SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. 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

Version 2.0

April 25, 2022

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

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]

[redacted]

TABLE OF CONTENTS

1. INTRODUCTION 9
2. STUDY OBJECTIVES 9
3. STUDY DESIGN AND MEASURES 10
3.1. Study Design 10
3.1.1. End-of-Study Definition 11
3.1.2. Schedule of Activities 11
3.2. Eligibility Criteria for Subject Selection 15
3.2.1. Inclusion Criteria 15
3.2.2. Exclusion Criteria 16
3.3. Study Treatment 19
3.4. Dose Interruption 19
3.5. Determination of Sample Size 19
3.6. Medical and Surgical History 20
3.7. Adhesive Capsulitis History 20
3.8. Substance Use 20
3.9. Prior and Concomitant Medications and Nondrug Therapies 20
3.10. Prohibited Medications 21
3.11. Passive External Rotation at 0°, 45°, and 90° of Abduction 21
3.12. Hand Dominance 21
3.13. Supervised In-office Physical Therapy 21
3.14. Home Exercises 22
3.15. Efficacy Assessments 22
3.15.1. Adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES) 22
3.15.2. Range of Motion (ROM) 23
3.15.3. Pain Upon Movement (PUM) 23
3.15.4. Patient-reported Global Severity of Adhesive Capsulitis 24
3.15.4.1. Patient-reported Change in Severity of Adhesive Capsulitis 24
3.15.5. Subject Satisfaction with Treatment 25
3.15.6. Investigator Assessment of Improvement with Treatment 27
3.15.7. Magnetic Response Imaging (MRI) and X-rays 27
3.16. Safety Assessments 27

[redacted]

3.16.1. Adverse Events 27
3.16.1.1. Adverse Events (AE) 27
3.16.1.2. Serious Adverse Events (SAEs) 28
3.16.1.3. Adverse Events of Special Interest (AESI) 28
3.16.2. Clinical Laboratory Determinations 28
3.16.3. Pregnancy Test 29
3.16.4. Height and Weight 29
3.16.5. Vital Signs 29
3.16.6. Electrocardiogram 30
3.16.7. Physical Examination 30
3.17. Immunogenicity 30
4. STUDY PARAMETERS 31
4.1. Subject Disposition 31
4.2. Protocol Deviations 31
4.3. Demographic and Baseline Characteristics 31
4.4. Prior and Concomitant Medications 32
4.4.1. Prior Adhesive Capsulitis (AC) Treatment 32
4.5. Passive External Rotation at 0°, 45°, and 90° of Abduction 32
4.6. Home Exercise Compliance 33
4.7. Efficacy Parameters 33
4.7.1. Adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES) 33
4.7.1.1. Pain Subscale 33
4.7.1.2. Function Subscale 33
4.7.1.3. Composite Score 33
4.7.2. Passive Range of Motion (PROM) and Active Range of Motion (AROM) 34
4.7.3. Pain Upon Motion (PUM) Scale 34
4.7.4. Patient-reported Global Severity of Adhesive Capsulitis Scale 35
4.7.5. Patient-reported Change in Severity of Adhesive Capsulitis Scale 35
4.7.6. Investigator Assessment of Improvement with Treatment 35
4.7.7. Subject Satisfaction with Treatment 35
4.7.8. [redacted]
4.8. Safety Parameters 35

[redacted]

4.8.1. Adverse Events 35
4.8.1.1. Treatment Emergent Adverse Events (TEAEs) 35
4.8.1.2. Intensity of Adverse Events 36
4.8.1.3. Relationship to Study Drug 36
4.8.1.4. Adverse Event Categorization by Treatment Session 36
4.8.2. Vital Signs and Clinical Laboratories 36
4.8.2.1. Laboratory Values 36
4.8.2.2. Vital Signs 37
5. ANALYSIS POPULATIONS 37
6. STATISTICAL METHODS 38
6.1. General Methodology 38
6.2. Derived Variables 39
6.3. Handling of Missing Data 40
6.3.1. Handling of Missing Data for Sensitivity Analysis of Primary Endpoint 41
6.3.2. Imputation of Partial Dates 41
6.3.2.1. TEAE Status for Completely Unknown Start Date 41
6.3.2.2. Concomitant Status of Medication/Non-drug Therapy for Completely Unknown Start Date 42
6.3.2.3. Missing Last Menstrual Date 42
6.4. Interim Analysis 42
7. STATISTICAL ANALYSES 42
7.1. Subject Disposition 42
7.2. Protocol Deviations 43
7.3. Demographics and Baseline Characteristics 43
7.4. Medical and Surgical History 43
7.5. Adhesive Capsulitis History 43
7.6. Prior/Concomitant Medications and Nondrug Therapies 43
7.7. Hand Dominance 44
7.8. Passive External Rotation 44
7.9. Efficacy Analyses 44
7.9.1. Primary Analysis 44
7.9.1.1. Change from Baseline in Adapted ASES Composite Score 44
7.9.2. Secondary Analysis 44

