institute
MCID	Minimal Clinically Important Difference
mL	Milliliter
ng/dL	Nanograms Per Deciliter
PDE5i	Phosphodiesterase 5 inhibitor
PPP	Platelet Poor Plasma
PRFM	Platelet Rich Fibrin Matrix
PRP	Platelet Rich Plasma
PSV	Peak Systolic Velocity
RCT	Randomized Controlled Trial
SAE	Serious Adverse Events
SGA	Subject Global Assessment
SOP	Standard Operating Procedure
SWT	Low-intensity Shockwave Therapy
TE-SAE	Treatment Emergent Serious Adverse Events
UM	University of Miami
VAS	Visual Analogue Pain Scale

Protocol Synopsis	
TITLE	Novel Treatment for Erectile Dysfunction Combining Shockwave Therapy and Platelet Rich Plasma (COCKTAIL)
SPONSOR	Desai Sethi Urology Institute, University of Miami, Miller School of Medicine
PHASE OF STUDY	Phase I/II
STUDY THERAPY	Autologous Platelet-Rich Plasma (PRP) + Low-intensity Shockwave Therapy (SWT)
STUDY DESIGN	Randomized, Double Blind, Placebo Controlled, Pilot Trial
ROUTE OF ADMINISTRATION	Intracavernosal Injection (PRP) + extracorporeal shockwave therapy (SWT)
SUBJECT POPULATION	60 male subjects between the age of 30-75 with Mild or Mild-to-Moderate ED
STUDY OBJECTIVES	Primary: To investigate and compare the treatment efficacy of PRP injection + SWT vs placebo injection / SHAM treatment in men with mild-moderate ED, as measured by IIEF. Secondary: To study incidence of adverse events and safety of PRP injection + SWT treatment in men with mild-moderate ED, as measured by IIEF.
INVESTIGATION PLAN	60 men with Erectile Dysfunction (ED) of organic origin, that meet all of the inclusion and none of the exclusion criteria, will be randomized to receive either PRP+SWT, or placebo/sham in a 1:1 double-blinded fashion. a) Group A (30 subjects): Autologous PRP injection + SWT therapy. All subjects in this group will receive 2 sessions of autologous PRP penile injection with 30 ± 7 day treatment interval. 5mL of PRP will be injected at each session. Additionally, patients will receive a total of 3600 shocks over a five-week period, starting at initial PRP injection. b) Group B (30 subjects): Placebo (Normal Saline) + SHAM. All subjects in this group will receive 2 sessions of normal saline penile injection with 30 ± 7 day treatment interval. 5mL of normal saline will be injected at each session. Additionally, patients will receive SHAM treatment over a five-week period, starting at initial placebo injection.
DURATION OF STUDY	7 months (1 month screening, 5 weeks of therapy sessions, 6 months of follow-up).
DEFINITION OF ENDPOINTS	Primary: - Incidence of treatment emergent serious adverse events (TE-SAEs) in all patients during the study period. Secondary: - Change in IIEF-EF score from baseline to 3 and 6 months post-therapy compared to control group. - Percentage of subjects that achieve minimal clinically important difference (MCID) in IIEF-EF from baseline to 3 and 6 months post-therapy compared to control group, - Percentage of subjects who either decrease or discontinue use of PDE5i after three months post-therapy compared to control group. Exploratory: - Differences in Doppler ultrasound parameters (PSV and EDV) from baseline to 6 months post-therapy compared to control group. - Treatment satisfaction as assessed by EDITS questionnaire in all subjects. -

Protocol Synopsis	
INCLUSION CRITERIA	1. Be Male 2. Be 30 to 80 years of age (inclusive). 3. Be able to provide written informed consent. 4. Have a diagnosis of mild to moderate ED (12-21) or mild ED (22-25) based on IIEF-EF questionnaire score. 5. Be in a stable heterosexual relationship, and have a minimum of 2 sexual attempts per month for at least one month prior to enrollment. 6. Agree to comply with all study related tests/procedures.
EXCLUSION CRITERIA	1. Previous penile surgery of any kind (except circumcision and condyloma removal), such as penile lengthening, penile cancer surgery, penile plication, grafting. 2. Previous history of priapism, penile fracture, Peyronie's Disease, or penile curvature that negatively influences sexual activity, 3. Abnormal morning serum testosterone level defined as a value lower than 300 ng/dL (±5%). 4. Psychogenic ED as determined by study investigator. 5. Patients using ICI for management of ED 6. Patients with generalized polyneuropathy, neurological conditions, or psychiatric disease (such as bipolar disorder or depression). 7. Have a serious comorbid illness or condition that, in the opinion of the investigator, may compromise the safety or compliance of the subject or preclude successful completion of the study. 8. History of consistent treatment failure with PDE5 inhibitors for therapy of ED. 9. Poorly controlled diabetes as indicated by Hemoglobin a1c > 9%. 10. Use of antiplatelet medication

1. Protocol Title

Novel Treatment for Erectile Dysfunction Combining Shockwave Therapy and Platelet Rich Plasma (The COCKTAIL Clinical Trial)

2. Background

2.1 Platelet-based therapies

Platelet-derived therapies are a growing trend across multiple medical and surgical specialties including dermatology, ophthalmology, cardiology, colorectal surgery, plastic surgery and mainly orthopedics [1-2]. One of the most well described platelet-based therapies is autologous platelet-rich plasma (PRP) [3]. PRP is derived from the centrifugation of whole blood with a separator gel to remove the red and white blood cells. The resulting supernatant has a greater than four-fold increase in platelets and other plasma proteins [1]. This concentrate is then administered via injection. PRP has been frequently used for orthopedic conditions such as bone and soft tissue trauma, inflammatory conditions, and chronic pain syndromes [3-4]. Evidence suggests that platelets play an important role not only in coagulation but also in regulation of body metabolism, promotion of the wound healing, tissue regeneration, vascular remodeling and inflammatory/immune responses through secretion of growth factors, cytokines and chemokines [4-5]. These biologically active proteins include transforming growth factor-β, platelet-derived growth factor, platelet-derived epithelial growth factor, insulin- like growth factor, vascular endothelial growth factor, basic fibroblast growth factor, as well as many others [6]. When platelets are activated, they release these growth differentiation factors, facilitating even nerve repair and regeneration [7-8]. Growth factors act locally and are implicated in many aspects of natural wound healing, including chemotaxis, cell proliferation, cell differentiation and angiogenesis. They also control and conduct synthesis, modification and degeneration of extracellular matrix proteins. Coordination of these cellular and molecular processes is integral to proper wound healing and tissue regeneration [9]. The key role of platelets in these processes makes them an attractive candidate for therapies aimed at accelerating natural healing, as well as tissue regeneration.

