Efficacy of a Novel Collagenase Clostridium Histolyticum Protocol for Peyronie's Disease Among Prior Non-responders: A Randomized, Controlled, Single-Blinded Study

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Funding Sponsor: Endo Pharmaceuticals

Protocol Number: (IRBe) CUREPD103

Initial version: June 5, 2021 Version **(1.0)**

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CCH	Collagenase clostridium histolyticum
HIPAA	Health Insurance Portability and Accountability Act
IIEF	International Index of Erectile Function
PDE5s	Phosphodiesterase-5 inhibitors
PTT	Penile traction therapy
PD	Peyronie's Disease

Study Summary

Title	Efficacy of a Novel Collagenase Clostridium Histolyticum Protocol for Peyronie's Disease Among Prior Non-responders: A Randomized, Controlled, Single-blinded Study
IRB Protocol Number	20213914
Methodology	Prospective, randomized, controlled, single-blinded
Overall Study Duration	2 years
Subject Participation Duration	1 year
Objectives	Compare key clinical outcomes between controls and men treated with a novel CCH protocol among men previously unresponsive to CCH administration.
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	Men >18 years of age with Peyronie's Disease, current curvature of 30 degrees or more, prior treatment with 6-8 injections of CCH, and prior minimal (<20% and/or <10 degrees) responsiveness to CCH administration.
Randomization	Patients will be randomized 1:3 to control (no treatment) or CCH (up to 8 injections). Patients in the control arm will subsequently be crossed over to CCH treatment after 6 months. Randomization tables will be created and pre-stratified based on baseline penile curvature.
Follow-up Period and Assessments	Men will have objective assessments of curvature and length and standardized and non-standardized questionnaires obtained at various time points (baseline, 6-weeks following completion of CCH, and at the end of the no treatment phase).
Statistical Methodology	Stratification of subjects prior to randomization to assure an equal representation based on baseline penile curvature (30-44, 45-59, 60-74, 75-89, 90 or above). Statistical comparisons between groups and to baseline will be made of responses to subjective questionnaires and objective measures.
Plan for Publication	It is anticipated that the primary study will be published following accumulation of data out to 1 year. Pending novelty of findings, additional studies may also be published if felt to be warranted (subset analyses).

1 Introduction

This document is a protocol for a randomized, controlled, single-blinded clinical trial. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Western International Review Board policies and procedures.

1.1 Background and Clinical Need for the Current Study

Collagenase Clostridium histolyticum (CCH) is the first FDA approved medication for the treatment of Peyronie's Disease and demonstrated significant improvements in penile curvature and bother in two phase III trials.[1] Results specifically demonstrated a mean 34%, or 17-degree improvement in curvature. Post-FDA release, multiple series, including the investigators' own data have confirmed similar findings, including among men with ventral curvatures and calcification.[2-8]

Beginning approximately 3 years ago, the investigators' team sought to achieve further improvements with CCH through the addition of more aggressive modeling therapies. Results from a comparison of CCH alone vs CCH and traction with RestoreX demonstrated a mean 33.8 degree (49%) curvature improvement with combined therapy compared to 19-20 degrees (30-31%) with CCH alone or CCH and other traction devices).[9] These results currently represent the greatest improvements with CCH in published literature and further build upon phase IIb results which demonstrated that mechanical traction (via manual modeling in the phase IIb trial) represents a critical factor in achieving improvements with CCH.[10]

The investigators' team additionally published a survey of men who had experienced suspected penile fractures with CCH and demonstrated greater curvature improvements without any loss / worsening of erectile function.[11] This critical study highlighted that conservative management of suspected fractures should not only be considered a standard of care in managing suspected fractures, but also that these men achieved better final outcomes (again highlighting the importance of the combination of mechanical curvature correction in addition to CCH management).

Based on the above findings, the investigators' team began performing a more aggressive manual modeling protocol. This novel protocol included several notable innovations: dilution of the 0.9 mg of CCH in 0.7 ml of diluent, injection to the erect penis to assure accurate injection, repeat curvature assessments with each series (due to changing of the point of maximal curvature), incorporation of RestoreX traction therapy post injection, and 'aggressive' manual modeling (equivalent of 10-15 lbs of force) to achieve curvature correction. Preliminary (unpublished – abstract submitted to SMSNA 2021) results from these men demonstrated a median ~60% curvature improvement. Importantly, several of the patients had previously undergone 8 CCH injections with outside providers and were able to similarly achieve a median 60% improvement with the investigators' injection / modeling protocol.