7.9.2.1. Absolute and Percent Change from Baseline in PROM 44
7.9.2.2. Absolute and Percent Change from Baseline in AROM 45
7.9.2.3. Change from Baseline in Adapted Pain and Function Subscale 46
7.9.2.4. Change from Baseline in PUM Scale 46
7.9.2.5. Change from Baseline in Patient-reported Global Severity of Adhesive Capsulitis Scale 47
7.9.2.6. Patient-reported Change in Severity of Adhesive Capsulitis Scale 47
7.9.2.7. Investigator Assessment of Improvement with Treatment 48
7.9.2.8. Subject Satisfaction with Treatment 48
7.9.3. Exploratory/Tertiary Analyses 48
7.9.3.1. [redacted]
7.9.4. Sensitivity Analysis 49
7.9.4.1. Primary Endpoint Sensitivity Analysis with MMRM using Tipping Point Analysis (TPA) 49
7.9.5. Supportive Analysis 51
7.9.5.1. Per-Protocol Population Analysis 51
7.10. Safety Analyses 51
7.10.1. Study Drug Exposure 51
7.10.2. Adverse Events 51
7.10.3. Clinical Laboratory 53
7.10.4. Vital Signs 54
7.10.5. 12-Lead ECG 55
7.10.6. Physical Examination 55
7.10.7. Immunogenicity 55
7.11. Other Analyses 55
7.11.1. X-Ray 55
7.11.2. Physical Therapy 55
7.11.3. Home Exercise 55
8. CHANGE FROM PROTOCOL 56
9. REVISION HISTORY 56
10. REFERENCES 57
11. TABLES, LISTINGS, AND GRAPH SHELLS 58

LIST OF TABLES

Table 1: Objectives and Endpoints 9
Table 2: Schedule of Activities 12
Table 3: Study Treatment 19
Table 4: ASES: Pain Subscale 22
Table 5: ASES: Function Subscale 23
Table 6: PUM Scale 24
Table 7: Patient-reported Global Severity of Adhesive Capsulitis Scale 24
Table 8: Patient-reported Change in Severity of Adhesive Capsulitis Scale 25
Table 9: Subject Satisfaction Prior to Receiving Treatment 26
Table 10: Subject Satisfaction Compared to Better Shoulder 26
Table 11: Investigator Assessment of Improvement with Treatment 27
Table 12: Clinical Safety Laboratory Parameters 29
Table 13: Potentially Clinically Important Laboratory Criteria 37
Table 14: Potentially Clinically Important Vital Sign Criteria 37
Table 15: Analysis Populations 38
Table 16: Derived Variables and Definition 40
Table 17: Changes from Protocol 56
Table 18: Revision History 56

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AC	Adhesive capsulitis
AE	Adverse event
AESI	Adverse event of special interest
AROM	Active range of motion
ASES	American Shoulder and Elbow Surgeons, American Shoulder and Elbow Surgeons Standardized Shoulder Form
ATC	Anatomical therapeutic chemical
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
[redacted]	[redacted]
CI	Confidence interval
CRF	Case report form
DBP	Diastolic blood pressure
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
HbA1c	Hemoglobin A1c
HBB	Hand behind back
ITT	Intent-to-treat
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Multiple imputation
mITT	Modified intent-to-treat
MMRM	Mixed model with repeat measurements
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug

Abbreviation	Definition
PCI	Potentially clinically important
PP	Per-protocol
PROM	Passive range of motion
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SoA	Schedule of activities
SOC	System organ class
TEAE	Treatment-emergent adverse event
TPA	Tipping point analysis
TSH	Thyroid stimulating hormone
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to evaluate the safety and efficacy of EN3835 compared to placebo in adults for the treatment of adhesive capsulitis (AC) of the shoulder, also known as frozen shoulder.

General information about the study is detailed in the EN3835-210 protocol; original protocol dated April 06, 2020, Amendment 1 dated July 10, 2020, Amendment 2 dated July 31, 2020, Amendment 3 dated November 06, 2020, and Amendment 4 on October 22, 2021.(1)

2. STUDY OBJECTIVES

The study objectives and corresponding endpoints are outlined in Table 1 below:

Table 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.