Autologous blood-based biomaterials are promising therapeutic options for varied pathology. Rapid generation of therapeutic material following collection allows for point-of- care therapy [10]. Furthermore, an autologous therapy avoids the need for immunosuppression and eliminates concerns of rejection. Newer strategies to prolong the anti-inflammatory and wound healing properties of platelets have focused on creating a fibrin matrix (platelet rich fibrin matrix, PRFM) to bind the platelets and prevent extravasation from the site of injection, thereby addressing the concern of early washout with PRP [11]. In addition, PRFM offers a potential scaffold for tissue ingrowth and may allow continued release of platelet-related factors for a longer duration. Across multiple disciplines, PRP has been used both as a primary treatment modality and as a supplement to other therapies in hopes of supplementing wound healing, tissue regeneration, and angiogenesis. Although most of the studies focusing on PRP injections have been relatively small and heterogenous, they largely support the concept of administration in terms of safety, while efficacy remains uncertain. Finally, the concept of

autologous therapy has be shown in the real world that it is particularly attractive to patients [10].

2.2 Platelet-rich plasma treatment for erectile dysfunction

Erectile dysfunction (ED) affects as many as 1 in 4 men, and evidence indicates that incidence is rising [12-13]. The pathophysiology is multifactorial, but the most common pathophysiology, vasculogenic erectile dysfunction, has as first sign endothelial dysfunction secondary to inflammation [14]. The most common treatments for ED aim to improve endothelial function through augmentation of the nitric oxide pathway [15]. Return of potency after surgical injury of CNS partially depends on axon regeneration in the remaining neural tissue [16]. The process of regeneration and functional recovery of peripheral nerve is slow and is influenced by many factors [17] such as extracellular matrix, neurotrophic factors, and cellular components [18]. Recent advances in the understanding of molecular pathways and their physiological role demonstrate that growth factors are an important part of the development, maintenance, and regeneration of the nervous system [19]. Various growth factor neuromodulatory strategies, including insulin-like growth factor (IGF-I) and neurotrophic factors, are investigated to identify agents that may have neuroprotective and regenerative function after the occurrence of peripheral nerve injury. Accumulating evidence indicates that neuroimmunophilin ligand (such as FK506) plays a significant role in neural regeneration and upregulation of neuronal nitric oxide synthase (nNOS), as well as in the recovery of erectile function after CN injury occurrence [20-21]. FK506 neuroprotection after CN injury is mediated by antioxidative/nitrosative and anti- apoptotic pathway [22]. When platelets are activated, they release many kinds of growth differentiation factors and a few types have been found to facilitate nerve repair and regeneration. Moreover, corporeal dysfunction due to smooth muscle atrophy or other inracavernosal pathology can lead to corporo-venous occlusive erectile dysfunction despite a normal arterial inflow. Rejuvenating the Corporeal tissues with PRP, which is well known for its growth and healing factors, is a possible modality as a potential treatment for erectile dysfunction according to Alkhayal et al [23]. In their retrospective study examining the efficacy of one intra-cavernosal PRP injection to 40 ED patients, they reported that mean IIEF-5 score before treatment was 13 (5-20) and post treatment IIEF-5 = 17 (7-24), ($p < 0.001$). Other studies have shown similar results with minimal side effects, no serious adverse reactions and potential efficacy (Table 1) [23-26].

Human Studies of PRP for ED							
Author	**Year**	**Number of Patients**	**Patient Population**	**Administration**	**Followup**	**Adverse Events**	**Conclusion**
Banno [26]	2017	N=9	Penile Rehab	PRP ICI into Pnies with Vacuum Device	4 weeks	No AEs reported	PRP may represent a safe and viable option as a supplementary therapy for penile rehabilitation. Particularly notable is the prospect of zero side effects.
Matz [24]	2018	N=16	Erectile dysfunction, Peyronies Disease	PRP with CaCl ICI	15.5m	Minor: Bruising 1, Mild Pain 4. Major: none	PRFM injections for ED, PD, and female SUI are feasible and safe. Although the limited data is suggestive of efficacy, a placebo control will be required in subsequent efforts for confirmation
Epifanova [25]	2019	N=10	Erectile Dysfunction	6 injections PRP with CaCl2 ans Shockwave	60 Days	No AEs reported	There were no serious adverse events as well as severe adverse events. Erectile dysfunction symptoms in all men participated in the study significantly decreased after treatment with PRP-therapy and extracorporeal shockwave therapy
Alkhayal [23]	2018	N=40	Erectile Dysfunction	1 injection PRP	> 1 month	No AEs reported	Platelet rich plasma is a safe and efficacious option for penile rejuvination and improvement of erectle dysfunction

Table 1: Summary of published studies and abstracts

To date, there are no treatments that address the underlying cause of endothelial dysfunction, although LIST treatment for ED has shown promising results. Platelet-derived therapies targeting inflammation and promoting tissue/nerve regeneration and may represent a potential treatment option towards this direction. Despite growing evidence to the efficacy of PRP, no randomized placebo-controlled studies exist.

2.3 Energy-based treatments for erectile dysfunction

Shockwave therapy has been utilized by urologists for other ailments, such as treatment of kidney stones through a non-invasive manner. Interest in the use of low-intensity shockwave therapy for erectile dysfunction was augmented with success seen in preclinical models. The hypothesis for SWT's mechanistic actions is neo-angiogenesis, recruitment of progenitor cells and resident stem cells, improvement of microcirculation, vasodilation with subsequent increase in nitric oxide, decrease in fibrosis, and nerve regeneration. There have been 13 published clinical studies regarding use of SWT for ED. Multiple systematic reviews and meta-analyses have been performed for SWT for ED, and there is consensus that SWT shows promise in the treatment for ED.

