Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355 USA

EN3835-210

A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF EN3835 FOR THE TREATMENT OF ADHESIVE CAPSULITIS OF THE SHOULDER

Brief Title: A study to assess safety and efficacy, using pain and function questionnaires, of injection near the shoulder joint of EN3835 versus placebo given in males and females 18 years of age and older with frozen shoulder

Sponsor Name: Endo Pharmaceuticals Inc.

Sponsor Legal Registered Address: 1400 Atwater Drive, Malvern, PA 19355 USA

Regulatory Agency Identifier Number: IND 8279

Original Protocol: 06 April 2020

Protocol Amendment 1: 10 July 2020

Protocol Amendment 2: 31 July 2020

Protocol Amendment 3: 06 November 2020

Protocol Amendment 4: 22 October 2021

The sponsor of the Investigational New Drug Application (IND) is Auxilium Pharmaceuticals, LLC (Auxilium); however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of Auxilium. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

[redacted]

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Overall Rationale for Amendment 4:

The primary purpose of this amendment was to increase the total number of subjects for the study to 180 due to a higher than expected early termination rate.

Minor changes throughout the protocol amendment included wording changes for clarity and correction of minor typographical errors.

Amendment 4 was incorporated into the protocol on 23 October 2021.

Major updates to specific sections of the protocol that are affected are outlined below.

Section No. and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	Summary of Changes updated.	Updated for Amendment 4.
Section 1.1 Synopsis	Estimated date of last subject completed updated from August 2021 to June 2022.	This update was made to reflect the increase in total number of subjects.
Section 1.1 Synopsis AND Section 4.1 Overall Study Design AND Section 9.1 Sample Size Determination	Total number of subjects for the study increased from 160 to 180.	Due to a higher than expected early termination rate, sample size was increased to 180 subjects.
Section 1.1 Synopsis AND Section 9.4 Interim Analysis	Specified the total number of subjects (86) who must have completed the Day 95/Early Termination (ET) Visit before interim analysis can be performed.	Total number of subjects for interim analysis was 86.
Section 1.2 Schedule of Activities	Schedule of Activities Footnote b changed to: Treatment sessions should be at least 21 days apart.	Removed example of timing of treatment sessions to avoid confusion.

Section No. and Name	Description of Change	Brief Rationale
Section 5.1 Subject Inclusion Criteria, Criterion #2 AND Section 6.5.1 Prohibited Medications and Nondrug Therapies	Removed barbiturates and benzodiazepines from the pain medication list. Specified that nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, etc) and Tylenol (acetaminophen) are allowed.	Barbiturates and benzodiazepines are not indicated for pain and should be available if necessary for subjects who experience anxiety during magnetic resonance imaging (MRI) scans.
Section 5.2 Subject Exclusion Criteria, Criterion #5, 4th bullet	Original Text: Uncontrolled thyroid disease defined as thyroid stimulating hormone (TSH) ≥ 4 uIU/mL at the Screening Visit. Note added: (Note: Uncontrolled thyroid disease is defined as a symptomatic medical condition not adequately controlled with medications.)	This change was made to clarify the definition of uncontrolled thyroid disease.
Section 7.2 Subject Withdrawal from the Study	Rewritten to clarify the difference between subject discontinuation and subject withdrawal of consent.	Procedures performed after subject discontinuation and subject withdrawal of consent were clarified.

Overall Rationale for Amendment 3:

The primary purpose of this amendment was to clarify exclusion criteria regarding related to coagulation and bleeding disorders. In addition, the unit of measure for TSH was updated to reflect current practice. Furthermore, the storage of injection site photographs was defined. Photographs are to be stored in a database and not in the subject source documents. Text to clarify exclusion criterion #3 was added for the MRI review committee.

Minor changes throughout the protocol amendment included wording changes for clarity and correction of minor typographical errors.

Amendment 3 was incorporated into the protocol on 30 October 2020.

Major updates to specific sections of the protocol that are impacted are outlined below.

Section No. and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	Summary of Changes updated.	Updated for Amendment 3.

Section No. and Name	Description of Change	Brief Rationale
Section 5.2 Subject Exclusion Criteria, Criterion #3	Changed from: Has any abnormalities/conditions in the affected shoulder that would be clinically significant or potentially confounding to the evaluations of safety and efficacy as determined by the investigator or central MRI review including but not limited to:	This change was made to remove responsibility from the investigators and to allow the MRI committee to determine eligibility based on their MRI grading criteria to ensure consistency.
	Changed to: Has any abnormalities/conditions in the affected shoulder that would be potentially confounding to the evaluations of efficacy as determined by the central MRI review committee grading criteria. The shoulder pathologies to be assessed include but are not limited to the following:	
Section 5.2 Subject Exclusion Criteria, Criterion #5	Criterion #5, 2 bullet points were removed including: 'Coagulation disorder' and 'A known bleeding disorder which, in the investigator's opinion, would make the subject unsuitable for enrollment in the study.'	Bullet points were removed from Exclusion Criteria #5 to be included in the revised Exclusion Criteria #7 for clarity.
	In addition, the unit of measure for TSH was changed from U/mL to uIU/mL.	To align with current practice.

Section No. and Name	Description of Change	Brief Rationale
Section 5.2 Subject Exclusion Criteria, Criterion #7	Criterion #7 changed from: Requires anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except ≤ 150 mg aspirin daily) within 7 days prior to the first injection of study treatment. To: Has a known coagulation disorder and/ or is taking any medication (ie, anticoagulants or antiplatelet medications, except for ≤ 150 mg aspirin daily) that would increase the risk of bleeding within 7 days of the first injection of EN3835 and for the duration of the study.	Revised language for Coagulation/Bleeding disorders for clarity and to be more consistent with other ongoing studies.
Section 5.4 Screen Failures	Updated to: Subjects will be allowed to repeat hematology, serum chemistry, urinalysis, or vital signs once, if necessary, if it is within the screening window.	Vital signs were added to the list of assessments to be repeated if the subject is retested.
Section 6.1 Study Treatment Administration	Updated to: 'A screen capture/photograph of the injection will be taken at each injection visit and retained within a database until the end of the study.'	Modified to reflect the location of archived images.

Overall Rationale for Amendment 2:

The primary purpose of this amendment was to clarify which pain medication would be considered exclusionary for the study, and to add clarity to the exclusion criteria or MRI contraindications for exclusion criterion #6 rationale to allow the technologist, radiologist, and investigator to determine whether or not a subject may undergo MRI.

Minor changes throughout the protocol amendment included wording changes for clarity and correction of minor typographical errors.

Amendment 2 was incorporated into the protocol on 31 July 2020.

Major updates to specific sections of the protocol that are impacted are outlined below.

Section No. and Name	Description of Change	Brief Rationale
Protocol Amendment Summary of Changes	Summary of Changes updated.	Updated for Amendment 2

Section No. and Name	Description of Change	Brief Rationale
Section 5.1 Subject Inclusion Criteria, Criterion #2 and Section 6.5.1 Prohibited Medications and Nondrug Therapies	New criterion #2 added to clarify the use of pain medication. Text added to beginning of section to clarify the use of pain medication.	Added to indicate that narcotic pain medication will not be allowed during the study period and for 2 weeks prior to the start of study.
Section 5.2 Subject Exclusion Criteria, Criterion #3	Criterion #3 modified to add the exclusion of abnormalities/ conditions in the affected shoulder that would affect the evaluation of safety or efficacy evaluations.	Modified to clarify that conditions of the affected shoulder that are deemed clinically significant by the investigator and central MRI committee would be exclusionary for the study.
Section 5.2 Subject Exclusion Criteria, Criterion #6	Exclusion criterion #6 changed to: Has any of the following contraindications for MRI, as determined by the technologist, the radiologist, and/or the investigator (in accordance with the MHRA Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use, March 2015): Note changed to: Any tattoo in the treated area will be exclusionary.	Modified to clarify that the technologist, radiologist, and investigator will determine subject eligibility for MRI, and that a tattoo in the treated area would exclude the subject from receiving and MRI.
Section 8.1.7 Magnetic Resonance Imaging	Added: A central MRI committee consisting of 2 blinded musculoskeletal radiologists who will serve as the primary readers and 1 blinded clinician who will serve as the adjudicator in discordant cases.	Text added to define the central MRI committee.

Overall Rationale for Amendment 1:

The primary purpose of this amendment was to align exclusion criteria on other shoulder pathologies seen on MRI with our MRI vendor to provide clarity and alignment for the MRI readers. The change was to clarify both the schedule of activities (SoA) and procedures detailed in the protocol. The other major reason for this amendment is to modify the protocol due to the potential interruption caused by the COVID-19 public health emergency. The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study subjects is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. In addition, subjects impacted by the health emergency will be allowed to continue in the study

and complete remaining dosing and assessments when the investigational sites re-open as follows:

- Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of the COVID-19 interruption but who had not been dosed with EN3835 may be rescreened. If a subject rescreens within 30 days of their original screening MRI date and adhesive capsulitis (AC) was confirmed in the affected shoulder by the MRI central review committee, and the unaffected shoulder MRI was unremarkable, the subject will not need to have a repeat MRI of either shoulder. Other adhesive capsulitis shoulder screening assessments will be determined on a case by case basis as to whether or not the subject will need to repeat. All repeat screening assessments must be completed within the screening window.

Minor changes throughout the protocol amendment included wording changes for clarity and correction of minor typographical errors.

Amendment 1 was incorporated into the protocol on 10 July 2020.

Major updates to specific sections of the protocol that are impacted are outlined below.

Section No. and Name	**Description of Change**	**Brief Rationale**
Protocol Amendment Summary of Changes	Summary of Changes Added	Added with Amendment 1
Section 1.2 Schedule of Activities, Table 1	New footnote ‘e’ added to Adapted ASES of the affected shoulder.	Added to indicate that all patient-reported outcomes (PROs) must be completed prior to study assessments/ beginning of visit.
Section 1.2 Schedule of Activities, Table 1	Footnote ‘g’ removed from pain upon movement (PUM) assessment of the affected shoulder. New footnote ‘g’ added to active range of motion (AROM) and passive range of motion (PROM) of the affected shoulder.	Removed as unnecessary. Added to indicate that all AROM measurements must be completed before PROM measurements.
Section 1.2 Schedule of Activities, Table 1	New footnote ‘h’ moved to Chemistry, hematology, urinalysis, HbA1c, TSH, serum pregnancy test Day 95 Visit.	Added to indicate that serum pregnancy testing is not to be done at the Day 95 Visit.
Section 1.2 Schedule of Activities, Table 1 Section 8.1.7 Magnetic Resonance Imaging and X-rays	Footnote ‘i’ updated. Text added.	Updated to indicate that the X-ray must be completed prior to MRI imaging. Added text indicating that any X-ray of the affected shoulder done within 30 days of Screening is acceptable.