1.2 Investigational Treatments

The current study would randomize men 1:3 into one of two treatment cohorts: 1. Observation followed by CCH or 2. CCH followed by observation. This study design offers the benefits of a randomized,

controlled trial (highest level of evidence), while also providing data for a second set of publications evaluating the cross-over to treatment phase (for controls). RCTs are particularly important in PD, where the disease changes over time in a percentage of men as a function of its natural history. This would also allow blinding of measurements using photographs (single-blinded assessments), which provides further study rigor. See Figure 1 for overall study schema.

1. No treatment (control) followed by CCH. Men in this cohort would undergo baseline assessments followed by no treatment for 6 months and then repeat assessments. Men would then cross-over to CCH treatment and undergo up to 8 injections (or until curvature is <15 degrees). Interval assessments would be performed with the 1st injection of each series, and final assessments would then be performed 6 weeks following the final injection.
2. CCH followed by no treatment. Men in this cohort would undergo baseline assessments followed by up to 8 injections of CCH (or until curvature is <15 degrees). Interval assessments would be performed with the 1st injection of each series and 6 weeks following completion of treatment. Men then would not undergo any additional treatments for 6 months, after which final assessments would then performed.

During CCH administration, several key differences from the IMPRESS protocols would be performed. Please note that each of these changes have been slowly implemented in the investigators' practice over time to improve overall efficacy of therapy:

	IMPRESS Protocol	Current Study Protocol
Amount administered	0.58 mg	0.9 mg
Suspension volume	0.37 ml	0.7 ml
Method of injection	Into plaque	To point of maximal curvature in the tunica, as determined with an erection at the first injection of each series
Administration schedule	1-3 days apart	1 day apart
Mechanical device traction	None	RestoreX 30-60 min daily until 6 weeks after final injection
Office modeling	Performed 1-3 days after initial injections (defined as "firm"	10-15 lbs of force performed at the time of 2nd injection
Home modeling	3x daily modeling performed, gentle attempts at straightening erection	10-15 lbs of force performed at least one daily; straightening during erection
Penile wrapping	No comments	Mandatory x 5 days after 2nd injection of each series

1.3 Preliminary Data

Please refer to the introductory section for a more complete description of preliminary data. The investigators' team has been implementing the above, novel techniques in a step-wise fashion over time. Data from men who have been treated since Jan 2020 demonstrates a median improvement of ~60% (compared to 30% with prior series). Importantly, this series included several patients who had

previously undergone prior CCH injections with other providers. These findings suggest a proof of concept for the novel approach and would represent the largest improvement in curvature ever achieved with CCH. Findings would also benefit Endo Pharmaceutical, as it would provide proof of concept data that additional series of CCH may be merited in many cases of men with PD.

1.4 Study Rationale and Risk Analysis (Risks to Benefits Ratio)

1.4.1 Study Rationale

As noted previously, the investigators' team had previously performed a survey of men who experience suspected fractures with CCH and showed greater curvature correction without worsening of erectile function.[11] More recent preliminary data from the investigators' prospective cohort also demonstrated significantly improvement outcomes with the protocol described above without any worsening of complications compared to historical series (SMSNA abstract 2021). These findings suggest data sufficient to perform a more rigorous study evaluating the use of CCH with this modified protocol.

1.5 Anticipated Duration of the Clinical Investigation

The overall study will be scheduled for approximately 1 year. Depending on the duration of CCH administration, this time period may fluctuate by several months.

2 Study Endpoints

2.1 Primary Endpoints

1. Compare penile curvature between control and treatment groups at 6 months
2. Compare PDQ outcomes between control and treatment groups at 6 months

2.2 Secondary Outcomes

1. Compare IIEF outcomes between control and treatment groups at 6 months
2. Compare penile curvature changes in control men at baseline and 12 months (i.e. prior to and following cross-over to CCH)
3. Compare penile length changes in control men at baseline and 12 months (i.e. prior to and following cross-over to CCH)
4. Compare PDQ changes in control men at baseline and 12 months (i.e. prior to and following cross-over to CCH)
5. Compare IIEF changes in control men at baseline and 12 months (i.e. prior to and following cross-over to CCH)
6. Compare penile length changes between control and treatment groups at 6 months
7. Report adverse events at 6 and 12-month time points

8. Report changes in penile curvature between 6 and 12-month assessments for CCH men

3 Study Design

3.1 Subject Selection

3.1.1 Inclusion Criteria

- Men with PD
- >18 years old
- Curvature ≥30 degrees
- Previously completed 6-8 CCH injections
- Prior minimal (<20% and/or <10 degrees) responsiveness to CCH administration
- Prior CCH injections must have been performed without use of a Restorex traction device and used the IMPRESS protocol
- Ability to achieve an erection satisfactory for intercourse with or without PDE5 inhibitors
- The patient exhibits a palpable plaque consistent with Peyronie's Disease

3.1.2 Exclusion Criteria

- Prior surgical treatment on the penis (other than circumcision)
- Any contraindications to CCH – as determined by the PI
- Inability to complete 8 additional CCH injections
- Severe plaque calcification (i.e. >1 cm shadowing)

3.2 Setting and Investigator

The current study will be conducted by CURE PD, a charity established to conduct studies in men with PD. All treatments will be performed at the Male Fertility and Peyronie's Clinic in Orem, UT by Dr. Landon Trost.