2.4 Combination Restorative Therapy for Erectile Dysfunction

The development of ED therapeutics that focus on neurovascular regeneration and repair strategies are of great importance. A large body of *pre-clinical* work has demonstrated the effect of SWT alone (monotherapy) on angiogenesis and progenitor / stem cell recruitment for ED [2, 3, 8-11]. PRP monotherapy importantly is also supported by well-defined mechanistic insights obtained from rigorously conducted animal studies [12-19]. All the previous studies in humans have evaluated either IIEF scores and / or penile Doppler ultrasound hemodynamic parameters, but there has not been evaluation of the treatment as a combination. The proposed mechanisms of both interventions would

suggest that the combination therapy would act in a synergistic manner, with superiority over monotherapy. Success of our proposed work could fundamentally change the standard of care for ED and substantially improve the quality of life for tens of millions of men.

3. Study Objectives

3.1 Primary Objective:

To investigate and compare the safety of PRP and SWT vs placebo/sham treatment in men with mild-moderate ED.

3.2 Secondary Objective:

To study the treatment efficacy of PRP and SWT treatment vs placebo/sham treatment in men with mild-moderate ED.

4. Study Endpoints

4.1 Primary Endpoint (safety):

- Incidence of treatment emergent serious adverse events (TE-SAEs) in all patients during the study period. Adverse events will be recorded at every visit. The following contains a list of the anticipated adverse events:
    - Pain
    - Bruising
    - Swelling
    - Edema
    - Allergy
    - Penile Fracture
    - New Penile Curvature

4.2 Secondary Endpoints (efficacy):

- Change in IIEF-EF score from baseline to 3 and 6 months post-therapy compared to control group.
- Percentage of subjects that achieve minimal clinically important difference (MCID) in IIEF-EF from baseline to 3 and 6 months post-therapy compared to control group,
- Percentage of subjects who either decrease or discontinue use of PDE5i after three months post-therapy compared to control group.

4.3 Exploratory Endpoints:

- Differences in Doppler ultrasound parameters (PSV and EDV) from baseline to 6 months post-therapy compared to control group.
- Treatment satisfaction as assessed by EDITS questionnaire in all subjects.
- Changes in IPSS questionnaire between treatment and control group.
- Perceptions of therapeutic allocation between treatment and control group.

5. Study Location

The study will be funded by the NIH (R01DK130991-01) and coordinated by the University of Miami (UM), Miller School of Medicine, Desai Sethi Urology Institute. The UM Interdisciplinary Stem Cell Institute (ISCI) will also support the project (logistics, quality control, management, storage of specimens and data). All study visits will be carried out in the Desai Sethi Urology Institute clinics, (Address: 1150 NW 14th Street, Suite 309, University of Miami Miller School of Medicine, Miami, FL) or Christine Lynn Rehabilitation Center (Address: 1611 NW 12th Ave, Miami, FL 33136).

5.1 Additional Study Sites

No additional study sites.

6. Study Population

60 males with ED of organic origin. All patients will be regular PDE5i users/responders. Men with ED will be evaluated by IIEF-EF domain and eligible patients will be randomized to one of 2 treatment groups with an equal allocation ratio (1:1). Participants who do not meet eligibility criteria will be considered a screen failure and will not receive the study therapy.

6.1 Inclusion criteria:

In order to participate in this study, a patient must:

1) Be Male
2) Be 30 to 80 years of age (inclusive).
3) Be able to provide written informed consent.
4) Have a diagnosis of mild to moderate ED (12-21) or mild ED (22-25) based on IIEF-EF questionnaire score.
5) Be in a stable heterosexual relationship, and have a minimum of 2 sexual attempts per month for at least one month prior to enrollment..
6) Agree to comply with all study related tests/procedures.

6.2 Exclusion criteria:

In order to participate in this study, a patient must not have any of the following:

1) Previous penile surgery of any kind (except circumcision and condyloma removal), such as penile lengthening, penile cancer surgery, penile plication, grafting.
2) Previous history of priapism, penile fracture, Peyronie's Disease, or penile curvature that negatively influences sexual activity,
3) Abnormal morning serum testosterone level defined as a value lower than 300 ng/dL (±5%).
4) Psychogenic ED as determined by study investigator.
5) Patients using ICI for management of ED
6) Patients with generalized polyneuropathy, neurological conditions, or psychiatric disease (such as bipolar disorder or depression).

7) Have a serious comorbid illness or condition that, in the opinion of the investigator, may compromise the safety or compliance of the subject or preclude successful completion of the study.
8) History of consistent treatment failure with PDE5 inhibitors for therapy of ED.
9) Poorly controlled diabetes as indicated by Hemoglobin a1c > 9%.
10) Use of antiplatelet medication

7. Identification and Enrollment of Subjects

7.1 Recruitment and Pre-screening

The research coordination team may develop materials to aide in recruitment. This may include, but is not limited to, informational videos and brochures which provide education about erectile dysfunction and include information about the study; physician referral letter templates which can be used to promote awareness of the study in the urology community; flyers/posters which can be utilized at approved clinic locations and as part of health fair materials; templates for print advertisements which can be utilized in newsprint and media campaigns. Not all materials have been developed prior to trial initiation, however each of these recruitment methods will be reviewed and approved by the IRB prior to use.

Pre-screening of subjects includes reviewing medical records and imaging studies for inclusion/exclusions prior to consent. From the review of subjects' medical records and imaging studies on file, subjects who are determined to have a diagnosis of erectile dysfunction of organic origin, and have mild-moderate erectile function as assessed by IIEF-EF, as stated in Section 6.1, and also do not have evidence in their medical record of study exclusions stated in Section 6.2, are eligible to be consented to the study.

Investigators will inform research staff of potential participants who have been identified through pre-screening so the subjects can be approached to discuss the study and conduct the informed consent session. No study procedures will take place prior to the subjects signing of the informed consent form.

7.1.1 Waiver of Authorization for Use and Disclosure of Protected Health Information (HIPAA)

A partial waiver of HIPAA is requested for recruitment purposes only. All Protected Health Information (PHI) collected by the study investigator and/or study personnel from patient records JHS and/or UHealth will be destroyed at the earliest opportunity. All Protected Health Inform (PHI) that is acquired from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

7.2 Payment to Subjects

No payments will be made to subjects as compensation for their participation in this study. The subjects will not be asked to pay for the treatments or participation in study either.