Section No. and Name	Description of Change	Brief Rationale
Section 1.2 Schedule of Activities, Table 1	In the SoA, 'X' has been removed from concomitant medications and nondrug therapies for Treatment Session Day 1 and Treatment Sessions Day 22 and Day 43 in the post-injection columns.	Procedure removed from postinjection time points listed in order to avoid repeating during a single visit.
Section 1.2 Schedule of Activities, Table 1	Remaining footnotes relettered.	Relettered to maintain footnote agreement.
Section 2.1 Study Rationale	The rationale for changes to the study due to the COVID-19 public health emergency (as outlined above) has been added to the end of this section.	

Section No. and Name	Description of Change	Brief Rationale
Section 5.2 Subject Exclusion Criteria	Exclusion Criterion #3 updated as follows: 3. Has any of the following conditions in the affected shoulder: • AC as a result of traumatic injury (ie, direct injury to the shoulder such as fracture of the humerus or clavicle immediately preceding the onset of this episode of AC). Traumatic events in the past that are not temporally related to the onset of this episode of AC would not necessarily exclude a subject from participating in the study. • Active subacromial impingement ~~in the affected shoulder~~ **(subacromial/subdeltoid bursitis, decreased subacromial space, or bursal sided fraying).** • Calcified tendonitis ~~in the affected shoulder~~. • Glenohumeral joint arthr**osis**~~itis in the affected shoulder~~. • **Glenohumeral joint inflammatory arthropathy.** • **Rotator cuff tears (supraspinatus, infraspinatus, teres minor, or subscapularis).** • **Fracture (humerus, glenoid, or clavicle).** ~~Arthrosis of the affected shoulder.~~ ~~• Chondrolysis of the affected shoulder.~~ ~~• Subscapularis tendon rupture of the affected shoulder.~~ • Acromioclavicular arthropathy. • ~~Rotator cuff pathologies of the affected shoulder unrelated to AC.~~	To align shoulder pathologies seen on MRI with our MRI vendor to ensure clarity for the MRI readers.

Section No. and Name	Description of Change	Brief Rationale
	• Biceps tendon pathologies. • Bursitis ~~of the shoulder~~. • Labr**~~alum~~** tears/**suspected labral tears.** • Bone pathologies. • ~~Polymyalgia rheumatica.~~ • Any other abnormalities/ conditions as determined by the central MRI review to be potentially confounding to the evaluation of safety and efficacy.	
Section 5.2 Subject Exclusion Criteria	For Exclusion Criteria #6, bullet 3, the following note has been added: Note: As determined by the technician performing the image and radiologist, with exemption of the area to be treated/reviewed. Any tattoo in this area will be exclusionary.	To clarify that the technician and radiologist can determine if the MRI can safely be performed in the presence of a tattoo not in the affected area.
Section 5.4 Screen Failures	An exception has been added for any rescreening process interrupted by COVID-19, subjects may be rescreened for a second time.	
Section 6.6 Visits Affected by COVID-19 Interruption	Protocol deviations will be recorded for all subjects who have visits outside of the windows outlined in the SoA, regardless of reason (including all subjects who experienced the COVID-19 interruption). The reason for out of window visits will be recorded.	
Section 8.2 Safety Assessments	Text was added to this section to allow virtual visits to assess safety during any COVID-19 interruption in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020).	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Study Treatment: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A phase 2, randomized, double blind, placebo controlled study of the safety and efficacy of EN3835 for the treatment of adhesive capsulitis of the shoulder

Lead Principal Investigator: Not applicable

Study period:	**Phase of development:** 2
Estimated date first subject enrolled: July 2020 Estimated date last subject completed: June 2022	

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using the adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES) composite score.	• The change from baseline in the adapted ASES composite score for the affected shoulder at the Day 95 Visit.
Secondary	
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using passive range of motion (PROM).	• The absolute and percent change from baseline in PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder at the Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline.
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using active range of motion (AROM).	• The absolute and percent change from baseline in AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder at the Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline.
• To assess the efficacy of EN3835 for treatment of AC of the shoulder using the adapted ASES.	• The change from baseline in the adapted ASES composite score, the adapted ASES function subscale, and the adapted ASES pain subscale for the affected shoulder at the Day 22, 43, 64, and 95 Visits.
• To assess the impact of EN3835 on pain upon movement (PUM) in subjects with AC of the shoulder.	• The change from baseline in the PUM Scale for the affected shoulder at the Day 64 and Day 95 Visits.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Study Treatment: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Objectives	Endpoints
Secondary (Continued)	
• To assess the impact of EN3835 on the severity of AC in subjects with AC of the shoulder.	• The change from baseline in the Patient-reported Global Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64 and 95 Visits. • The rating (response) in the Patient-reported Change in Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64, and 95 Visits.
• To assess subject satisfaction with treatment and investigator assessment of improvement with treatment of EN3835 for AC of the shoulder.	• Investigator assessment of improvement with treatment at the Day 64 and Day 95 Visits. • Subject satisfaction with treatment at the Day 64 and Day 95 Visits.
• To assess the safety and immunogenicity of EN3835 for the treatment of AC of the shoulder.	• The proportion of subjects reporting each adverse event, treatment-emergent adverse event, adverse event of special interest, and serious adverse event. • The change from baseline in vital signs and clinical laboratory values at each visit where these parameters are measured. • The presence and titer levels of anti-AUX-I and anti-AUX-II antibodies and the presence of neutralizing antibodies at each visit where these parameters are measured.
Exploratory/Tertiary	
• [redacted]	• [redacted]

Overall Design:

This study is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of EN3835 for the treatment of AC of the shoulder. To be eligible for treatment, a subject must have unilateral idiopathic AC of the shoulder with restricted range of motion (ROM) and function in the affected shoulder. Subjects will be screened for study eligibility within 28 days before the first injection of study treatment.

During screening subjects will undergo MRIs of both shoulders. These images will be reviewed through a central blinded read to determine subject eligibility (that each subject has AC without confounding pathologies). Following screening, eligible subjects will be randomized 1:1 to receive EN3835 0.58 mg/1 mL or volume matched placebo. EN3835 or placebo will be administered by ultrasound-guided injection at the injection site [redacted] following the administration of a local anesthetic. Subjects will receive

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Study Treatment: EN3835
Name of Active Ingredient: Collagenase clostridium histolyticum
up to 3 injections of study treatment (total dose: 1.74 mg) separated by a minimum of 21 days. Following each injection, subjects will remain under observation for at least 30 minutes. All subjects will undergo standardized, supervised, in-office physical therapy (PT) sessions after each treatment visit. In addition, subjects will complete standard home exercises starting 3 days after each injection of study treatment through the Day 95 Visit. Subjects will be evaluated for shoulder ROM, AC severity, function, and pain at each subsequent study visit. Dosing may be withheld at the Day 22 and 43 Visits if functional parameters are met. Subjects will be expected to complete all study visits, even if they do not receive study treatment at the Day 22 and/or Day 43 Visits. Follow-up visits will be conducted approximately 64 and 95 days after the first dose of EN3835 or placebo. An interim analysis for safety and futility is planned for when approximately 86 subjects have completed the Day 95/Early Termination Visit. Enrollment will continue during this analysis.
Disclosure Statement: This is a placebo-controlled safety and efficacy study with 2 blinded treatment cohorts.
Number of Study Subjects (planned): Approximately 180 subjects will be randomly assigned to EN3835 or placebo so that approximately 142 evaluable subjects will complete the study.
Treatment Groups and Duration: All subjects will receive up to 3 treatment sessions at least 21 days apart and consisting of 0.58 mg of EN3835 or placebo in the affected shoulder. The total amount of EN3835 to be administered per subject over the course of the study will not exceed 1.74 mg.
Independent Data and Safety Monitoring Committee: An interim analysis for safety and futility is planned for when approximately 86 subjects have completed the Day 95/Early Termination Visit. An independent unblinded data monitoring committee will review the interim data and provide recommendations for study continuation.

1.2. Schedule of Activities

Table 1: Schedule of Activities

Activity	Screening Visit Day -28 to Day -1	Treatment Session 1 Day 1		Days 4-7	Days 8-21	Treatment Session 2[a] Day 22 + 3 days[b] And Treatment Session 3[a] Day 43 + 3 days[b]		Days 25-28 and Days 46-49	Days 29-42 and Days 50-63	Follow-up Day 64 (± 5 days)	End of Study Day 95 (± 5 days)/Early Termination
		Pre-injection	Post-injection			Pre-injection	Post-injection				
Informed consent[c]	X										
Inclusion/exclusion criteria review	X										
Demography	X										
Medical and surgical history	X										
AC history	X										
Prior medications and nondrug therapies	X	X									
Complete physical examination	X										X
Height	X										
Weight	X										X
Hand dominance	X										
Vital signs (blood pressure, respiratory rate, pulse rate, body temperature)	X	X[d]	X[d]			X[d]	X[d]			X	X
12-lead ECG	X										
Adapted ASES of the affected shoulder[e]	X[e]	X				X				X	X
Confirm external rotation[f]	X[e]										
Passive external rotation at 0°, 45°, and 90° of the affected shoulder	X[e]										
AROM and PROM of the contralateral shoulder	X										
AROM and PROM of the affected shoulder[g]	X					X				X	X

Table 1: Schedule of Activities (Continued)

Activity	Screening Visit Day -28 to Day -1	Treatment Session 1 Day 1		Days 4-7	Days 8-21	Treatment Session 2[a] Day 22 + 3 days[b] And Treatment Session 3[a] Day 43 + 3 days[b]		Days 25-28 and Days 46-49	Days 29-42 and Days 50-63	Follow-up Day 64 (± 5 days)	End of Study Day 95 (± 5 days)/Early Termination
		Pre-injection	Post-injection			Pre-injection	Post-injection				
PUM Assessment of the affected shoulder	X	X								X	X
Patient-reported Global Severity of Adhesive Capsulitis[e]	X	X				X				X	X
Patient-reported Change in Severity of Adhesive Capsulitis[e]						X				X	X
Chemistry, hematology, urinalysis, HbA1c, TSH, serum pregnancy test	X										X[h]
Urine pregnancy test		X				X					
Immunogenicity sample collection		X									X
X-ray of affected shoulder	X[i]										
MRI of affected shoulder	X										X
MRI of unaffected shoulder	X										
Randomization		X									
Ultrasound-guided study treatment injection and screen capture/photo of injection		X				X					
Supervised in-office PT[j]					X				X		
Train subjects on home exercise and diary use, distribute home exercise instructions and diary			X					X			
Home exercises[k]				X				X			
Review diary (for home exercise compliance)						X				X	X
Investigator Assessment of Improvement with Treatment										X	X