Objectives	Endpoints
	• 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]

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 2b, double-blind, placebo-controlled study of the safety and efficacy of EN3835 for the treatment of AC of the shoulder.

This study will randomize approximately 180 subjects to receive EN3835 or placebo so that approximately 142 evaluable subjects will complete the study. 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. During screening subjects will undergo MRIs of both shoulders. The affected shoulder MRI will be reviewed through a central blinded read to determine subject eligibility (that each subject has AC without clinically significant confounding pathologies).

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 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 AC 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.

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 at least 21 days (on Day 1, Day 22, and Day 43). 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 starting 7 days after each treatment session and will complete 2 sessions per week for 2 weeks with a minimum of 2 days between each PT session. 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 (approximately 50% of subjects) have completed the Day 95/Early Termination (ET) Visit. Enrollment will continue during this analysis.

The study is expected to screen subjects over approximately 12 months. The entire study is expected to require approximately 18 months to complete.

3.1.1. 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 visit is defined as the completion of the final assessment for the last subject enrolled in the trial.

A subject is considered evaluable if the subject is randomized, received at least 1 injection of study treatment, and has a valid baseline ASES composite score in the affected shoulder and at least 1 valid adapted ASES composite score after administration of study treatment. This includes both completers and early terminated subjects.

3.1.2. Schedule of Activities

Table 2 below describes the schedule of events and assessments performed during the Screening Visit, Treatment visits, and Follow-up visits.

Table 2: 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 2: 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

Table 2: 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				
Investigator Assessment of Improvement with Treatment										X	X
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 3.4 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 assessment.

[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 withdraw early from the study. There is no time limit on collection of SAEs assessed as related to study treatment.

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

[redacted]

3.2. Eligibility Criteria for Subject Selection

3.2.1. 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 patient reported outcome 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 Protocol Section 10.1.3.

3.2.2. 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 injection(s) of lidocaine, suprascapular nerve blocks, or electroanalgesic and/or thermoanalgesic modalities within 1 month before the Screening Visit.
    - Intra-articular or intrabursal injection(s) of corticosteroids within 8 weeks before the Screening Visit.
    - Intra-articular or intrabursal injection(s) of sodium hyaluronate and/or glenohumeral distension arthrography within 3 months before the Screening visit.
    - Manipulation under anesthesia (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 arthritis.
- 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 object(s) 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.

3.3. Study Treatment

Subjects will be given a dose of 0.58 mg of EN3835 or placebo per treatment session for up to 3 treatment sessions at least 21 days apart (the Day 1, 22, and 43 Visits).

The injection concentration for each treatment visit is outlined in Table 3 below.

Table 3: Study Treatment

Cohort	Route of Administration	Number of Injections at Each Treatment Visit	Dose at Each Treatment visit (mg)	Number of Treatment Visits	Total Dose Administered (mg)
EN3835	Pericapsular (periarticular) Injection	1	0.58	3	1.74
Placebo	Pericapsular (periarticular) Injection	1	--	3	--

3.4. 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 the 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.

3.5. Determination of Sample Size

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 in adapted ASES composite score at Day 95 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 complete the study.

3.6. Medical and Surgical History

A medical and surgical history of the subject will be taken during the Screening Visit. Medical history will include relevant diagnoses and procedures/therapies with onset/resolutions dates.

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, with onset/resolutions dates 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, Peyronie's disease, AC of other joints, etc) will be recorded (the current AC episode will not be recorded on the medical history case report form [CRF] - see next section).

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.

3.7. Adhesive Capsulitis History

A history of all past episodes of AC of the shoulder will be recorded at the Screening Visit. 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 in the affected shoulder (right or left), onset date of symptoms, and determination of idiopathic or traumatic AC will be recorded at screening.

3.8. Substance Use

History of tobacco and alcohol use will also be taken during screening and the following information will be recorded:

- Type of substance (Alcohol/Tobacco).
- History of usage (Never/Currently/Former).
- Number of years the product was used (for current or former users).
- Stop date of using the product (for former users).

3.9. Prior and Concomitant Medications and Nondrug Therapies

Any medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) taken during the study or within 90 days prior to the Screening Visit will be recorded.

In addition, all prior medications and nondrug therapies for AC will be recorded.

3.10. Prohibited Medications

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 is taken during the study, all pertinent information will be recorded.

3.11. 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.

3.12. Hand Dominance

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

3.13. Supervised In-office Physical Therapy

All subjects will undergo a standard supervised in-office physical therapy regimen. The physical therapy regimen will consist of 2 sessions per week for 2 weeks with a minimum of 2 days between each session starting 7 days after each study treatment until the next scheduled injection and until the Day 64 Visit. In-office physical therapy 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 physical therapy regimen found in the Study Operations Manual.