7.3 Informed Consent

7.3.1 Consenting Process

All subjects must provide written consent to participate in this study. An informed consent form (ICF) will be given to each subject. The ICF will contain all United States federally required elements, all International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) required elements, and Health Insurance Portability and Accountability Act Authorization (HIPAA) information in language that is understandable to the subject. The informed consent includes descriptions of all study related procedures, all possible risks to participant, and the time commitment involved with participating. All consent forms will have IRB approval. The ICF and review must be in a form understandable to the subject. Translation of ICFs will be done in accordance with local IRB procedures.

Potential participants will be approached by one of the study investigators or research coordinators. Information regarding study participation will be provided to the potential participant prior to consent. Subjects will be given ample time to review the ICF and ask questions before signing. The Investigator or designee and the subject must both sign and date the ICF after review, and before the any study procedures are performed. The subject will receive a copy of the signed and dated form, and the original will be retained in the site study files. The research staff member obtaining consent will document the informed process in the subject's chart for monitoring purposes. The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

7.3.2 Non-English Speaking Subjects

In addition to English-speaking subjects, Spanish-speakers will also be included in the trial. A certified translated version of the IRB approved English consent form will be made available to non-English speakers. Spanish version questionnaires and other patient-facing materials will also be made available.

7.4 Withdrawal Criteria

All subjects who either screen fails, is withdrawn from the study, or has completed all visits should be de-enrolled from the research database within 2 business days, in accordance with university policies (or respective institutional policy).

Subjects may be withdrawn from the study for any of the following reasons:

a) A subject does not meet the eligibility criteria (the subject will be considered a screen failure).

b) A subject withdraws consent.

c) If a new treatment for erectile dysfunction is made available during the study duration, the investigator will inform the patient at a follow-up visit, and be offered withdrawal to utilize new treatment.

d) A subject expires during protocol participation from causes other than the study treatment (not due to adverse events).

e) At the discretion of the principal investigator for issues of non-compliance, or other behavioral factors.

8. Procedures Involved

60 men with Erectile Dysfunction (ED) of organic origin, that meet all of the inclusion and none of the exclusion criteria, will be randomized to receive either PRP+SWT, or placebo/sham in a 1:1 double-blinded fashion.

a) Group A (30 subjects): Autologous PRP injection + SWT therapy. All subjects in this group will receive 2 sessions of autologous PRP penile injection with 30 ± 7 day treatment interval. 5mL of PRP will be injected at each session. Additionally, patients will receive a total of 3600 shocks over a five-week period, starting at initial PRP injection.

b) Group B (30 subjects): Placebo (Normal Saline) + SHAM. All subjects in this group will receive 2 sessions of normal saline penile injection with 30 ± 7 day treatment interval. 5mL of normal saline will be injected at each session. Additionally, patients will receive SHAM treatment over a five-week period, starting at initial placebo injection.

8.1 Schedule of Events:

The events table for the conduct of this study is shown below:

Table 1:

Schedule of Events		Screening	Treatment					Follow Up	
Time Point / Event		0-30 days before randomization	Week 1 Day 0	Week 2 Day 7 ± 2	Week 3 Day 14 ± 2	Week 4 Day 21 ± 2	Week 5 Day 28 ± 2	Month 3 Day 90 ± 14	Month 6 Day 180 ± 14
Informed Consent		X							
Demographics		X							
Medical History		X							
Physical Exam		X							
Doppler Ultrasound		X							X
Questionnaires	**IIEF**	X						X	X
	EDITS							X	X
	VAS		X	X	X	X	X		
	IPSS	X							X
	SGA								X
Laboratory Tests		X							
Randomization			X						
PRP/Placebo			X				X		
Shockwave/Sham			X	X	X	X	X		
Concomitant Medications/Therapy		X	X	X	X	X	X	X	X
Review Adverse Events			X	X	X	X	X	X	X

8.2 Description of Study Procedures

8.2.1 ***Informed Consent:*** Refer to Section 7.3 for details regarding the informed consent process. Study procedures will be completed only after participants have signed the informed consent documentation.

8.2.2 ***Demographics:*** Demographic characteristics will be recorded including: date of birth, gender, marital status, race and ethnicity.

8.2.3 ***Medical History:*** Assessment of current and past medical, surgical, and social history will be conducted.

8.2.4 ***Physical Examination:*** Genitourinary/Reproductive system physical exam will be performed.

8.2.5 ***Phone Call:*** Participants will be contacted by telephone to assess safety outcomes during long term follow up.

8.2.6 ***Doppler Ultrasound:*** Penile Doppler ultrasound will be performed as standard of care for the management of erectile dysfunction. Results from within the past 12 months can be extracted from the medical record for use in this study.

8.2.7 ***International Index of Erectile Function (IIEF) Questionnaire*:** This validated 15-item self-evaluation scale provides pre and post treatment clinic evaluations of erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and general satisfaction. If the subject has completed the IIEF questionnaire within the past 6 months, those results may be requested and used for the purpose of this research study. Questionnaires will be completed prior to therapy at injection visits.

8.2.8 ***Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questionnaire*:** This is a psychometrically sound questionnaire used to assess satisfaction with medical treatment modalities for erectile dysfunction.

8.2.9 ***Visual Analogue Pain Scale (VAS)*:** The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a line that represents a continuum between “no pain” and “worst pain”.

8.2.10 ***International Prostate Symptom Score (IPSS):*** This eight-question screening tool used to track symptoms of benign prostatic hyperplasia (BPH)

8.2.11 ***Subject Global Assessment (SGA):*** In this single-question survey, subjects will be asked which treatment arm they believe that they had received (placebo/sham or active therapy).

8.2.12 ***Randomization:*** Refer to Section 9.3 for details about randomization plan

8.2.13 ***PRP/Placebo Injection*:** Approximately 120mL of blood will be collected from participants for preparation of investigational product. Refer to Section 9.2 for description of IP preparation and administration.

8.2.14 ***Concomitant Medications:*** Review of current use of prescription and over the counter (OTC) medications. Participants must discontinue use of PDE5i medications throughout the duration of the study.

8.2.15 ***Review Adverse Events:*** Refer to Section 12 for description and reporting of adverse and serious adverse events.

8.2.16 ***SWT/Sham Treatment*****:** In the treatment group, patients randomized will receive 5 weekly sessions, in which 720 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura). In the sham group, patients will have the same number of sessions, and the machine will be set to deliver 720 shock treatments, but the machine will not fire shockwaves.