Table 1: Schedule of Activities (Continued)

Activity	Screening Visit Day -28 to Day -1	Treatment Session 1 Day 1		Days 4-7	Days 8-21	Treatment Session 2[a] Day 22 + 3 days[b] And Treatment Session 3[a] Day 43 + 3 days[b]		Days 25-28 and Days 46-49	Days 29-42 and Days 50-63	Follow-up Day 64 (± 5 days)	End of Study Day 95 (± 5 days)/Early Termination
		Pre-injection	Post-injection			Pre-injection	Post-injection				
Subject Satisfaction with Treatment										X	X
Concomitant medications and nondrug therapies				X	X	X		X	X	X	X
Adverse events[l]	Monitored throughout study										

[a] Subjects may receive up to a maximum of 3 treatment sessions. Treatment sessions (Day 22 and Day 43) should be determined based on the guidelines provided in Section 6.1.1. Subjects who are not eligible for treatment at the Day 22 and/or Day 43 Visits will continue in the study, completing all other activities and visits.

[b] Treatment sessions should be at least 21 days apart.

[c] Performed prior to any study-related activities.

[d] On treatment session days, vital signs will be taken prior to the injection and at 15 and 30 minutes after the injection (except for body temperature which will be taken prior to the injection and 30 minutes after the injection). Vital signs must be stable for a period of at least 30 minutes before the subject can be discharged from the study site on treatment days.

[e] All patient-reported outcomes (PROs) must be completed prior to study assessments/ beginning of visit. Must be completed and criteria met prior to MRI.

[f] Subject must be able (in a supine position) to have the affected arm passively externally rotated to at least a neutral position within the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90°.

[g] AROM measurements must be completed before PROM measurements.

[h] Serum pregnancy assessment will not be done on the Day 95 Visit.

[i] Must be completed prior to MRI. Previous X-rays of the affected shoulder may be used if they were taken within 30 days of the Screening Visit.

[j] Subjects must complete supervised in-office PT 2 days per week for 2 weeks after each treatment session. Subjects must wait a minimum of 7 days after each treatment session prior to starting PT and there should be a minimum of 2 days between PT sessions.

[k] Home exercises will be completed at least 2 times per day and no more than 3 times per day, every day starting 3 days after each dose of study treatment through the Day 95 Visit. In-office PT will count as 1 of the home exercise sessions on PT days.

[l] AEs/SAEs will be captured from time of informed consent signature until the Day 95 Visit or for 28 days after last dose of study treatment for subjects who discontinue early from the study. There is no time limit on collection of SAEs assessed as related to study treatment.

Note: Unless otherwise stated above, all assessments should be completed prior to dosing on treatment days (the Day 1, 22, and 43 Visits).

2. INTRODUCTION

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (Clostridial class I collagenase [AUX-I]) and Collagenase II (Clostridial class II collagenase [AUX-II]). EN3835 (XIAFLEX®) is currently approved for use in adult patients with Dupuytren's contracture (DC) with a palpable cord and for the treatment of adult men with Peyronie's disease (PD) with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

2.1. Study Rationale

The histopathology of adhesive capsulitis (AC) bears similarities to that seen in Dupuytren's contracture (Bunker and Anthony, 1995; Bunker et al, 2000; Rodeo et al, 1997; Tamai et al, 2014) with:

- An initial phase of synovial hyperplasia that progresses to fibrosis of the synovium and capsule, likely the result of increased fibroblast activity and cellular proliferation.
- New and excessive collagen deposition within the capsule likely the result of increased expression of multiple pro-inflammatory cytokines.
- A residual stage in which fibroblast activity is diminished and reduced collagen maturation and remodeling take place, culminating in a protracted stiffening of the capsule.

Therefore, DC treatments such as EN3835 may be effective in other collagen mediated conditions such as AC. Based on the limitations of currently available treatments; there is an unmet need for a less invasive, cost effective treatment option that reduces the burden of illness due to AC.

The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study subjects is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. In addition, subjects impacted by the health emergency will be allowed to continue in the study and complete remaining dosing and assessments when the investigational sites re-open as follows:

- Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of the COVID-19 interruption but who had not been dosed with EN3835 may be rescreened. If a subject rescreens within 30 days of their original screening MRI date and adhesive capsulitis was confirmed in the affected shoulder by the MRI central review committee, and the unaffected shoulder MRI was unremarkable, the subject will not need to have a repeat MRI of either shoulder. Other adhesive capsulitis shoulder screening assessments will be

determined on a case by case basis as to whether or not the subject will need to repeat. All repeat screening assessments must be completed within the screening window.

2.2. Background

EN3835, marketed as XIAFLEX, is currently approved for use in adults with DC and PD. These collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions, which may result in lysis of collagen deposits in a Dupuytren's cord and/or Peyronie's plaque.

A description of the chemistry, pharmacology, efficacy, and safety of EN3835 is provided in the Investigators Brochure (Endo, 2020).

AC is a prolonged, painful condition of the shoulder that is associated with loss of range of motion (ROM) in the glenohumeral joint. An American Shoulder and Elbow Society (ASES) consensus definition of AC is: "a condition characterized by functional restriction of both active and passive shoulder motion for which radiographs of the glenohumeral joint are essentially unremarkable" (Zuckerman and Rokito, 2011).

Management of AC is controversial and depends on the phase of the disease. Decision making is often based on quality of life and whether the patients are able to cope with the pain and/or stiffness until its eventual resolution. Treatment options include a range of conservative and surgical measures.

Both oral and intra-articular corticosteroids have been shown to have a benefit in reducing pain and increasing ROM in AC, but these benefits are short-lived and there are significant risks associated with long term systemic steroid use (Buchbinder et al, 2004; Buchbinder et al, 2006; Canbulat et al, 2015; Carette et al, 2003; Lorbach et al, 2010; Takase, 2010; Yoon et al, 2013).

Physical therapy (PT) to the limit of pain is widely accepted as part of the management of AC, at least in the early stages of the disease where it is thought to reduce pain and increase ROM (D'Orsi et al, 2012; Jain and Sharm, 2014; Russell et al, 2014; Struyf and Meeus, 2014; Wilson et al, 2015).

O'Kane et al (1999) reported that patients treated with home exercise alone improved in a self-assessed shoulder rating system, physical function, and pain after an average of 25 months of follow-up; however, 30% to 40% of these patients could not place an 8 pound object on a shelf or carry a 20 pound object at their side.

Studies of treatment with suprascapular nerve blocks, intra-articular hyaluronic acid, intra-articular injection of botulism toxin type A, hydrodilation (also known as distention arthrography), and manipulation under anesthesia (MUA) have found little difference in pain or ROM between these therapies and treatment with intra-articular corticosteroids and/or PT (Corbeil et al, 1992; Dahan et al, 2000; De Carli et al, 2012; Gam et al, 1998; Harris et al, 2011; Jacobs et al, 1991; Jones and Chattopadhyay, 1999; Joo et al, 2013).

More recent nonrandomized studies have indicated that there may be some long term benefit to hydrodilation compared to corticosteroids (Ahn et al, 2015) or MUA (Clement et al, 2013; Simpson and Budge, 2004; Watson and Dalziel, 2000). However, there are significant risks associated with both procedures (D'Orsi et al, 2012; Loew et al, 2005; Magnussen and Taylor,

2011; Redler and Dennis, 2019; Vastamäki and Vastamäki, 2013). Complications from MUA include humeral fracture, subscapularis rupture, labral tears, and injury to the biceps tendon (Jacobs et al, 1991; Jacobs et al, 2009).

Arthroscopic capsular release has been used to treat AC effectively, particularly in patients who have been unresponsive to other treatments, by reducing pain and restoring ROM; however, risks associated with this procedure include postoperative pain, postoperative AC, and axillary nerve damage, as well as the risks associated with general anesthesia (Baums et al, 2007; Jerosch et al, 2013; Le Lievre and Murrell, 2012; Smith et al, 2014; Walther et al, 2014; Watson et al, 2007).

AC remains a disease that is difficult to diagnose and there is little consensus in the literature regarding preferred treatment or the preferred time for treatment (D'Orsi et al, 2012; Georgiannos et al, 2017; Hannafin and Chiaia, 2000; Le et al, 2017; Manske and Prohaska, 2008; Nagy et al, 2013; Stupay and Neviaser, 2015).

Three clinical studies with EN3835 have been conducted to date and results are outlined in Section 2.3, Section 4.2, and Section 4.3. Detailed information about these studies can be found in the Investigator's Brochure (Endo, 2020).

2.3. Benefit/Risk Assessment

Although a thorough benefit of EN3835 has not been fully established in the treatment of AC, the post hoc analyses from the previous phase 2b study (AUX-CC-871) and previous AC studies indicate that EN3835 should be further explored as a treatment. In addition, the lack of consensus regarding treatment of AC and the risks associated with surgical or drug treatment or with long-term corticosteroid use suggest that safe and effective treatments for this condition are needed.

In the most recent study of EN3835 in AC (AUX-CC-871), the most common (≥ 5% of subjects) treatment-related, treatment-emergent adverse events (TEAEs) were musculoskeletal pain (34.2%), contusion (28.7%), injection site pain (21.1%), ecchymosis (19.8%), injection site bruising (19.4%), localized edema (8.0%), and pruritus (5.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications, and postmarketing safety data are consistent with the safety data reported in clinical trials.

Use caution when administering EN3835 so as not to inject intra-articularly. A single animal study indicated significant adverse events associated with intra-articular injection of EN3835. While the effect in humans is not known, intra-articular injection (misapplication) of EN3835 during treatment of AC must be avoided.

More information about the known and expected benefit, risks, and reasonably expected adverse events (AEs) can be found in the Investigator's Brochure (Endo, 2020).