3.14. 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/ET Visit. In-office PT will count as 1 of the home exercise sessions on PT days.

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 (SoA) (Table 2) to ensure compliance.

3.15. Efficacy Assessments

3.15.1. Adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES)

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.(2,3) All subjects will complete the adapted ASES at times outlined in the SoA (Table 2).

The adapted ASES is a self-administered patient reported outcome measure, comprised of 2 subscales: pain subscale and function subscale.

Pain subscale: Numeric rating scale about pain in the affected shoulder on the day of assessment. Scale ranges from 0 (No pain at all) to 10 (Pain as bad as it can be).

Table 4: ASES: Pain Subscale

	Responses										
Question	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
How bad is the pain in your affected shoulder today?											

Function subscale: This scale 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.(4) Scale ranges from 0 to 3.

The responses are: 0 = Unable to do; 1 = Very difficult; 2 = Somewhat difficult; 3 = Not difficult.

Table 5: ASES: Function Subscale

No.	Question Is it difficult for you to ...	Responses for Affected Shoulder			
		0	1	2	3
1	Put on a coat				
2	Sleep on your painful or affected side				
3	Wash back/do-up bra in back				
4	Manage toileting				
5	Comb hair				
6	Reach a high shelf				
7	Lift 10 lbs. (4.5kg) above shoulder				
8	Throw a ball overhand				
9	Do usual work				
10	Do usual sport/leisure activities				

3.15.2. Range of Motion (ROM)

PROM and AROM will be measured for the affected and contralateral shoulder at times specified in the SoA (Table 2) using a goniometer. The below range of motion measurements will be recorded:

- Forward flexion.
- Internal rotation.
- External rotation.
- Abduction.
- Shoulder extension.

The unit to measure PROM and AROM is degrees (°).

In addition, Hand Behind the Back (HBB) assessment will be performed for active internal rotation. The response for HBB assessment will be free text with no unit.

3.15.3. Pain Upon Movement (PUM)

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).

Table 6: PUM Scale

Question	Responses										
	0	1	2	3	4	5	6	7	8	9	10
When you move your arm to the point where pain limits your movement in the affected shoulder (forward and backwards circles keeping elbow straight, lifting arms out to the side, reaching your arm behind your back as if you were getting something out of your pocket, positioning your arms as if you were carrying serving trays keeping your elbows glued to your sides, and extending your arms straight behind you) please rate your worst pain on a scale of 0-10 when you do these movements with your affected shoulder.											

All subjects will complete the PUM at times outlined in the SoA (Table 2).

3.15.4. 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 severity) to 10 (Severe as can be).

Table 7: Patient-reported Global Severity of Adhesive Capsulitis Scale

Question	Responses										
	0	1	2	3	4	5	6	7	8	9	10
What is the severity of your frozen shoulder in the last 24 hours?											

All subjects will complete the Patient-reported Global Severity of Adhesive Capsulitis scale at times outlined in the SoA (Table 2).

3.15.4.1. 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.

Table 8: Patient-reported Change in Severity of Adhesive Capsulitis Scale

No.	Question	Responses	
		Numeric	Description
1	Have there been any changes in overall severity of your frozen shoulder since you started the study?	-1	Worse (Complete Question 2)
		0	About the same (Stop)
		1	Better (Complete Question 3)
2	How much worse would you say the overall severity of your frozen shoulder is since you started the study?	0	Almost the same, hardly worse at all
		-1	A little worse
		-2	Somewhat worse
		-3	Moderately worse
		-4	A good deal worse
		-5	A great deal worse
		-6	A very great deal worse
3	How much better would you say the overall severity of your frozen shoulder is since you started the study?	0	Almost the same, hardly better at all
		1	A little better
		2	Somewhat better
		3	Moderately better
		4	A good deal better
		5	A great deal better
		6	A very great deal better

All subjects will complete the Patient-reported Change in Severity of Adhesive Capsulitis questionnaire at times outlined in the SoA (Table 2).

3.15.5. Subject Satisfaction with Treatment

Subjects will rate their satisfaction with treatment on a 7-point Likert scale from Very Dissatisfied to Very Satisfied at times specified in the SoA (Table 2).