8.2.17 ***Laboratory Testing:*** Hematology, chemistry, hemoglobin A1C, and serum testosterone lab test results will be collected at screening. If any standard of care labs testing have been performed within 12 months of the date of the screening visit, those results may be used for the purpose of this study.

8.3 Description of Study Visits

8.3.1 Screening Visit

Visit 1 (0 – 28 days before therapy): The basic work-up will take place, including medical and sexual history, as well as necessary lab tests (testosterone, prolactin, hematology, chemistry), if not available during the last 12 months prior to screening. Subjects will complete the IIEF questionnaire. We will ensure that patients have 4 attempts for intercourse. Screening visit can occur on same day as first injection + SWT/SHAM. Refer to table 1 for procedures to be performed at the Screening visit.

8.3.2 Treatment Visits: Week 0 – Week 4

Upon evaluation of eligibility, subjects will be randomized to one of the two parallel study groups using an online program, and initiate treatment on the same day.

There will be 5 treatment visits for all groups, each occurring at weekly intervals (± 2 days), for a total duration of five weeks. Subjects will complete a Visual Analogue Scale (VAS) pain score after the end of each treatment. Refer to table 1 for all procedures to be performed at the treatment visits.

8.3.3 Follow Up Visits: Months 3 and 6 Post-Treatment

Follow up visits will occur within 90 ± 14 days (Month 3) and 180 ± 14 days (Month 6) days after final treatment visit. Refer to table 1 for procedures to be performed at the follow up visits visit.

9. Investigational Product

9.1 Preparation of IP

Autologous Platelet-Rich Plasma (PRP) is prepared by taking 120 mL aliquots of anticoagulated blood (120 mL whole blood and 16 ml anticoagulant citrate dextrose formula A) obtained from each treatment subject by venipuncture. Each aliquot is processed by an autologous platelet separator (Arthrex Angel, Arthrex Inc., Naples, Florida) to yield 3-10 mL of PRP from each subject. Platelet poor plasma (PPP) can be

added to PRP to achieve the desired injection volume. This system is FDA approved by 501k for “clinical laboratory or intraoperatively at the point of care for the safe and rapid preparation of platelet poor plasma and platelet concentrate (platelet rich plasma) from a small sample of whole blood or a small mixture of blood and bone marrow”. For patients randomized to the control arm, they will still have their blood drawn, however it will not be processed to make PRP.

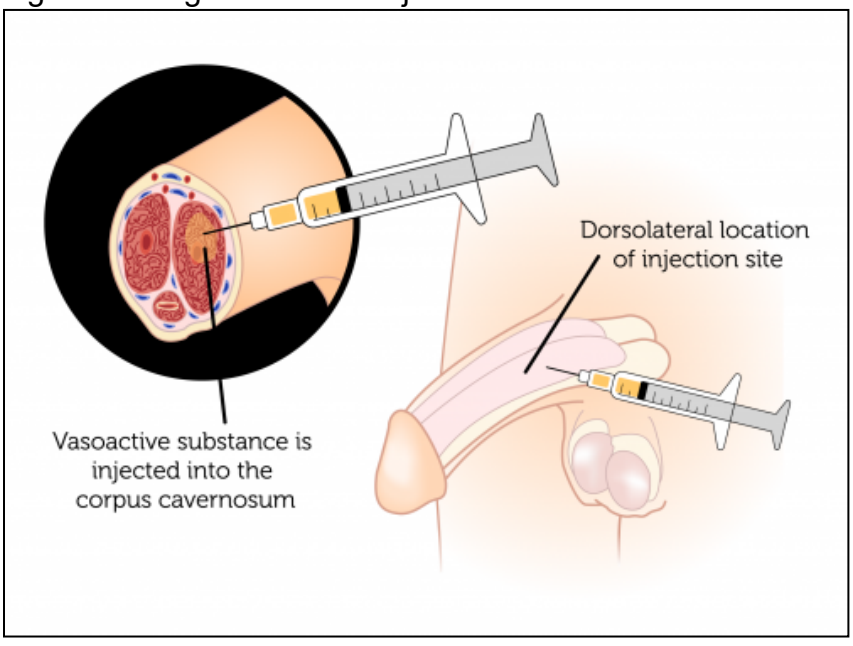
9.2 Administration of Investigational Therapies

9.2.1 Platelet-Rich Plasma

The patient will be positioned supine. A sterile field will be developed with Betadine prep of the genitalia, sterile gloves and a sterile extremity drape. A total of 20 ml of 1% lidocaine will be drawn up using an 18-gauge needle and will be subcutaneously administered using a 27-gauge needle into the subcutaneous tissue at the base of the penis to obtain a dorsal nerve block. A 1/4-inch Penrose drain will be used as a tourniquet by placing it at the base of the penis and maintaining it in place under tension by a sterile clamp. A maximum of 5mL of PRP will be infused steadily over a two-minute period – approximately 2.5 ml each into the right and left corpus cavernosum. The infusion will be performed at this slow speed (each side over 2 minutes of infusion) to minimize injury to the platelet cells. In the control arm, men will be administered injectable normal saline that will be injected in a similar manner as the PRP.

Following administration of PRP or normal saline, compression of the penis will be achieved with a clenched fist for 20 minutes. At 20 minutes, the tourniquet will be removed, and a compressive dressing will be placed around the penile shaft. The patient will be instructed to remove the compression bandage in 4 hours and to contact the study coordinators if he experiences any problems.