Risks associated with the use of a local anesthetic include bruising, pain, tingling, blurred vision, dizziness, headache, muscle twitching, weakness, and continuing numbness. Local anesthetics can sometimes cause allergic reactions including hives, itching, and difficulty breathing. In rare cases, cyanosis can occur at the site of injection; and very rarely, use of a local anesthetic can lead to depressed central nervous system syndrome.

The baseline shoulder X-ray exposes subjects to a very low level of radiation. Extensive exposure to radiation can lead to cancer. Exposure to any radiation can harm an unborn fetus in a pregnant woman.

Risks associated with ultrasound are rare; however, subjects undergoing ultrasound may experience slight heating of tissues and the creation of cavitations (small pockets of gas) within the body. The long term effects of these events are unknown.

Due to the use of the strong magnet, magnetic resonance imaging (MRI) cannot be performed on subjects with any implant containing metal or those who have other internal or external metallic objects as it may cause these objects to move.

All other procedures and activities in this study are generally accepted as standard of care for patients with AC and do not present any increased risk to the subjects.

3. OBJECTIVES AND ENDPOINTS

3.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using the adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES) composite score.	• The change from baseline in the adapted ASES composite score for the affected shoulder at the Day 95 Visit.
Secondary	
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using passive range of motion (PROM).	• The absolute and percent change from baseline in PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder at the Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline.
• To assess the efficacy of EN3835 for the treatment of AC of the shoulder using active range of motion (AROM).	• The absolute and percent change from baseline in AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder at the Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline.
• To assess the efficacy of EN3835 for treatment of AC of the shoulder using the adapted ASES.	• The change from baseline in the adapted ASES composite score, the adapted ASES function subscale, and the adapted ASES pain subscale for the affected shoulder at the Day 22, 43, 64, and 95 Visits.
• To assess the impact of EN3835 on pain upon movement (PUM) in subjects with AC of the shoulder.	• The change from baseline in the PUM Scale for the affected shoulder at the Day 64 and Day 95 Visits.
• To assess the impact of EN3835 on the severity of AC in subjects with AC of the shoulder.	• The change from baseline in the Patient-reported Global Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64 and 95 Visits. • The rating (response) in the Patient-reported Change in Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64, and 95 Visits.
• To assess subject satisfaction with treatment and investigator assessment of improvement with treatment of EN3835 for AC of the shoulder.	• Investigator assessment of improvement with treatment at the Day 64 and Day 95 Visits. • Subject satisfaction with treatment at the Day 64 and Day 95 Visits.

Objectives	Endpoints
• To assess the safety and immunogenicity of EN3835 for the treatment of AC of the shoulder.	• The proportion of subjects reporting each AE, TEAE, adverse event of special interest (AESI), and serious adverse event (SAE). • The change from baseline in vital signs and clinical laboratory values at each visit where these parameters are measured. • The presence and titer levels of anti-AUX-I and anti-AUX-II antibodies and the presence of neutralizing antibodies at each visit where these parameters are measured.
Exploratory/Tertiary	
• [redacted]	• [redacted]

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of EN3835 for the treatment of AC of the shoulder. To be eligible for treatment, a subject must have unilateral idiopathic AC of the shoulder with restricted ROM and function in the affected shoulder. Subjects will be screened for study eligibility within 28 days before the first injection of study treatment. Approximately 180 subjects will be randomly assigned to EN3835 or placebo so that approximately 142 evaluable subjects will complete the study.

During screening subjects will undergo MRIs of both shoulders. These images will be reviewed through a central blinded read to determine subject eligibility (that each subject has AC without confounding pathologies). Following screening, eligible subjects will be randomized 1:1 to receive EN3835 0.58 mg/1 mL or volume matched placebo. EN3835 or placebo will be administered by ultrasound-guided injection at the injection site [redacted] following the administration of a local anesthetic. Subjects will receive up to 3 injections of study treatment (total dose: 1.74 mg) separated by a minimum of 21 days. Following each injection, subjects will remain under observation for at least 30 minutes. All subjects will undergo standardized, supervised, in-office PT sessions after each treatment visit. In addition, subjects will complete standard home exercises starting 3 days after each injection of study treatment through the Day 95 Visit. Subjects will be evaluated for shoulder ROM, AC severity, function, and pain at each subsequent study visit. Dosing may be withheld at the Day 22 and 43 Visits if functional parameters are met. Subjects will be expected to complete all study visits, even if they do not receive study treatment at the Day 22 and/or Day 43 Visits. Follow-up visits will be conducted approximately 64 and 95 days after the first dose of EN3835 or placebo.

An interim analysis for safety and futility is planned for when approximately 86 subjects have completed the Day 95/Early Termination Visit. Enrollment will continue during this analysis.

The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The study is expected to screen subjects over approximately 12 months. The entire study is expected to require approximately 18 months to complete.

4.2. Scientific Rationale for the Study Design

A placebo-controlled, double-blind, parallel-arm study design was chosen in accordance with the FDA Guidance for Industry, *E 10 Choice of Control Group and Related Issues in Clinical Trials*. The use of a placebo control helps to prevent subjects from automatically thinking that all effects they experience are attributable to the active treatment since there is a 50% chance they are actually receiving inactive injection (placebo). In addition, no active control is used because there are no generally accepted pharmacologic treatments for AC.

4.3. Justification for Dose

In a dose ranging study (AUX-CC-870) of EN3835 in AC, doses of 0.58 mg (at volumes of 0.5 mL, 1 mL, and 2 mL) were well tolerated with most TEAEs occurring at the site of injection with a profile consistent with that observed in previous clinical trials of EN3835 in the treatment of DC and PD. Statistically significant improvements from baseline in AROM forward flexion, ASES composite score, and ASES pain and function subscale scores were seen at doses of 0.58 mg/1 mL and 0.58 mg/2 mL compared to a home exercise alone group. In addition, the dose of 0.58 mg/1 mL had statistically significant improvement in AROM abduction, PROM forward flexion, PROM abduction, and PROM external rotation compared to the home exercise alone group. The dose of EN3835 0.58 mg/1 mL was equally well tolerated in the AUX-CC-871 study where results similar to those for AUX-CC-870 were observed. Based on these results, the EN3835 0.58 mg/1 mL dose was selected for the AC clinical development program.

4.4. Justification for Magnetic Resonance Imaging

The diagnosis of AC is difficult to make on the basis of clinical findings and is usually a diagnosis of exclusion as other causes of shoulder pain and stiffness such as rotator cuff tear, impingement syndrome, calcific tendinitis, or osteoarthritis may mimic AC. Arthrography, ultrasonography, and MRI play an important role in identifying AC (Hsu et al, 2011; Zappia et al, 2016).

Arthrography is not an optimal diagnostic tool for routine AC diagnosis as it is invasive and cannot be used to observe changes such as inflammation, thickening, or fibrosis in the glenohumeral joint capsule and synovium. While ultrasonography may aid in the diagnosis of AC, its role is still controversial (Zappia et al, 2016).

MRI is a noninvasive diagnostic tool that has been commonly used to help differentiate underlying disease that can mask the symptoms of AC (Hsu et al, 2011). MRI is capable of diagnosing AC early and can rule out confounding pathology through reliable imaging indicators including thickening of the CHL, the joint capsule in the rotator interval and axillary recess, as well as obliteration of the fat triangle under the coracoid process (Connell et al, 2002; Emig et al, 1995; Gokalp et al, 2011; Harris et al, 2013; Jung et al, 2006; Mengiardi et al, 2004; Sofka et al, 2008; Song et al, 2011).

4.5. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 95 Visit.

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the trial.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

In order to be eligible to participate in the study, prior to randomization subjects must:

1. Be ≥18 years of age at the time of consent, and can be male or female.
2. Agree not to use pain medications for the duration of the study period and for 2 weeks prior to the Screening Visit. Pain medications include but are not limited to: methadone, buprenorphine, opioids (eg, codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone), and cannabis.
   Note: Nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, etc) and Tylenol (acetaminophen) are allowed.
3. Have idiopathic unilateral AC defined as subjects with passive external rotation that demonstrates at least a 30% loss of ROM tested at 0°, 45°, and 90° abduction in the affected shoulder compared to the contralateral shoulder in the supine position. In the event that 45° and 90° cannot be achieved due to pain or restriction, the amount of external rotation available at maximum attainable abduction ROM is permissible as the second and third measurements.
4. Have an adapted ASES function subscale score of < 35 in the affected shoulder at the Screening and Day 1 Visits.
5. Have unaffected ROM in the contralateral shoulder as determined by the investigator.
6. Be able (in a supine position) to have the affected arm passively rotated to at least a neutral position within their level of pain tolerance with the elbow at the side (against the body) and flexed to 90°.
7. Be willing to undergo x-ray of the affected shoulder and MRI of the affected and contralateral shoulder as required by the protocol.
8. Agree to participate in supervised, in-office PT sessions and to complete home exercises at designated time points during the study.
9. Agree to avoid general lifting and carrying of no more than 10 pounds, and lifting of no more than 5 pounds overhead for 21 days after each treatment, except during supervised PT sessions.
10. Be able to read, understand, and independently complete PRO instruments in English.
11. If female, be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual

flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study (and for 28 days after any active treatment period for subjects who early terminate). Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, and injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.

12. If male with reproductive potential, agree to use effective contraception (abstinence, surgical sterilization [vasectomy], or condom with spermicide) with a female partner of child-bearing potential for the duration of the study (and for 28 days after any active treatment period for subjects who early terminate).
13. Be willing and able to comply with all protocol required visits and assessments.
14. Be adequately informed and understand the nature and risks of the study and be able to provide consent as outlined in Section 10.1.3.

5.2. Subject Exclusion Criteria

A subject is ineligible for study participation if, at the Screening Visit and/or on Day 1, the subject:

1. Has a known allergy to collagenase or any other excipient of EN3835 or any other procedural medication (including local anesthetics).
2. Has received treatment for AC (in the timeframes outlined below) or is planning to receive any treatment (other than study treatment) for AC at any time during the study in the affected shoulder, including but not limited to:
    - PT or acupuncture within 2 weeks before the first injection of study treatment.
    - Intra-articular or intrabursal injections of lidocaine, suprascapular nerve blocks, or electroanalgesic and/or thermoanalgesic modalities within 1 month before the Screening Visit.
    - Intra-articular or intrabursal injections of corticosteroids within 8 weeks before the Screening Visit.
    - Intra-articular or intrabursal injections of sodium hyaluronate and/or glenohumeral distension arthrography within 3 months before the Screening Visit.
    - MUA at any time prior to the study.
    - Surgery (including arthroscopic or open capsular release, capsulectomy, or capsulotomy) at any time prior to the study.