Table 9: Subject Satisfaction Prior to Receiving Treatment

No.	Question	Responses	
		Numeric	Description
1	In your treated shoulder, how satisfied are you with the relief of pain now compared to the pain prior to treatment?	3	Very Satisfied
		2	Satisfied
		1	Somewhat Satisfied
		0	Neither Satisfied nor Dissatisfied
		-1	Somewhat Dissatisfied
		-2	Dissatisfied
		-3	Very Dissatisfied
2	In your treated shoulder, how satisfied are you with the relief of stiffness now compared to the stiffness prior to treatment?	3	Very Satisfied
		2	Satisfied
		1	Somewhat Satisfied
		0	Neither Satisfied nor Dissatisfied
		-1	Somewhat Dissatisfied
		-2	Dissatisfied
		-3	Very Dissatisfied

Table 10: Subject Satisfaction Compared to Better Shoulder

No.	Question	Responses	
		Numeric	Description
1	Compared to your better shoulder, overall how satisfied are you with the relief of pain in your treated shoulder?	3	Very Satisfied
		2	Satisfied
		1	Somewhat Satisfied
		0	Neither Satisfied nor Dissatisfied
		-1	Somewhat Dissatisfied
		-2	Dissatisfied
		-3	Very Dissatisfied
2	Compared to your better shoulder, overall how satisfied are you with the relief of stiffness in your treated shoulder?	3	Very Satisfied
		2	Satisfied
		1	Somewhat Satisfied
		0	Neither Satisfied nor Dissatisfied
		-1	Somewhat Dissatisfied
		-2	Dissatisfied
		-3	Very Dissatisfied

3.15.6. 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 SoA (Table 2).

Table 11: Investigator Assessment of Improvement with Treatment

No.	Question	Responses	
		Numeric	Description
1	At the follow-up visit, please rate the degree of change in the severity of the subject's treated shoulder compared with screening	3	Very Much Improved
		2	Much Improved
		1	Minimally Improved
		0	No Change
		-1	Minimally Worse
		-2	Much Worse
		-3	Very Much Worse

3.15.7. Magnetic Response Imaging (MRI) and X-rays

An X-ray of the affected shoulder is required at screening unless there is a historic X-ray of the affected shoulder that was taken within 30 days of the Screening Visit.

MRIs of the affected shoulder will be performed for all subjects at Screening and Day 95 and of the contralateral shoulder at the Screening Visit only. [redacted] Subjects should complete all other screening activities prior to the MRIs required at screening and must meet the entry criteria.

3.16. Safety Assessments

Virtual visits are allowed to assess safety during any COVID-19 interruption.

3.16.1. Adverse Events

All adverse events (AEs) will be recorded from the time informed consent is signed through the Day 95/ET Visit, or for 28 days after the last dose of study treatment for those who early terminate.

Conditions existing prior to screening will be recorded as part of subject's medical history.

3.16.1.1. Adverse Events (AE)

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 pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. 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.

3.16.1.2. Serious Adverse Events (SAEs)

SAEs are those AEs that meet any of the following criteria:

- Results in death.
- Life-threatening event.
- Results in or prolongs an inpatient hospitalization.
- Results in permanent or substantial disability.
- Is a congenital anomaly or birth defect.
- Any important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

3.16.1.3. Adverse Events of Special Interest (AESI)

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 electronic case report form (eCRF). All AESIs will be evaluated for seriousness and severity. AESIs will be sponsor-defined by the AE preferred term prior to database lock.

3.16.2. Clinical Laboratory Determinations

Blood and urine samples will be collected for testing the clinical laboratory parameters in Table 12 below at the time points outlined in the SoA.

Table 12: Clinical Safety Laboratory Parameters

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 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.

Any clinically significant laboratory abnormality observed will be considered as an AE or SAE as appropriate.

3.16.3. Pregnancy Test

All female subjects of childbearing potential must have a negative pregnancy test at Screening to be enrolled in the study. Female subjects of childbearing potential will undergo a serum pregnancy test at the Screening Visit and urine pregnancy tests before injection on treatment visits (Day 1, 22 and 43).

3.16.4. Height and Weight

Height will be collected at screening only. Weight will be obtained at the Screening and Day 95/ET Visit.

Any clinically significant abnormality in weight compared to the screening value, will be considered as an AE or SAE as appropriate.

3.16.5. Vital Signs

Vital sign measurements will include systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and body temperature and will be taken at Screening, treatment visits (Day 1, 22 and 43), Day 64 and Day 95/ET Visits.

On days that study treatment is administered, 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

post dose time point). The subject's vital signs must be stable, or repeated until stable, before the subject can leave direct observation.

Any clinically significant abnormality in vital signs observed will be considered as an AE or SAE as appropriate.

3.16.6. Electrocardiogram

A 12-lead ECG recording will be performed during the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted.

If the ECG report shows QT prolongation with QTc ≥ 450 ms for males or QTc ≥ 470 ms for females, the investigator will exclude the subject from study participation.