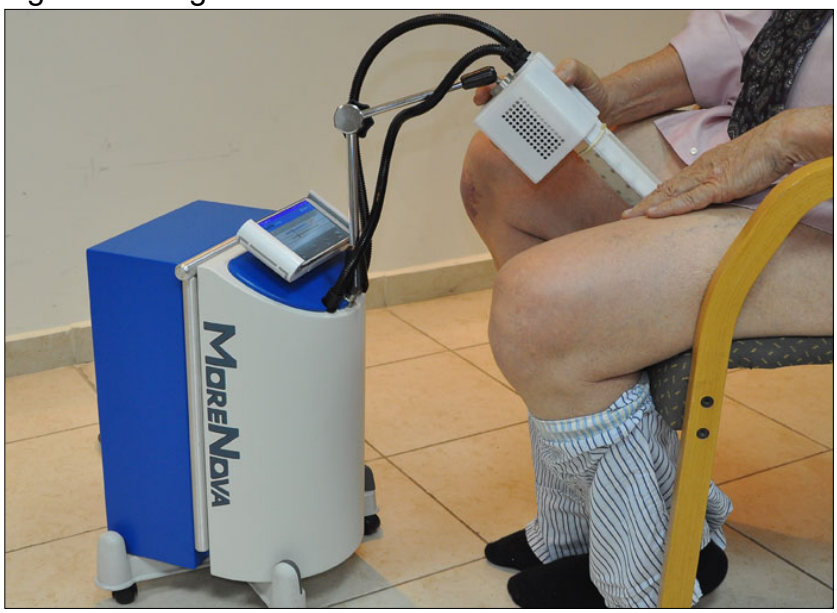
Figure 1: Diagram of PRP Injection



9.2.2 Low Intensity Shockwave Therapy

MoreNova is a Linear Shockwave (LISW) device, which incorporates a shockwave transducer operable to deliver shockwaves to a treatment region confined to a narrow rectangle. Shockwaves generation follows the electromagnetic principle. Linear Shockwaves (LISW), as a treatment for ED has been in evaluation in contemporary medicine. It has been in use for the last five years. The present study will utilize a device called “MoreNova”, in which shockwaves are focused onto line segments for improved organ coverage. Shockwaves produced by "MoreNova" are aimed at the left and right corpora cavernosa and the crura. The study is aimed at determining the safety and effectiveness of this new type of LISW in the treatment of ED. The treatment session lasts approximately 20 minutes and may be performed in an office environment. Treatment is applied in the physician’s office.

Figure 2: Image of MoreNova SWT Device



In the treatment group, patients randomized will receive 5 weekly sessions, in which 720 shocks of treatment energy will be applied in every session to each treated region (left and right corpora cavernosa and crura). In the sham group, patients will have the same number of sessions, and the machine will be set to deliver 720 shock treatments, but the machine will not fire shockwaves.

9.3 Randomization

On Day 0, participants who remain eligible for the trial will be randomized to one of two groups in a 1:1 ratio. The randomization sequence will be computer generated by the study coordinating team.

9.4 Blinding

The study will remain double-blinded by having both blinded and unblinded study teams. All subjects (active-therapy and placebo groups) will undergo blood collection procedure on day of intervention visits.

Preparation of PRP and normal saline injections will be conducted only by unblinded research team members. In the interest of safety, the study product must be inspected to

ensure it is free of air bubbles, clumping, etc. The 10cc syringes used will be colored and covered in both groups in order to ensure the double-blindness of the study.

For participants allocated to the control arm, a sham procedure will be performed in a manner similar to active shockwave therapy arm. Patients will have the same number of sessions, and the machine will be set to deliver 720 shock treatments, however a shield will be placed over the probes to prevent the shockwaves from being transmitted to the penis. In order to maintain the blind, the technician who administers the study therapies will not be involved in assessing outcomes of the study.

If for important medical reasons unblinding of additional team members is thought to be necessary, the investigator may identify the treatment assignment by obtaining randomization records from unblinded study team.

10. Data Management

Data will be entered from source documents into eCRFs which are maintained in an online research database. The investigator will ensure data integrity by confirming the CRF's are attributable, legible, contemporaneous, original, accurate, and complete.

10.1 Case Report Forms (CRFs)

The Investigator or designee must record all required subject data, and an explanation must be documented for any missing data. This study will use electronic case report forms (eCRF) for data entry and database storage.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and records kept at medical technical departments involved in the clinical trial. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary, in accordance with good clinical practice (GCP) guidelines.

10.3 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities.

11. Data and Specimen Banking

11.1 Storage of Data

Data will be maintained on research team hardware, and subject charts will be stored in a filing room maintained by Department of Urology. Clinical follow up and laboratory data will be stored in a locked room, with access only to authorized personnel. It is up to the

principal investigator's discretion as to how long non-FDA study essential documents are retained.

11.2 Specimen Banking

Bio-specimens will be reserved for future testing and stored at -80 degrees Celsius in equipment maintained by ISCI in the Biomedical Research Building (BRB) (address: 1501 NW 10th avenue Miami FL 33136). Each specimen must have a corresponding requisition form to track the chain of custody from time of collection to time of processing and/or storage.

12. Safety Monitoring and Reporting

12.1 Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study. The event does not need to have a causal relationship with treatment. Common Terminology Criteria for Adverse Events Version 5 (CTCAE) will be used for describing AEs. All urological and/or reproductive system AEs will be recorded. For all other AEs, only events greater than grade 2 will be recorded.

Based on our own pilot data assessing SWT and PRP monotherapy, we have compiled the following data on adverse events (Table 2):

We anticipate there to be few adverse events related to the study. Based on the four published studies and abstracts, including 75 men, only minor adverse events were reported (Bruising 1, Mild Pain 4). No serious adverse events were observed [23-26].

SWT related adverse events	
Transient mild cutaneous purpura	0.10%
Local erythema	0.50%
Local swelling/edema	1.00%
Transient local anesthesia or paranesthesia	1.10%

PPR related adverse events	
Pain greater than 5/10 at time of injection	5.00%
Pain lasting > 5 days	5.00%
Penile bruising	0.00%
Penile fracture	0.00%

12.1.1 Expectedness

An adverse event is considered "unexpected" if it is not listed in the investigator brochure, protocol, ICF, or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Anticipated adverse events for this study include: Pain, Bruising, Swelling, Edema, Allergy, Penile Fracture, and/or New Penile Curvature.

12.1.2 Severity

Common Terminology Criteria for Adverse Events, Version 5 (CTCAE v5.0) will be used to assess severity of adverse events. All grade 3-5 adverse events, regardless of association with the investigational therapy, will be entered into study database and reviewed at research committee meetings.

12.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined as an AE which, in the view of the Investigator results in: 1) Death; 2) a life-threatening event (i.e. 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); 3) inpatient hospitalization of > 24 hours or prolongation of existing hospitalization; 4) a significant disability/incapacity; or 5) a congenital anomaly/birth defect. Other important medical events may be considered SAEs if, in the opinion of the Investigator, they jeopardize the subject or require intervention to prevent one of the other outcomes listed above. Based on prior investigations, we do not anticipate any SAEs related to the study procedures [23-26].