3. Has any abnormalities/conditions in the affected shoulder that would be potentially confounding to the evaluations of efficacy as determined by the central MRI review committee grading criteria. The shoulder pathologies to be assessed include but are not limited to the following:
    - AC as a result of traumatic injury (ie, direct injury to the shoulder such as fracture of the humerus or clavicle immediately preceding the onset of this episode of AC). Traumatic events in the past that are not temporally related to the onset of this episode of AC would not necessarily exclude a subject from participating in the study.
    - Active subacromial impingement (subacromial/subdeltoid bursitis, decreased subacromial space, or bursal sided fraying).
    - Calcified tendonitis.
    - Glenohumeral joint arthrosis.
    - Glenohumeral joint inflammatory arthropathy.
    - Rotator cuff tears (supraspinatus, infraspinatus, teres minor, or subscapularis).
    - Fracture (humerus, glenoid, or clavicle).
    - Acromioclavicular arthropathy.
    - Biceps tendon pathologies.
    - Bursitis.
    - Labral tears/suspected labral tears.
    - Bone pathologies.
4. Has a prosthesis or replacement of right or left shoulder, elbow, wrist, and/or hand.
5. Has any of the following systemic conditions:
    - Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years.
    - Uncontrolled hypertension, defined as a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 100 mmHg at the Screening Visit or before dosing on Day 1.
    - Uncontrolled diabetes, defined as hemoglobin A1c (HbA1c) ≥ 8% at the Screening Visit.
    - Uncontrolled thyroid disease defined as thyroid stimulating hormone (TSH) ≥ 4 uIU/mL at the Screening Visit. (Note: Uncontrolled thyroid disease is defined as a symptomatic medical condition not adequately controlled with medications.)
    - History of thrombosis or post-thrombosis syndrome.
    - Physical impairment that would preclude performing the protocol defined exercises.
    - Active infection in the area to be treated.

- Any other significant medical condition (eg, morbid obesity, cervical disc disease), which in the investigator's opinion would make the subject unsuitable for enrollment in the study.

6. Has any of the following contraindications for MRI, as determined by the technologist, the radiologist, and/or the investigator (in accordance with the MHRA Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use, March 2015):
   - An implant containing metal, including but not limited to intracranial aneurysm clips, cochlear implants, prosthetic devices containing metal, implanted drug infusion pumps, neurostimulators or bone growth stimulators, intrauterine contraceptive devices containing metal, or any other type of iron based metal implant.
   - Internal metallic objects such as bullets or shrapnel, as well as surgical clips, pins, plates, screws, metal sutures, or wire mesh.
   - Any tattoo or permanent cosmetics/make-up including but not limited to, permanent lip liner or permanent eye liner.

     Note: Any tattoo in the treated area will be exclusionary.
   - Severe claustrophobia.
   - A history of uncontrolled hypertension, epilepsy, asthma, anemia, or sickle cell disease.
7. Has a known coagulation disorder and/or is taking any medication (ie, anticoagulants or antiplatelet medications, except for ≤ 150 mg aspirin daily) that would increase the risk of bleeding within 7 days of the first injection of EN3835 and for the duration of the study.
8. Has received oral or parenteral steroids for any reason within 3 weeks before the Screening Visit.
9. Has, at any time, received collagenase for the treatment of AC (including subjects who received treatment in Study AUX-CC-870 or AUX-CC-871).
10. Has received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the first dose of study treatment.
11. Has received collagenase treatments (eg, Santyl® ointment and/or XIAFLEX/XIAPEX®) for any other indication within 30 days prior to study treatment administration, or is planning to be treated with collagenase (other than study treatment) at any time during the study.
12. Has donated blood within 30 days prior to the Screening Visit or has plans to donate blood during the study.
13. Has a corrected QT interval (QTc) of ≥ 450 ms for male subjects or ≥ 470 ms for female subjects on the screening electrocardiogram (ECG).
14. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full-time, etc) or a family member of

the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the IRB/IEC.

15. Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being, (eg, evidence of any significant hematological, endocrine, cardiovascular, respiratory, neurological, renal, hepatic, or gastrointestinal disease). If there is a history of such disease but the condition has been stable for more than 5 years and is judged by the investigator not to interfere with the subject's participation in the study, the subject may be included, with the documented approval of the Medical Monitor.
16. Has any other conditions that, in the investigator's opinion, might indicate that the subject is unsuitable for the study.

5.3. Lifestyle Considerations

From the signing of the informed consent through the Day 95/Early Termination Visit, subjects should refrain from any movements or activities that require pushing, pulling, running or jumping (except as directed in PT sessions or home exercises). Additionally, subjects should refrain from doing pushups, pull-ups, taking spin classes, and swimming. Purses should not be carried on the treated side.

Subjects who are avid exercisers may do lower body workouts that do not involve the arms and/or shoulders keeping in mind the weight lifting restrictions (see Section 5.1, Item 9). General stationary bike and treadmill walking are acceptable forms of cardiovascular strength training; however, subjects should refrain from road biking and the elliptical.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently randomized.

Subjects will be allowed to repeat hematology, serum chemistry, urinalysis, and/or vital signs once, if necessary, if it is within the screening window. The subject will not be considered a screen failure unless the repeat assessment/procedure result does not meet eligibility criteria. The period from the start of screening related procedures at the Screening Visit to the Day 1 Visit must not exceed 28 days, inclusive of any repeat screening procedures.

Subjects who do not meet all of the eligibility criteria will be deemed a screen failure and the following information must be recorded for all subjects who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which eligibility criterion was not met.
- Any AE/SAE experienced by the subject.

Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of any COVID-19 interruption but who had not been dosed with EN3835 may be rescreened. If a subject rescreens within 30 days of their original screening MRI

date and adhesive capsulitis was confirmed in the affected shoulder by the MRI central review committee, and the unaffected shoulder MRI was unremarkable, the subject will not need to have a repeat MRI of either shoulder. Other adhesive capsulitis shoulder screening assessments will be determined on a case by case basis as to whether or not the subject will need to repeat. All repeat screening assessments must be completed within the screening window.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed product, placebo, or device intended to be administered to a study subject according to the study protocol. Table 2 provides general information regarding the treatments to be used in this study.

Table 2: Study Treatment

Cohort Name	EN3835	Placebo
Product Name	EN3835 (0.9 mg of collagenase clostridium histolyticum with 0.5 mg of hydrochloric acid, 18.5 mg of sucrose and 1.1 mg of tromethamine) plus diluent	Placebo (0.5 mg of hydrochloric acid, 18.5 mg of sucrose and 1.1 mg of tromethamine) plus diluent
Type	Biologic	NA
Dose Formulation	Vial	Vial
Unit Dose Strengths	0.9 mg per vial	NA
Dose Amount and Frequency	0.58 mg/mL given in each of up to 3 treatment sessions at least 21 days apart	Volume matched placebo given in each of up to 3 treatment sessions at least 21 days apart
Route of Administration	Pericapsular (periarticular) injection	Pericapsular (periarticular) injection
Sourcing	Provided centrally by the sponsor or designee	Provided centrally by the sponsor or designee
Packaging and Labeling	Product will be provided in kits containing 1 vial of EN3835 and 1 vial of diluent. Each kit will be labeled per country requirements	Product will be provided in kits containing 1 vial of placebo and 1 vial of diluent. Each kit will be labeled per country requirements

6.1. Study Treatment Administration

EN3835 and its placebo are sterile lyophilized powders that are reconstituted with a sterile diluent made of 0.9% sodium chloride and 0.03% calcium chloride dihydrate in water. Subjects who qualify for the study will be given a dose of 0.58 mg of EN3835 or placebo per treatment administered in up to 3 treatment sessions at least 21 days apart (the Day 1, 22, and 43 Visits).

Treatment sessions should be at least 21 days apart. For example, if the Day 22 treatment session occurs late but within window (ie, on Day 24) the next treatment session should be 21 days later on Day 45 (+1 days) to maintain the minimum 21 days between doses.

For dosing, the subject will be supine on the examination table and the affected arm must be passively externally rotated to the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90° such that their hand extends straight out from their body. If the affected arm cannot be passively externally rotated to at least the neutral position, the injection cannot be administered; however, the subject will continue in the study, complete all other activities and may be reassessed for dosing at a subsequent visit (see Section 6.1.1).

EN3835/placebo will be administered pericapsularly (pariarticularly) by ultrasound guided injection at an injection site [redacted] following administration of local anesthesia. A screen capture/photograph of the injection will be taken at each injection visit and retained within a database until the end of the study. Following the injection of study treatment, the subject should remain supine for 20 minutes.

To evaluate the subject for immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of acute allergic reactions for the first 30 minutes after receiving an injection of EN3835/placebo. A crash cart will be available in the immediate area during this time.

Specific instructions for EN3835/placebo administration, including reconstitution will be provided in the Pharmacy Manual, and for the injection technique in the Study Operations Manual.

6.1.1. Dose Interruption

All eligible subjects will receive their first dose of study treatment on Day 1. At each subsequent treatment visit (the Day 22 and 43 Visits) each subject will be evaluated to determine if they can continue treatment.

Subjects that have all 5 measurements of AROM and PROM (forward flexion, internal rotation, external rotation, abduction, and shoulder extension) of the affected shoulder that are > 90% of the baseline contralateral shoulder ROM and have an adapted ASES function subscale score of > 40 in affected shoulder should not be dosed unless the investigator believes that the clinical benefit outweighs the risk.

Subjects who are not treated at the Day 22 Visit will continue in the study and will be reassessed at the Day 43 Visit and may be treated based on these assessments and investigator discretion. Subjects who are not treated at the Day 22 and/or Day 43 Visits will complete all other activities required for those visits and are also expected to complete the Day 64 and Day 95 Visits.

6.2. Study Treatment Preparation/Handling/Storage/Accountability

EN3835/placebo will be supplied in glass vials. EN3835/placebo must be kept in a locked, monitored temperature-monitored refrigerator at 2°C to 8°C with limited access until used or returned to the sponsor or designee. Vials should be allowed to stand at room temperature for at least 15 minutes and no longer than 60 minutes before using.

Reconstituted EN3835/placebo solution can be kept at room temperature (20°C to 25°C) for up to 1 hour or refrigerated (2°C to 8°C) for up to 4 hours prior to administration. If the reconstituted EN3835/placebo solution is refrigerated, allow the solution to return to room temperature for approximately 15 minutes before use.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit and while the study treatment is in the investigator's possession for all study treatments received and that any discrepancies are reported and resolved prior to study treatment administration.