ECGs will be assessed by the Investigator and graded as:

- Normal.
- Abnormal, not clinically significant.
- Abnormal, clinically significant.

Any clinically significant abnormality in ECG observed will be considered as an AE or SAE as appropriate.

3.16.7. Physical Examination

The complete physical examination (by body system) on each subject will be performed at the Screening and Day 95/ET Visits. 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.

The investigator will assess the physical examination findings as normal or abnormal. If physical examination findings meet the Investigator's criteria for clinical significance, then it will be reported as an AE or SAE as appropriate.

3.17. Immunogenicity

Immunogenicity variables include anti-AUX-I /anti-AUX-II binding antibodies (ie, anti-drug antibodies) and neutralizing antibody results. Serum samples will be collected at the Day 1 Visit (prior to study treatment administration) and at the Day 95/ET Visit for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II.

4. STUDY PARAMETERS

4.1. Subject Disposition

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

Subjects who discontinue or are withdrawn from the 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 reason and date for study treatment discontinuation will be recorded in the eCRF.

If a subject withdraws from the study, all early termination procedures will be conducted as detailed in the SoA (Table 2). The reason and date for early withdrawal will be recorded in the eCRF for subjects who do not complete the study. If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information will be recorded in the source documentation and the eCRF.

Subjects who have been withdrawn from the study at any time after the first dose of study treatment will not be replaced. The reason for screen failure will also be recorded in the eCRF for subjects who consent to participate in this study but are not subsequently randomized.

4.2. Protocol Deviations

Potential deviations will be identified prior to database lock. Protocol deviations will be derived from the eCRF data, electronic vendor data and will be obtained from the clinical monitoring reports. All deviations from these sources will be reconciled and duplicate deviations will be removed.

Possible protocol deviations include, but are not restricted to the following deviation types:

- Ineligible subject/study entry criteria not satisfied.
- Informed consent not completed correctly.
- Non-compliance of study treatment.
- Prohibited medications/procedure.
- Visit/procedure missing or out of window.

The Endo study team will approve all final protocol deviation assignments and classify them as either major or minor during ongoing protocol deviation review meetings held throughout the study and a final meeting prior to the database lock.

4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics include the following parameters:

- Age.
- Height (at Screening).

- Weight (at Screening).
- Body Mass Index (BMI) in kg/m^2 (at Screening) (refer to Table 16).
- Gender.
- Race.
- Ethnicity.
- Time since last menstrual period for female subjects.
- Report of tobacco and alcohol use
  - Alcohol use (Never, Current, and Former).
  - Tobacco use (Never, Current, and Former).

4.4. Prior and Concomitant Medications

All medications will be coded using World Health Organization (WHO) Drug Dictionary, by active ingredient and WHO anatomical therapeutic chemical (ATC) classification of ingredients. The dictionary version to be used will be defined in the Data Management Plan (DMP).

A prior medication (or non-drug therapy) is defined as any medication (or non-drug therapy) taken prior to the Screening Visit and stopped before the Screening Visit.

A concomitant medication (or non-drug therapy) is any medication (or non-drug therapy) taken on or after the Screening Visit through the Day 95/ET Visit or taken prior to the Screening Visit and continuing during the study.

4.4.1. Prior Adhesive Capsulitis (AC) Treatment

Prior AC treatment will be obtained from the prior/concomitant medication and/or prior concomitant non-drug therapy pages of the eCRF. If on either of these pages a medication or nondrug therapy is reported with the indication 'Adhesive capsulitis' prior to the Screening Visit, then the medication or procedure will be considered a prior AC treatment.

All AC treatment medications will be classified as an "AC drug". All AC treatment procedures will also be classified. The classification will be reviewed and approved by the study medical monitor. Any AC treatment used after the Day 1 Visit will be noted and reported as a protocol deviation.

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

Degrees and percent deficit of the affected shoulder compared to the contralateral shoulder will be calculated as:

Let

PS: Measurement from affected shoulder

PC: Measurement from contralateral unaffected shoulder

then

Degrees deficit = PS - PC

Percent deficit = (PS - PC) / PC) * 100

4.6. Home Exercise Compliance

The compliance to home exercise will be calculated as:

Compliance (%) = (No. of days with at least 2 home exercises / total number of days required home exercises) * 100

In-office physical therapy will count as 1 of the home exercise sessions when attended and completed.

4.7. Efficacy Parameters

4.7.1. Adapted American Shoulder and Elbow Surgeons Standardized Shoulder Form (ASES)

4.7.1.1. Pain Subscale

The adapted ASES pain subscale score is calculated as:

Pain subscale score = (10 - Pain Raw score) * 5

The score range for pain subscale is 0-50 representing the worst pain (0) to no pain (50).