12.3 Treatment Emergent Serious Adverse Events (TE-SAEs)

A treatment emergent serious adverse event (TE-SAE) is defined as any serious adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. For the purposes of safety reporting, “a reasonable possibility” means there is evidence to suggest a causal relationship between the study product/procedures and the adverse event.

13. Data and Safety Monitoring Board (DSMB) Charter

13.1 Introduction

This charter defines the roles and responsibilities of the Data and Safety Monitoring Board (DSMB) for the COCKTAIL trial which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The DSMB will serve in accordance with the guidelines set forth in this charter. Typically DSMB members review and agree to the charter at the initial meeting. If changes to the charter are necessary, the DSMB reviews and affirms their agreement with the changes. Their concurrence will be noted in the DSMB meeting summary

13.2 DSMB Responsibilities

Generally, the first responsibility of the DSMB will be to approve the final protocol of the clinical study named above, or the study/studies being undertaken by the research network named above so that the study/studies can begin enrolling patients. After initial approval, and at periodic intervals during the course of the study, the DSMB responsibilities are to:

- Provide input to assist the investigator(s) in protecting the safety of the study participants;
- Provide input to the investigator(s) on major changes to the research protocol, informed consent documents and plans for data and safety monitoring;
- Provide input to the investigator(s) on the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study sites, and other factors that may affect study outcomes;
- Review areas of concern regarding the performance of individual sites and provide comment to the investigator(s) on actions to be considered regarding sites that perform unsatisfactorily;

- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- Provide input to the investigator(s) on modification of the study protocol or possible early termination of the study because of attainment of study objectives, safety concerns, low likelihood of showing a benefit of the intervention, or inadequate performance (such as enrollment and retention problems);
- If appropriate, review the interim analysis of efficacy in accordance with stopping rules which are clearly defined in the protocol and have the concurrence of the DSMB;
- Provide input to the investigator(s) on the desirability of proceeding to the full-scale study at the completion of a feasibility phase, if appropriate;
- Provide input to the investigator(s) on the potential impact of ancillary studies on the integrity of the parent study; and
- Monitor clinical ancillary studies unless an independent monitoring is established

13.3 Membership

The members have been appointed by the investigator(s) and approved by NIDDK. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study. Collaborators or associates of the investigators in this study are not eligible to serve on the DSMB. Written documentation attesting to absence of conflict of interest is required at least annually, and each time there is a change in site investigators and/or institutions involved in the study.

The investigator(s) will appoint a DSMB chairperson. He or she is responsible for overseeing the meetings and developing the agenda in consultation with the investigator(s).

13.4 DSMB Meetings

The DSMB will typically meet twice a year, or as deemed necessary. A quorum of more than half of the DSMB members is required in order to convene a meeting of the DSMB.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings are attended, when appropriate, by the principal investigator and members of his/her staff, as well as the study statistician. Meetings may be convened as conference calls or webinars, as well as in person. In special circumstances, the meetings may also be conducted by email. An emergency meeting of the DSMB may be called at any time by the DSMB chairperson should questions of patient safety arise.

13.4.1 Meeting Format

An appropriate format for DSMB meetings consists of an open, closed (if the DSMB is monitoring a study in which the investigators are masked in any way), and executive session. This format may be modified as needed.

13.4.1.1 Open Session

Members of the DSMB, the principal investigator and members of the steering committee, including the study biostatistician may attend the open session. Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Proposed protocol amendments will also be presented in this session. Patient-specific data and treatment group data may not be presented in the open session.

13.4.1.2 Closed Session

The closed session will be attended only by DSMB members, and the unmasked study biostatistician. The discussion at the closed session is completely confidential. All materials from the closed session will be destroyed at the end of the meeting.

Analyses of outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. The DSMB may request unmasking of the data for either safety or efficacy concerns. Procedures to accomplish unmasking of either individual or treatment group data are to be specified in the Data and Safety Monitoring Plan.

13.4.1.3 Executive Session

The executive session will be attended by DSMB members only, who will discuss the information presented during the closed and open sessions and provide input on the continuation or termination of the study, protocol modification or other changes to the conduct of the study. The DSMB can be unmasked at any time if trends develop either for benefit or harm to the participants.

The DSMB will make a recommendation for either continuation or termination of the study. Termination may be suggested by the DSMB at any time. Reasons for early termination include:

- Serious adverse effects in entire intervention group or in a dominating subgroup;
- Greater than expected beneficial effects;
- A statistically significant difference by the end of the study is improbable;
- Logistical or data quality problems so severe that correction is not feasible.

Sound rationale for either decision (continuation or termination of the study) should be presented.

13.5 Reports to the DSMB

Reports will be prepared by the unmasked biostatistician on a quarterly or semi-annual basis as decided by the investigator(s) and the DSMB. The reports will be distributed to the DSMB at least 10 days prior to a scheduled meeting. These reports shall be provided in sealed envelopes within an express mailing package, by secure email, or by access to a secure website, as the DSMB prefers.

Data reports for randomized clinical studies or any study in which the investigators are masked generally consist of two parts: an Open Report and a Closed Report.

13.5.1 Open Session Report

This portion of the report provides information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical study. The reports contained in this section generally include:

- Comparison of Target Enrollment to Actual Enrollment by Month;
- Comparison of Target Enrollment to Actual Enrollment by Site;
- Overall Subject Status by Site, including: Subjects Screened, Enrolled, Active,
- Completed and Terminated;
- Demographic and Key Baseline Characteristics by Group;
- Treatment Duration for Subjects who Discontinue Therapy;
- Adverse Events/Serious Adverse Events by Site and Subject.

13.5.2 Closed Session Report

This report may contain data on study outcomes, including safety data. Data will be presented by masked treatment groups; however, the DSMB may request that the treatment groups be unmasked to ensure that there are no untoward treatment effects. The Closed Session Report is considered confidential and should be destroyed at the conclusion of the meeting. Data files to be used for interim analyses should have undergone established editing procedures to the extent possible. This report should not be viewed by any members of the clinical study except the designated unmasked study statistician.