Dr. Landon Trost is the former head of male infertility and Andrology at the Mayo Clinic in Rochester, MN, and he has previously completed several investigator-initiated randomized, controlled trials.

3.3 Recruitment

Men who are seen in the Male Fertility and Peyronie's Clinic for Peyronie's Disease and who have prior histories of CCH administration with minimal / no improvements will be offered entry into the trial at the time of their clinical visit. Additional recruitment will be performed by contacting other PD providers around the country and through advertising in common PD forums.

3.4 Consent and Enrollment

Patients attending the Male Fertility and Peyronie's Clinic or noting interest via email will receive a description of the study. Those interested in participating, will be given the opportunity to meet with the study coordinator to further review study details and formal consent.

Patients that would like additional time to consider their participation will be given another opportunity to meet with the study coordinator at a later time. If the patient expresses interest in participating at any time, a formal consent will be reviewed.

At enrollment, all participants will be assigned a study identifier, with a master list maintained in a password protected database linking the patient to the identifier. A total of up to 40 patients will be enrolled to achieve outcomes of at least 30 men (total study power 40 given that each participant will serve as a control as well as treatment comparator).

3.5 Study Schema

Patients meeting criteria who have consented will be randomized to either control or CCH x 6 months, followed by a cross-over phase where controls will receive CCH. See Figure 1 for full study schema.

1. Control. Men in this cohort would undergo baseline assessments followed by no treatment for 6 months and then repeat assessments. Men would then cross-over to the CCH treatment phase and undergo up to 8 injections (or until curvature is <15 degrees, whichever comes first). Final assessments would then be performed 6 weeks following the final injection.
2. CCH followed by observation. Men in this cohort would undergo baseline assessments followed by up to 8 injections of CCH (or until curvature is <15 degrees). Assessments would then be performed 6 weeks after completion of treatment. Men then would not undergo any additional treatments for 6 months, after which they would have final assessments performed.

The following table provides an overview of the objective and subjective questionnaire administration:

	Baseline	1st CCH of each series	6-weeks after CCH completed	End of no treatment phase
Baseline disease specific questionnaire	X			
Baseline subjective questionnaire	X			
IIEF	X	X	X	X
PDQ	X	X	X	X
1st injection Xiaflex questionnaire		X	X	

Post Xiaflex subjective questionnaire			X	
Post no treatment subjective questionnaire				X
Length measurement	X	X	X	X
Curve measurement	X	X	X	X
Penile ultrasound	X			

3.6 Randomization Protocol

Following enrollment and completion of the consent, a length and curvature assessment will be performed as well as baseline questionnaires. Men will then be randomized based on a previously created randomization table that takes into account baseline curvatures (see attached Randomization Table). Groupings are divided based on initial curvature of 30-44, 45-59, 60-74, 75-89, 90 or above to assure equal representation in each study arm. Men will then undergo treatment as noted above.

4 Study Procedures

4.1 Screening Assessments

- Potential patient questioned to assure that they meet all inclusion / exclusion criteria
- Participant consented

4.2 Assessments

- Please refer to the table schema above (Section 3.5) for details as to timing of questionnaire administration.
- Objective measurements
    - Penile length obtained (pubic symphysis to corona and tip) – obtained by two separate providers with experience in PD therapies
    - Erection induced with alprostadil (dose to be determined by PI, with a goal to achieve a penetration-quality erection).
    - Curvature assessed in two planes as well as with photography (obtained in two planes)
    - Penile ultrasound performed to evaluate for plaque calcification. Plaques classified as none, mild (stippling), moderate (shadowing), and severe (>1 cm).
- Questionnaires

- Baseline disease specific questionnaire
- Baseline subjective questionnaire
- IIEF-15
- PDQ
- 1st injection Xiaflex questionnaire
- Post Xiaflex subjective questionnaire
- Post no treatment subjective questionnaire
- Adverse events (completed by study personnel only – not completed by study subjects)

5 Statistical Plan

5.1 Data Handling

All data will be recorded either by the patient themselves or by the provider directly onto printed forms. Information will remain de-identified throughout the remainder of the study period and will remain on password protected, CURE PD servers.

After completion of the study, de-identified information will be shared with individuals associated with Endo Pharmaceuticals who may assist with portions of the data analysis and/or manuscript drafting if desired. No identifiable information will be sent.