Only subjects enrolled in the study will receive study treatment and only authorized study staff can dispense study treatment.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator must be able to account for all study treatment furnished to the study site. An accountability record must be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study treatment received, to whom it was administered (subject-by-subject accounting) and accounts of any study treatment accidentally or deliberately destroyed.

Refer to the Pharmacy Manual for complete information regarding preparation, handling, storage, and accountability of study treatment.

6.3. Measures to Minimize Bias

Subjects will be randomized according to a validated computer-generated allocation scheme to receive the study treatment described above in a 1:1 ratio using an interactive response technology (IRT) system. Subjects, investigators, site personnel, and Endo personnel (except clinical supplies personnel) will be blinded to treatment assignment.

6.3.1. Interactive Response Technology

The investigator or designee will utilize an IRT system to register subjects at screening. Each subject's unique identification number (ID) will be assigned by the IRT system and will be used to identify the subject for the duration of the study within all systems and documentation. If the subject is not eligible to receive study treatment, or should withdraw from the study, the ID number will not be reassigned to another subject. Specific instructions for the use of the IRT system will be included in the Pharmacy Manual.

The investigator must maintain a subject master log linking the subject ID to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject must be masked on material received by the sponsor.

6.3.2. Emergency Identification of Study Treatment

The blind may be broken if, in the opinion of the investigator, it is in the subject's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, the sponsor must be notified

within 24 hours after breaking the blind. The date and time that the blind is broken must be recorded in the source documentation. Specific instructions for breaking the blind in the IRT system are provided in the Pharmacy Manual.

6.4. Study Treatment Compliance

All subjects will receive study treatment administered by the investigator at the study site. All dosing information will be recorded for each subject visit. Study treatment inventory will be maintained in the IRT system, and all original containers of used and unused study treatment and diluent will be returned to the sponsor (or designee) at the end of the study.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 8.4).

6.5. Prior and Concomitant Medications and Nondrug Therapies

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 95 Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, etc) received will be recorded.

In addition, all prior medications and nondrug therapies for AC will be recorded with start and stop date, dose, unit, frequency and route of administration.

6.5.1. Prohibited Medications and Nondrug Therapies

To be eligible for the study, subjects will agree not to use pain medications for the duration of the study period and for 2 weeks prior to the Screening Visit. Pain medications include, but are not limited to:

- opioids (eg, codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone, methadone, buprenorphine),
- cannabis.

Note: NSAIDs (ibuprofen, etc) and Tylenol (acetaminophen) are allowed.

In addition, the following medications or nondrug therapies will not be permitted during the study (from the Screening Visit through the Day 95 Visit):

- Anticoagulant or antiplatelet medication (except ≤ 150 mg aspirin daily).
- Any other medications or nondrug therapies for the affected shoulder other than those outlined in this protocol.
- Any collagenase treatments (eg, Santyl ointment, XIAFLEX) other than study treatment.
- Any investigational product, device, or procedure administered as part of a research study other than the treatment in this study.

If any prohibited medication/nondrug therapy is taken during the study, all pertinent information will be recorded. The designated study medical monitor must be informed immediately so the sponsor may determine whether to continue the subject in the study.

6.6. Visits Affected by COVID-19 Interruption

Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of the COVID-19 interruption but who had not been dosed with EN3835 may be rescreened. If a subject rescreens within 30 days of their original screening MRI date and adhesive capsulitis was confirmed in the affected shoulder by the MRI central review committee, and the unaffected shoulder MRI was unremarkable, the subject will not need to have a repeat MRI of either shoulder. Other adhesive capsulitis shoulder screening assessments will be determined on a case by case basis as to whether or not the subject will need to repeat. All repeat screening assessments must be completed within the screening window.

Protocol deviations will be recorded for all subjects who have visits outside of the windows outlined in the Schedule of Activities, regardless of reason (including all subjects who experienced a COVID-19 interruption). The reason for out-of-window visits will be recorded.

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects who discontinue study treatment for any reason, will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations. The date of and reason for study treatment discontinuation will be recorded.

Permanent study treatment discontinuation is required if:

- The subject becomes pregnant during the study.
- Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a subject meets the conditions outlined in Section 10.6.
- If a clinically significant cardiac finding is identified (including but not limited to changes from baseline in QTc after the start of study treatment), the investigator in consultation with the medical monitor will determine if the subject can continue in the study and if any change in management is needed.

Subjects who discontinue from study treatment at any time after the first dose of study treatment will not be replaced.

7.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The date of withdrawal and the reason for withdrawal will be recorded.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any biological samples taken and not yet tested. The investigator must document this in the site study records.

A subject may be discontinued from the study for the following medical or administrative reasons:

- Withdrawal by subject (reason must be specified).
- An AE.
- Death.
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- The subject was lost to follow-up.
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, sponsor decision to terminate trial, etc).

If a subject discontinues from the study, all early termination procedures should be conducted as detailed in the Schedule of Activities. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and electronic case report form (eCRF). If, however, a subject withdraws consent, no additional procedures are required. This information should be recorded in the source documentation and the eCRF.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address; or local equivalent methods). These attempts will be documented.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

Subjects who have been lost to follow-up at any time after the first dose of study treatment will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.2). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. Protocol waivers or exemptions are not

allowed. Activities outlined in the Study Operations Manual must be followed or will result in a protocol deviation.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue study treatment and/or be withdrawn from the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Passive External Rotation at 0°, 45°, and 90° of Abduction

Passive external rotation at 0°, 45°, and 90° of abduction will be measured in both shoulders using a goniometer at screening in the supine position. In the event that 45° and 90° cannot be achieved due to pain or restriction in the affected shoulder, the amount of external rotation available at maximum attainable abduction ROM is permissible as the second and third measurements.

Hand Dominance

The subject's self-reported hand dominance will be recorded at screening.

Supervised In-office Physical Therapy

All subjects will undergo a standard supervised in-office PT regimen. The PT regimen will consist of 2 sessions per week for 2 weeks starting 7 days after each study treatment until the next scheduled injection and until the Day 64 Visit. In-office PT will last approximately 30 to 60 minutes. Subjects will be provided with verbal and hands-on instructions for the exercises to be completed. Physical therapists will follow the standard PT regimen found in the Study Operations Manual. All subjects will continue the PT regimen regardless of dose interruption or withdrawal from the study.

Home Exercises

Study personnel will train each subject how to conduct a standard set of home exercises and provide each subject with a set of instructions and any necessary equipment (ie, pulleys) to complete the home exercises. These home exercises should be performed by each subject at least 2 times per day and no more than 3 times a day. Home exercises will begin 3 days after each study treatment and will end at the Day 95 Visit. In office PT will count as 1 of the home exercise sessions on PT days. All subjects will continue the home exercises regardless of dose interruption or withdrawal from the study.

Subjects will document their home exercise completion and frequency using a diary. The site will train the subject on the use of the diary and will review the diary at visits specified in the Schedule of Activities to ensure compliance.

8.1. Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the Schedule of Activities. Below is a general description of each of these assessments. Specific instructions and questionnaires

and/or forms (where appropriate) will be provided in the Study Operations Manual. All PROs must be completed prior to any other assessments.

8.1.1. Adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form

The adapted ASES is a questionnaire to assess AC patient rated shoulder pain and function that has been modified from the ASES Standardized Shoulder Form (McClure and Michener, 2003; Michener, 2002). The adapted ASES is a self-administered PRO measure, divided into 2 sections: a pain subscale and a function subscale. The pain subscale is a single item, numeric rating scale about pain in the affected shoulder on the day of assessment. The 11-point numeric rating scale ranges from 0 (No pain at all) to 10 (Pain as bad as it can be). The function subscale consists of 10 activities of daily living where the subject is asked to indicate on a 4 point ordinal scale their ability to do the activity with the affected arm (Evidera, 2016).

All subjects will complete the adapted ASES at times outlined in the Schedule of Activities. These data will be entered by the subject directly into an electronic clinical outcomes assessment (eCOA) instrument while the subject is alone with no study site personnel in the room. On treatment days (Days 1, 22 and 43), the adapted ASES must be completed prior to study treatment injection.

8.1.2. Range of Motion

PROM (for forward flexion, internal rotation, external rotation, abduction, and shoulder extension) and AROM (for forward flexion, internal rotation, external rotation, abduction, and shoulder extension) will be measured using a goniometer, and a spinal level (for internal rotation) at times specified in the Schedule of Activities for the affected and contralateral shoulder. These measurements will be completed with the subject in the supine position.

8.1.3. Pain Upon Movement

The PUM Scale is a single item 11-point numerical rating scale of pain that asks subjects to rate the pain in their affected shoulder after AROM forward flexion, internal rotation, external rotation, abduction, and shoulder extension on a scale from 0 (No pain at all) to 10 (Pain as bad as it can be).

All subjects will complete the PUM at times outlined in the Schedule of Activities. The PUM data will be entered by the subject directly into an eCOA instrument while the subject is alone with no study site personnel in the room.

8.1.4. Patient-reported Global Severity of Adhesive Capsulitis

The Patient-reported Global Severity of Adhesive Capsulitis is a single item 11-point numerical rating scale that asks subjects to rate the overall severity of their AC symptoms on a scale from 0 (No symptoms) to 10 (Symptoms as bad as they can be).

All subjects will complete the Patient-reported Global Severity of Adhesive Capsulitis scale at times outlined in the Schedule of Activities. The Patient-reported Global Severity of Adhesive Capsulitis data will be entered by the subject directly into an eCOA instrument while the subject is alone with no study site personnel in the room.

8.1.4.1. Patient-reported Change in Severity of Adhesive Capsulitis

The Patient-reported Change in Severity of Adhesive Capsulitis is a questionnaire that asks subjects if their AC symptoms are "Better, About the Same, or Worse" since the last time the questionnaire was administered. Subjects who report that their symptoms are better or worse are then asked to rate the change in their symptoms on a 7-point ordinal scale.

All subjects will complete the Patient-reported Change in Severity of Adhesive Capsulitis questionnaire at times outlined in the Schedule of Activities. The Patient-reported Change in Severity of Adhesive Capsulitis questionnaire answers will be entered by the subject directly into an eCOA instrument while the subject is alone with no study site personnel in the room.