13.6 Documentation of DSMB Meetings

13.6.1 Meeting Summary

A formal summary containing the DSMB's input on the conduct of the study and their recommendation regarding continuation of the study will be prepared by the DSMB Executive Secretary. Each DSMB summary will include the DSMB's recommendation regarding continuation or termination of the study. The DSMB meeting summary will not include unmasked data, discussion of the unmasked data, or any other confidential data. Once completed, the summary is sent to the DSMB members for their review and concurrence. When the summary is satisfactory to the DSMB members and concurrence with the summary is received, the summary will be sent to the PI. It is the responsibility of the PI to distribute the summary to all co-investigators.

It is the responsibility of the study investigators to assure that the DSMB summary is submitted to all the Institutional Review Boards (IRBs) associated with the study.

13.7 Confidentiality and Objectivity

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality. Closed session meeting materials should be destroyed in a secure manner (shredding) following each meeting.

In order to maintain their objectivity, DSMB members are expected not to discuss the study/studies with the investigators except during DSMB meetings.

14. Statistical Considerations

14.1 Data Analysis Plan

Analysis plan: Continuous data will be analyzed using ANOVA with repeated measures, or student's T-Test (where applicable) in order to compare differences between the treatment and control groups. For categorical data, Fisher's Exact test to determine differences between groups. Statistical significance will be evaluated using $\alpha=0.05$.

14.2 Sample Size

Inclusion Criteria are men with IIEF scores >11 which includes men with mild (IIEF 16-21) and mild/moderate (12-16) Erectile dysfunction. Minimal clinically important differenced (MCID) for these groups are an increase of 2 for mild and 5 for moderate ED. Previous studies on the effect of placebo show about a 15% improvement in men with mild to moderate ED. Therefore, 15% of the placebo group is expected to meet MCID. Results from the PRP safety study by Matz et al. 2018, which showed a mean improvement in IIEF of 4.14 points in seven patients with ED after PRP. In the interventional group, we expect 50% to meet MCID. At 80% power, we will therefore need 30 patients in each group to detect a difference of 35% between treatment and placebo arms.

$$\text{Sample size} = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 P(1-P)}{(p_1 - p_2)^2}$$

$24 = (2*(1.96+0.84)^2 * (0.25*(1-0.25)) / (0.35^2)$

Assuming attrition of approximately 20%, an additional 6 participant slots will be added to each group for a total sample size of 60 subjects.

15. Risks and Benefits

15.1 Risks to Subjects

We anticipate there to be few adverse events related to the study. Based on the four published studies and abstracts, including 75 men, only minor adverse events were reported (Bruising 1, Mild Pain 4). No serious adverse events were observed [23-26]. After literature review, we believe this product to be of non-significant risk to patients (NSR) and for investigational use in a clinical study protocol.

Based on published studies, we will record anticipated adverse events to patients include: local injection site reaction, penile pain, penile hematoma (bleeding into the tissue), penile swelling, allergic reaction to the anesthetic, local infection, penile fracture, or new penile curvature. In addition, there may be uncommon or previously unknown risks that might occur. We will record every adverse event at every visit systematically.

15.2 Potential Benefits to Subjects

The potential benefits for men randomized to the treatment arm will include improvement in erectile function and sexual performance.

16. Privacy & Confidentiality

Each subject's protected health information will remain strictly confidential and shall be excluded from the database. Patients deemed eligible to participate in the study following evaluation of inclusion/exclusion criteria will be assigned a unique study participant identifier number (ex.: COC-01). The first two characters indicate the enrolling site, next 5 characters describe the study and phase, and final 3 characters are the unique identification number assigned to subjects in sequential order.

The Investigator will retain a cross-referencing record of each subject's name and assigned identifier number. All study data and results will be stored in the electronic database. Each study subject will give explicit consent for representatives of the IRB/IEC and regulatory authorities to inspect and verify each subject's medical records and collected information. In turn, each study subject will be assured that all their personal information will be maintained in the strictest of confidence, and in compliance with HIPAA, and all other federal and local laws regulating privacy and data protection.

Data will be collected from the EMR or subjects at UHealth or JHS. Research subjects will sign a HIPAA Authorization before collection of data for this research study.

16.1 Data collection

Data will include Protected Health information or Personally Identifiable Information.

16.2 Data Storage

Information will be stored on a University of Miami electronic device (e.g. encrypted, password-protected computer), and on a cloud-based storage system that is approved by the University of Miami. Research data will be entered into the Velos secure electronic database.

The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers of any subject. Instead, the Principal Investigator and/or Study Team members will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

16.3 Biospecimens

Biospecimens obtained for this research will be stored in a de-identified, coded manner without any direct or indirect identifiers. Biospecimens obtained for this research will be stored. When required to transport data or biospecimens for this research, the research team will transport the data and biospecimens in a de-identified (or anonymous)manner with a link to the individual subject's identity maintained separately from the data and/or biospecimen.

17. Ethical Considerations

17.1 Regulatory Authority Approval

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on

Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

According to FDA guidance issued to institutional review boards and investigators, we will use PRP for ED (an indication not approved on the labeling) while simultaneously "bearing the responsibility to be well informed about the product, base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."

We believe that according to FDA regulation**,** the clinical investigation of PRP and SWT for ED does not require submission of an IND / IDE since all six of the following conditions are met:

i. it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
ii. it is not intended to support a significant change in the advertising for the product;
iii. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
iv. it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
v. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
vi. it does not intend to invoke 21 CFR 50.24.

17.2 Ethics Approval

The investigators agree to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

It is the Investigator's responsibility to ensure that, prior to initiating this study, this protocol is reviewed and approved by the appropriate local and/or external IRB. The composition and conduct of this committee must conform to the United States CFR. The IRB/IEC must also review and approve the site's informed consent form (ICF), other written information provided to the subject.

If it is necessary to amend the protocol or the ICF during the study, the Sponsor-Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new subjects are consented to participate in the study using the amended version of the ICF.

17.3 Conflict of Interest

Any investigator who has a conflict of interest with the study must have the conflict reviewed by a properly constituted Conflict of Interest Committee with the Committee-sanctioned conflict management plan that has been reviewed and approved by the study

sponsor prior to participation in this study. All investigators will follow the University of Miami's (or applicable institution's) conflict of interest policy.

18. Publications

The preparation and submission of manuscripts for publication that contain results from this study shall comply with all applicable privacy laws and in accordance with processes determined by the University of Miami, Miller School of Medicine.

19. References

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