5.2 Statistical Analysis

The current study is considered exploratory in nature. Analyses will be performed using comparisons within and between patient cohorts. All captured data will be utilized as a point of comparison based on accepted standards (e.g. IIEF subdomains, PDQ subdomains, etc.). All data will be analyzed to determine if it is normative / non-normative and will be described and compared appropriately (mean, SD versus median, IQR).

Patients with partial missing data will have all available data included for analysis, with no attempts made to statistically replace missing variables. All data will be analyzed using an intent-to-treat analysis.

Adverse events will be reported as a total as well as compared between cohorts.

A power analysis was performed using historical data from another one of the investigators' RCTs to determine the standard deviation for control men between two sequential assessments. Results of absolute curvature improvements demonstrated a standard deviation of 16 degrees or 27% relative improvement. Using a 0.05 alpha threshold, power of 80%, and expected cohort size of 30 (assuming 30 with 6-month data) this would allow us to distinguish differences over 17 degrees or 29%. Given the investigators' current improvements of 60% with the investigators' preliminary data, we would expect this study to have sufficient power to demonstrate a clinically and statistically significant finding.

6 Safety and Adverse Events

Definition of Adverse Event

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) - any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) breach of confidentiality and (6) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, AND

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event - an untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include:

- Death
- Life threatening adverse experience
- Hospitalization
- Inpatient, new, or prolonged; disability/incapacity
- And/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All AEs that do not meet any of the criteria for serious, should be regarded as non-serious AEs.

6.1 Adverse Event Reporting Period

For the current study, the treatment follow-up period is defined as 6 weeks following the last administration of study treatment (for new symptoms).

6.2 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

6.3 Post-study Adverse Event

All unresolved AEs will be followed by the study team until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. A review of AEs which the subject or subject's physician believe might reasonably be related to participation in the study will be performed up to 12 months following treatment.

6.4 Hospitalization, Prolonged Hospitalization or Surgery

Any AE related to the study intervention that results in hospitalization or surgery should be documented and reported as a serious AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

6.5 Recording of Adverse Events

The study team will seek information on adverse events by specific questioning between baseline and the follow-up visits. Information on all adverse events will be recorded immediately in the adverse event section of the specific questionnaire as well as in an adverse event form.

All adverse events occurring during the study period will be recorded. The clinical course will be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period will be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation will be recorded and reported immediately.

6.6 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Adverse Event Form. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

6.6.1 Sponsor-investigator Reporting: Notifying the Western IRB

An adverse event form will be completed for any serious adverse event. This will be reported to the Western IRB in a de-identified manner.

The study team will report to the Western IRB any UPIRTSOs and Non-UPIRTSOs.

Information collected on the adverse event form (and entered into the research database)
- Subject's ID
- Description of adverse event
- The date the adverse event occurred and resolved (if applicable)
- Intensity
- Outcome
- Action taken to address
- Relationship to study
- Impact on study withdrawal
- Classification as serious or not

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

6.6.2 Stopping Rules

Any serious adverse event which is determined to reasonably be related to the study treatment by the sponsor-investigator will result in immediate discontinuation of the therapy. If 5 patients develop serious adverse events, the study will be halted with re-review required by the Western IRB prior to consideration of study resumption.

6.6.3 Medical Monitoring

Medical monitoring of serious adverse events will be performed by the study investigator on a monthly-basis if serious adverse events have been reported.

7 Data Handling and Record Keeping

7.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

7.2 Source Documents

Source data comprise 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, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

7.3 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports during the study and for a period of 2 years after the investigation is terminated or completed.

8 Study Finances

8.1 Funding Source

This study is funded by Endo Pharmaceuticals.

8.2 Conflict of Interest

Dr. Landon Trost is the inventor and developer of the RestoreX® device. His conflict has previously been reviewed with the Mayo Clinic Conflict of Interest Review Board, and following review, it has been determined that Dr. Trost is able to conduct clinical studies as a Primary Investigator (IRB17-001283).

8.3 Subject Stipends or Payments

Subjects will receive payment for their participation, including stipends for travel, and all treatments provided at no cost.

8.4 Regulatory Information

CCH is an FDA approved therapy for the treatment of PD. The current FDA label includes an indication for men with PD who have a palpable plaque and at least 30 degrees of curvature at the beginning of therapy. These indications are consistent with the current protocol (i.e. no new indications would be sought).

PathRight Medical has registered the RestoreX® device with the FDA as a Class I device, similar to limb orthotics (see Attachment – RCRI Position Paper). The device is available without a prescription and may be purchased by the general public. As such, clinical studies are not required prior to its routine use, and the current studies are being done as an investigator-initiated project to determine its potential role in length of penile prosthesis inserted.

9 References

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