Change from baseline in the adapted ASES pain subscale for the affected shoulder at the Day 22, 43, 64, and 95 Visits will be analyzed.

4.7.1.2. Function Subscale

The adapted ASES function subscale score is calculated by multiplying the total score for 10 items by 5 and then dividing it by 3. The calculation is:

Function subscale score = [(Sum of scores of 10 items) * 5]/3

If the responses to 1 or 2 items in the ASES function subscale are missing, the ASES function subscale score will be calculated as = 10 × (mean of the scores for the non-missing activity items) × 5/3. If more than 2 items of the responses to the ASES function subscale are missing, then the ASES function subscale score will be considered as missing.

The score range for function subscale is 0-50 representing no function (0) to full function (50).

Change from baseline in the adapted ASES function subscale for the affected shoulder at the Day 22, 43, 64, and 95 Visits will be analyzed.

4.7.1.3. Composite Score

The adapted ASES composite score is the sum of the pain subscale score (50% of the composite score) and the function subscale score (50% of the composite score). The calculation is:

Composite score = Pain subscale score + Function subscale score

[redacted]

The range for the composite score is 0-100, where 0 is the worst pain and least functional and 100 is least pain and most functional. If either of the pain subscale or function subscale score is missing, then the ASES composite score will be considered as missing.

Change from baseline in the adapted ASES composite score for the affected shoulder at the Day 22, 43, 64, and 95 Visits will be analyzed. Positive change from baseline score means an improvement in pain and/or shoulder function from baseline.

4.7.2. Passive Range of Motion (PROM) and Active Range of Motion (AROM)

The PROM and AROM in affected shoulder at Day 22, 43, 64 and 95 will be analyzed for the following motions:

- Forward flexion.
- Internal Rotation.
- External rotation.
- Abduction.
- Shoulder extension.

The PROM and AROM will be analyzed at Day 22, 43, 64 and 95 using the following endpoints:

- Absolute change from baseline in affected shoulder
- Absolute and percent change from baseline in affected shoulder compared to the contralateral shoulder. The calculation is as below:

Let

ASi: Measurement from affected shoulder at visit i

CS1: Measurement from contralateral unaffected shoulder at baseline

then

Di = ASi - CS1

D1 (Baseline value) = AS1 - CS1

Absolute change = Di - D1

Percent change from baseline at Visit i = ((Di - D1) / D1) * 100

In addition, the HBB values will be ordinal ranked based on the level a subject can reach behind the back. The higher ranked assessment value signifies the ability to reach higher up behind the back. The lower the ranked value signifies the ability to reach behind the back low. A value of 0 will be assigned to subjects that cannot reach behind the back at all (the lowest rank possible).

The observed and change from baseline in HBB values will be analyzed at the Day 22, 43, 64 and 95 Visits.

4.7.3. Pain Upon Motion (PUM) Scale

The change from baseline in the PUM scale for the affected shoulder at the Day 64 and Day 95 Visits will analyzed.

[redacted]

4.7.4. Patient-reported Global Severity of Adhesive Capsulitis Scale

The change from baseline in the Patient-reported Global Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64 and 95 Visits will be analyzed.

4.7.5. Patient-reported Change in Severity of Adhesive Capsulitis Scale

The rating (response) in the Patient-reported Change in Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64, and 95 Visits will be analyzed.

4.7.6. Investigator Assessment of Improvement with Treatment

Investigator assessment of improvement with treatment at the Day 64 and Day 95 Visits will be analyzed.

A responder is defined as a response of "Very Much Improved", "Much Improved" or "Minimally Improved" in the investigator assessment of improvement with treatment.

4.7.7. Subject Satisfaction with Treatment

Subject satisfaction with treatment at the Day 64 and Day 95 Visits will be analyzed separately for individual questions of subject satisfaction prior to receiving treatment and subject satisfaction compared to better shoulder.

A responder is defined as a subject with a response of "Very Satisfied", "Satisfied" or "Somewhat Satisfied" in the subject satisfaction with treatment.

[redacted]

4.8. Safety Parameters

4.8.1. Adverse Events

Adverse event verbatim terms as reported by the investigator will be mapped to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The dictionary version to be used will be defined in the DMP.

4.8.1.1. Treatment Emergent Adverse Events (TEAEs)

TEAEs are defined as any AEs that occur or worsen (increase in severity) on the same day or after the treatment initiation.