8.1.5. Subject Satisfaction with Treatment

Subjects will rate their satisfaction with treatment on a 5-point Likert scale from Very Dissatisfied to Very Satisfied at times specified in the Schedule of Activities. The response will be entered directly into an eCOA instrument and completed while the subject is alone with no study site personnel in the room. The subject will be instructed to refrain from discussing their rating with the investigator and any other site personnel.

8.1.6. Investigator Assessment of Improvement with Treatment

Investigators will provide their assessment of improvement with treatment for each subject using a 7-point Likert scale from Very Much Worse to Very Much Improved at times specified in the Schedule of Activities. The response will be entered directly into an eCOA instrument. The investigator will refrain from discussing their rating with the subject.

8.1.7. Magnetic Resonance Imaging and X-rays

MRIs of the affected and contralateral shoulder will be performed for all subjects at times specified in the Schedule of Activities. Subjects should complete all other screening activities, including an X-ray of the affected shoulder, prior to the MRIs required at screening, and must meet the entry criteria of passive external rotation assessment at 0°, 45°, and 90° abduction and have an adapted ASES function subscale score (< 35) in the affected shoulder prior to the conduct of the screening MRIs. Previous X-rays of the affected shoulder may be used if they were taken within 30 days of the Screening Visit.

Additionally, subjects must be able (in a supine position) to have the affected arm passively externally rotated to at least a neutral position within the subject's level of pain tolerance with the elbow at the side (against the body) and flexed to 90° prior to the MRI at screening.

A central MRI committee consisting of 2 blinded musculoskeletal radiologists who will serve as the primary readers and 1 blinded clinician who will serve as the adjudicator in discordant cases. All screening MRIs of the affected shoulder will be reviewed through a blinded central read, performed by specialists with expertise in musculoskeletal imaging to determine if the subject has any clinically significant confounding pathologies and to confirm subject eligibility. MRI-based determinations of eligibility made by the central MRI committee are final, and will supersede any previous MRI analyses made by investigational site personnel or MRI imaging center personnel.

Specific instructions for the MRI procedures will be provided in the Study Operations Manual. All MRIs from this study are the property of Endo and de-identified images may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

8.2. Safety Assessments

All safety assessments will be performed at the times outlined in the Schedule of Activities. Additional (unscheduled) safety assessments may be performed as needed.

In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 02 July 2020), will allow virtual visits for safety assessments. In addition, subjects impacted by the health emergency will be allowed to continue in the study and complete remaining dosing and assessments when the investigational sites re-open.

8.2.1. Demography

The subject's birth date, gender, race, and ethnicity will be collected at screening.

8.2.2. Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit. Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions, including date of last menstrual period for female subjects, will be recorded.

In addition, any history or current collagen mediated disorders (including but not limited to Garrod's pads, Dupuytren's nodules, plantar nodules, PD, AC of other joints, etc) will be recorded (excluding the current AC episode).

History of tobacco and alcohol use (never, current, former) will also be collected.

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery completed at any time in the affected shoulder.

8.2.3. Adhesive Capsulitis History

A history of all past episodes of AC of the shoulder will be recorded at screening. Details of each past episode to be collected include: the affected shoulder (right or left), onset date, resolution date, and any procedures or medical treatments provided.

In addition, the history of the current AC episode including the affected shoulder (right or left), onset date of symptoms, and determination of idiopathic or traumatic AC will be recorded at screening.

8.2.4. Physical Examination

The complete physical examination will include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral

pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles), neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical exam findings for clinical significance. Any new, or change from the Screening Visit in, physical examination findings that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

Any clinically significant physical exam finding will be recorded as medical history at screening.

8.2.5. Height and Weight

Height will be collected at screening only. Weight will be collected as outlined in the Schedule of Activities. Any change from the Screening Visit in subject weight that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

8.2.6. Vital Signs

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded.

On days that study treatment is administered (the Day 1, 22, and 43 Visits), vital signs will be taken up to 4 hours prior to dosing and at 15 and 30 minutes after dosing (body temperature is not required at the 15-minute postdose time point). The subject's vital signs must be stable, or repeated until stable, before the subject can leave direct observation.

The investigator will review all vital sign values for clinical significance. Any change from the Screening Visit in vital signs that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

8.2.7. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

If the ECG report shows QT prolongation (QTc $\geq$ 450 ms for males or QTc $\geq$ 470 ms for females), the investigator will exclude the subject from study participation.

The investigator will review all ECG results for clinical significance. Any ECG result meeting the investigator's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

8.2.8. Clinical Laboratory Determinations (Chemistry, Hematology, Urinalysis, HbA1c, TSH, Serum and Urine Pregnancy Test)

Blood and urine samples will be collected for clinical laboratory testing at the time points outlined in the Schedule of Activities. Required clinical laboratory tests are outlined

in Section 10.2. Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. The results of the tests will be returned to the investigational sites.

Samples for laboratory testing may be collected under fasted or nonfasted conditions. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs (or SAEs, if appropriate).

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion. Any additional testing will be performed by the designated central laboratory.

8.2.9. Pregnancy Testing

All female subjects of childbearing potential will have serum and/or urine pregnancy tests performed at the time points outlined in the Schedule of Activities. Results must be available prior to protocol mandated study treatment administration. Subjects with positive results at the Screening Visit or the Day 1 Visit will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately discontinued from study treatment, but may continue in the study (see Section 7.1). All pregnancies will be reported as per Section 8.3.5.

If applicable, the subject's agreement to use contraception throughout their study participation (from Screening to the Day 95 Visit), or for 28 days after the last dose of study treatment for subjects who early terminate, will be documented.

8.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs and SAEs, including both observed or volunteered problems, complaints, signs, or symptoms must be recorded, regardless of whether associated with the use of study treatment. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected by the investigator from the time of signing the informed consent form (ICF) through the Day 95 Visit, or for 28 days after the last dose of study treatment for those who early terminate.

Investigators are not obligated to actively seek AEs and SAEs after conclusion of subject study participation. However, if the investigator learns of any SAE, including death, at any time after the subject has been discharged from the study, and the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor within 24 hours as described in Section 10.3.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and submitting SAE reports are provided in Section 10.3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a nonleading question such as, “How do you feel?” Study site personnel will then record all pertinent information. The study treatment compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

Any AEs identified in the subject diaries will be reported in the appropriate electronic case report form (eCRF) module, and if SAEs, as described in Section 10.3.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All nonserious AEs must be followed until resolution or until the last study visit whichever comes first; except for subjects who withdraw early from the study for whom nonserious AEs will be followed until resolution or for 28 days after the last administration of study treatment, whichever comes first.

All SAEs and nonserious AESIs will be followed to resolution, stabilization, the event is otherwise explained, or until follow-up is no longer possible. Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities regarding the safety of the study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy, and forwarded to investigators as necessary.

An investigator who receives a SUSAR (IND Safety Report) describing an SAE or other specific safety information (ie, summary or listing of SAEs) from the sponsor will review and then file it

with the Investigator's Brochure, and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred at any time during the study or (within 28 days of the last study treatment for those who terminate early) must be reported, followed to conclusion, and the outcome reported, even if the subject is withdrawn from the study. Pregnancies that occur in the partner of a treated subject (ie, female partner of male subject) also must be reported. The investigator must report (as outlined above) all pregnancies within 24 hours using the Pregnancy Report Form. Monitoring of the pregnancy should continue until conclusion, and follow-up information detailing the progress and outcome must be submitted on 1 or more Pregnancy Report Forms. A Two-Month Follow-up Pregnancy Report Form detailing the status of the infant must also be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects, or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form (see Section 10.3). Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects will be instructed to immediately notify the investigator of any pregnancies.

A subject who becomes pregnant must be immediately discontinued from study treatment but may remain in the study (see Section 7.1). Should a subject discontinue study treatment due to pregnancy, alternative treatment (if available) should be arranged according to standard of care, as determined by the investigator. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject withdraws from the study because of pregnancy.

8.3.6. AEs/SAEs Experienced by Nonsubjects Exposed to Study Treatment

Nonsubjects are persons who are not enrolled in the study but have been exposed to study treatment, including instances of diversion of study treatment. Any AEs/SAEs occurring in nonsubjects from such exposure will be reported to the Endo PVRM Department (when the nonsubject agrees) on the Serious Adverse Event (SAE)/Reportable Event Form regardless of whether the event is serious or not. Instructions for completing the form for events experienced by nonsubjects will be provided. SAEs occurring in nonsubjects exposed to study treatment will be processed within the same SAE reporting timelines as described in Section 10.3. Additionally, the treatment accountability source documentation at the site should reflect this occurrence.

8.3.7. Adverse Events of Special Interest

AESIs for this study include:

- Bruising, ecchymosis, hematomas, and contusions that occur remote to the site of treatment administration.

- Any hypersensitivity reactions.

These events will be reported as AEs in the eCRF. All AESIs will be evaluated for seriousness and severity. If any of these events meet the criteria for an SAE, they will also be reported as such using the procedure outlined in Section 10.3.

8.4. Overdose

Study treatment overdose is any accidental or intentional use of treatment in an amount higher than the dose indicated by the protocol for that subject. Study treatment compliance should be reviewed to detect potential instances of overdose (intentional or accidental).

Any treatment overdose during the study should be noted on the study treatment eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the AE eCRF and reported using the procedures detailed in Section 10.3, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the AE eCRF.

8.4.1. Study Treatment Abuse/Misuse

AEs associated with misuse or abuse will be appropriately reported as AEs or SAEs, and monitored per Section 10.3.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

8.8.1. Immunogenicity Assessments

Serum samples will be collected at times outlined in the Schedule of Activities and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing. When immunogenicity samples are required on a Treatment Day, the sample will be collected prior to study treatment administration. The antibody-positive samples also will be tested for neutralizing antibodies.

The serum samples obtained will be processed, stored and then shipped frozen on dry ice to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies. Specific instructions for the collection, processing, storage, handling, and shipment of the immunogenicity samples will be provided in the Study Operations Manual.

De-identified immunogenicity samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to study treatment; develop methods, assays, prognostics and/or companion diagnostics related to specify the treatment target, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment.

8.9. Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

A post hoc analysis was conducted using a subgroup of AUX-CC-871 subjects who were rated with moderate/severe AC based on baseline MRI images. This subgroup displayed a notable treatment effect (EN3835 vs placebo) on the pain and composite components of the adapted ASES questionnaire. This subgroup also displayed a treatment effect trend for the functional component of the adapted ASES. Given this result, the sample size calculation is based on the mean and SD found in this subgroup for the adapted ASES composite score on Day 95. Given a mean change from baseline value of 38.6 for the EN3835 group and 27.6 for the placebo group with an SD of 21.6, a sample size of approximately 142 subjects would be required given a 1:1 randomization and a type I error of 0.05 with a power of 85%. With an expected drop-out rate of approximately 20%, 180 subjects (90 EN3835 and 90 placebo) should be dosed to ensure 142 subjects complete the study.

9.2. Populations for Analysis

For the purposes of analysis, the following populations are defined:

- The Safety Population is defined as all randomized subjects who received at least 1 injection of study treatment (EN3835 or placebo). All safety analyses will be based on this population.
- The Intent-to-Treat (ITT) Population is defined as all randomized subjects who received at least 1 injection of study treatment (EN3835 or placebo).
- The Modified Intent-to-Treat (mITT) Population is defined as all ITT subjects who have a valid baseline adapted ASES composite score in the affected shoulder and at least 1 valid adapted ASES composite score after the injection of the study treatment. All efficacy analyses will be based on this population.
- The Per-Protocol (PP) Population is defined as those subjects in the mITT Population who do not have any major protocol deviations. Determination of PP subjects will be completed before the study database is closed and locked. If more than 10% of the mITT Population is excluded from the PP Population, then all efficacy summaries will be repeated using the PP Population for the sensitivity analysis.

9.3. Statistical Hypotheses and Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan (SAP) will be developed and finalized prior to the interim analysis.

9.3.1. Efficacy Analysis

The primary endpoint is the change from baseline to the Day 95 Visit in the adapted ASES composite score.

A mixed-model ANOVA with factors for treatment group and visit will be performed to compare active to placebo for the change from baseline to the Day 95 Visit in adapted ASES composite score.

A mixed-model ANOVA with factors for treatment group and visit will be performed to compare active to placebo for the absolute and percent change from baseline to the Day 22, 43, 64, and Day 95 Visits in PROM, AROM, adapted ASES function subscale, and adapted ASES pain subscale.

For the Investigator Satisfaction with Treatment and Subject Satisfaction with Treatment at the Days 64 and Day 95 Visits, a Wilcoxon rank sum nonparametric test will be performed to compare active to placebo. A Wilcoxon rank sum nonparametric test will also be used to compare active to placebo for the change from baseline in Patient-reported Global Severity of Adhesive Capsulitis at the Day 22, 43, 64 and 95 Visits.

For Patient-reported Change in Severity of Adhesive Capsulitis at the Day 22, 43, 64, and 95 Visits, a chi-square test will be performed to compare active to placebo.

Endpoints of the affected shoulder in the EN3835 group will be compared to the endpoints of the affected shoulder in the placebo group.

The tertiary/exploratory analysis plan will be provided in the SAP.

9.3.2. Safety Analyses

All subjects who receive at least 1 dose of study treatment will be included in the safety analyses. Subjects will be included in the safety analyses based on the actual treatment received.

Treatment comparisons for safety parameters will be performed using Fisher exact tests for categorical data such as event rates or Student *t* test for continuous data such as changes from baseline in the laboratory tests and vital signs using type 1 error rate of 0.05.

9.3.2.1. Adverse Events

AEs will be coded using MedDRA by preferred term within system organ class (SOC). The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by SOC, preferred term, severity, and causality for each treatment group. Only TEAEs (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be summarized.

9.3.2.2. Vital Signs and Laboratory Evaluations

Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

9.3.3. Other Analyses

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at Day 1 and at the Day 95 Visit by treatment group. Average antibody levels will be summarized on logarithmically transposed titer values. In addition, by-treatment percentages of neutralizing anti-AUX-I and anti-AUX-II antibodies will be summarized at the Day 95 Visit.

9.4. Interim Analysis

An interim analysis for safety and futility is planned for when approximately 86 subjects have completed the Day 95/Early Termination Visit. Details of the interim analysis will be provided in the SAP. The study will remain blinded to the subjects, investigators, site staff, and Endo personnel (with the exception of the drug supply personnel).

An independent unblinded data monitoring committee (DMC) will review the interim data and provide recommendations for study continuation.

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6(R2), the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the investigator. A copy of approval documentation will be supplied to Endo along with a roster of IRB/IEC members that demonstrates appropriate composition or other documentation of assurance of appropriate composition per local and national regulations (eg, a Department of Health and Human Services Assurance Number will satisfy this requirement for IRBs in the United States).

The study protocol, the ICF, advertisements, materials being provided to subjects, and amendments (if any) will be approved by IRB/IECs at each study site in conformance with ICH E6(R2), CFR Title 21 Part 56, and any other applicable local laws. The investigator is responsible for supplying the IRB/IEC with a copy of the current Investigator's Brochure, Package Insert, or Summary of Product Characteristics, as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo.

Any amendment to this protocol will be provided to the investigator in writing by Endo. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by Endo. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo.

The investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the completion of the study.

10.1.3. Informed Consent Process

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations, including confidentiality.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

At the Screening Visit (and at other times as may be required by the study or when changes are made to the consent form), subjects will read the consent forms and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), after being given an explanation of the study. Before signing the consent forms and the privacy authorization form (if applicable), subjects will have an opportunity to ask questions about the study and discuss the contents of these forms with study site personnel. The consent/assent process shall be recorded in source documents.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time for any reason.

All versions of each subject's signed ICF must be kept on file by the site for possible inspection by regulatory authorities and the sponsor. Signed copies of the consent forms and the privacy authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

10.1.4. Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committee Structure

A DMC will be used for the interim analysis. The DMC charter and composition are available upon request.

10.1.6. Dissemination of Clinical Study Data

Aggregate results data will be provided to the sites that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

10.1.7. Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the sponsor or sponsor representative. Significant and/or repeated noncompliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites.

The data will be entered into the clinical study database in a timely fashion and will be verified for accuracy, following procedures defined by the sponsor (or designee). Data will be processed and analyzed following procedures defined by the sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol, ICH E6(R2) consolidated guidelines, and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

All data recordings and source documentation (including electronic health records) must be made available to the sponsor (or designee), FDA and any other regulatory agencies that request access to study records for inspection and copying, in keeping with national and local regulations.

The investigator shall permit audits and inspections by the sponsor, its representatives, and members of regulatory agencies. The investigator should immediately notify the sponsor of an upcoming FDA or other regulatory agency inspection.

10.1.8. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site unless otherwise outlined in this protocol.

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, laboratory and other test results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, photographs, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

10.1.9. Study and Site Closure

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

10.1.10. Publication Policy

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the investigator will be subject to mutual agreement between the investigator and Endo.

10.2. Appendix 2: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis	Other
Hemoglobin	Glucose	Glucose	TSH
Hematocrit	Sodium	Protein	HbA1c
Red blood cell	Potassium	Specific gravity	Human chorionic gonadotropin (hCG) (serum and urine pregnancy)
White blood cell (WBC)	Calcium	pH	
Platelets	Chloride	Ketones	
WBC with differential	Carbon dioxide (CO_2)	Bilirubin	
	Inorganic phosphate	Urobilinogen	
	Blood urea nitrogen	Nitrite	
	Creatinine	Blood[a]	
	Creatinine clearance (estimated)	Leukocytes[a]	
	Aspartate transaminase (AST)		
	Alanine transaminase (ALT)		
	Gamma-glutamyl transferase (GGT)		
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)		
	Albumin		
	Alkaline phosphatase (ALP)		
	Uric acid		

[a] Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a preexisting condition associated temporally with the use of the study treatment whether or not considered related to the study treatment. AEs will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject.
- Participative symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease.
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

A TEAE is any condition that was not present prior to treatment with study treatment but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

An SAE is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or preplanned surgery, procedure, or treatment therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study treatment regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical treatment to prevent 1 of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of treatment dependency or treatment abuse.

10.3.2. Relationship to Study Treatment

The degree of "relatedness" of the AE to the study treatment must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study treatment.
- **Unlikely related** indicates that there are other, more likely causes and study treatment is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study treatment and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study treatment.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study treatment.

It is the sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Causality assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

10.3.3. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic treatment therapy or other treatment.

10.3.4. Reporting Adverse Events and Serious Adverse Events

10.3.4.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment related.

10.3.4.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject in this study, must be reported via email or fax by the investigator using the Endo Serious Adverse Event (SAE)/Reportable Event Form within 24 hours of first becoming aware of the SAE. Follow-up

information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

All SAEs should be reported via email [redacted] or fax [redacted].

The sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the sponsor (or the sponsor's representative) will report the event to the appropriate regulatory authorities. The investigator will report SAEs to the IRB/IEC per their IRB/IEC policy.

10.3.4.3. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or nonserious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the Serious Adverse Event (SAE)/ Reportable Event Form and the investigator should consider whether the event is related or not related to study treatment. All events determined to be nonserious should be reported on the eCRF.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

See Section 5 and Section 8.2.9.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

All events of alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and with total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured) which may indicate severe liver injury (possible Hy's Law cases) must be reported as an SAE as outlined in Section 10.3.4 (excluding studies of hepatic impairment or cirrhosis).

Subjects with confirmed Hy's Law liver injury will be immediately withdrawn from study treatment and no rechallenge will be allowed.

10.7. Appendix 7: Medical Device Incidents

Not applicable.

10.8. Appendix 8: Abbreviations

Abbreviation	Explanation
AC	Adhesive capsulitis
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AROM	Active range of motion
ASES	American Shoulder and Elbow Surgeons, American Shoulder and Elbow Surgeons Standardized Shoulder Form
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CHL	Coracohumeral ligament
DC	Dupuytren's contracture
DMC	Data monitoring committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcomes assessment
eCRF	Electronic case report form
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification number
INR	International normalized ratio
IRT	Interactive response technology
ITT	Intent-to-treat
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MUA	Manipulation under anesthesia
NSAID	Nonsteroidal anti-inflammatory drug
PD	Peyronie's disease
PP	Per-protocol

Abbreviation	Explanation
PRO	Patient-reported outcome
PROM	Passive range of motion
PT	Physical therapy
PUM	Pain upon movement
QTc	Corrected QT interval
ROM	Range of motion
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone

11. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed/Printed Name of Investigator

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Signature Manifest

Document Number: RDM-CLIN-DOC-02201 **Revision:** 1
Title: EN3835-210 Protocol Amendment 4

All dates and times are in Eastern Time.

EN3835-210 Protocol Amendment 4 for Approval

RDM Approval Step