The following rules will apply in cases where the start date of an AE is known:

- If the AE onset date is prior to first administration of the study drug, then the AE will not be considered a TEAE.
- If the AE onset date or date of AE worsening is equal to or later than first administration of the study drug, then the AE will be considered a TEAE.

Refer to section 6.3.2.1 to identify TEAE status when start date of an AE is unknown.

[redacted]

4.8.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as "Mild", "Moderate" or "Severe". For AEs with missing severity, the most severe assessment will be imputed for analyses as "Severe", following worst case principle.

4.8.1.3. Relationship to Study Drug

Causal relationship of AEs to study drug will be classified by the Investigator and will be reported as follows:

- Not related.
- Unlikely related.
- Possibly related.
- Probably related.

Related adverse events are AEs with the relationship described by the investigator as "Probably related" or "Possibly related". "Not related" or "Unlikely related" causality assessments are considered as negative causality.

Any AE with a missing relationship to study drug will be considered as related to study drug for the analyses, following worst case principle.

4.8.1.4. Adverse Event Categorization by Treatment Session

- The AEs will be associated with the treatment session based on the start date of the AE compared to injection date, as below:
- Treatment session 1: First injection date until start of second injection.
- Treatment session 2: Second injection date until start of third injection.
- Treatment session 3: Third injection date until start of Day 64 Visit.

4.8.2. Vital Signs and Clinical Laboratories

4.8.2.1. Laboratory Values

Clinical laboratory data (hematology and chemistry only) will be analyzed for observed value and change from baseline at Day 95/ET Visit. Refer to Table 16 for definition of baseline.

In addition, subjects reporting any sponsor-defined potentially clinically important (PCI) laboratory values during the study will be analyzed.

PCI laboratory values are presented in Table 13 below.

Table 13: Potentially Clinically Important Laboratory Criteria

Parameter	PCI Low: Less than or equal to	PCI High: Greater than or equal to
Hemoglobin (g/L)	100	190
Hematocrit (%)	30	60
Platelets (10^9/L)	100	650
ALT (U/L)		3×ULN
AST (U/L)		3×ULN
Creatinine (µmol/L)		200
BUN (mmol/L)		14

ALT=Alanine transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; PCI=Potentially clinically significant; ULN=Upper limit of normal

4.8.2.2. Vital Signs

Vital signs will be analyzed for observed value and change from baseline separately for vital signs on injection days and vital signs at each visit (excluding post injection time points on injection days). Refer to Table 16 for the definition of baseline.

In addition, subjects reporting any sponsor-defined PCI vital sign values during the study will be analyzed.

Vital sign values are PCI if they meet both the observed value criteria and the change from baseline criteria. The PCI vital sign values are presented in Table 14 below.

Table 14: Potentially Clinically Important Vital Sign Criteria

Parameter	PCI Low	PCI High
Systolic blood pressure	≤90 mm Hg and decrease ≥20 mm Hg from baseline	≥140 mm Hg and increase ≥20 mm Hg from baseline
Diastolic blood pressure	≤60 mm Hg and decrease ≥15 mm Hg from baseline	≥100 mm Hg and increase ≥15 mm Hg from baseline
Pulse rate	≤50 bpm and decrease ≥15 bpm from baseline	≥125 bpm and increase ≥15 bpm from baseline
Respiratory rate	≤12 brpm and decrease ≥7 brpm from baseline	≥25 brpm and increase ≥7 brpm from baseline
Temperature		≥38.3°C and increase ≥1.1°C from baseline

bpm=Beats per minute; brpm=Breaths per minute; PCI=Potentially clinically significant

5. ANALYSIS POPULATIONS

The study will use the following analysis populations for data summaries.

Table 15: Analysis Populations

Population	Definition	Displays
Safety Population	The Safety Population is defined as all randomized subjects who received at least 1 injection of study treatment (EN3835 or placebo). Subjects will be included in the Safety Population based on the actual treatment received.	All demographic, baseline characteristics and safety parameters will be summarized based on this population.
Intent-to-Treat (ITT) Population	The ITT Population is defined as all randomized subjects who received at least 1 injection of study treatment (EN3835 or placebo). Subjects will be included in the ITT Population based on the planned treatment.	
Modified Intent-to-Treat (mITT) Population	The 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 administration of study treatment. Subjects will be included in the mITT Population based on the planned treatment. Any subjects in the mITT Population are considered evaluable subjects, including early terminated subjects and/or completers.	All efficacy analyses will be based on this population.
Per-Protocol (PP) Population	The PP Population is defined as those subjects in the mITT Population who do not have any major protocol deviations which have a significant effect on the primary endpoint.	If more than 10% of the mITT Population is excluded from the PP Population, then select efficacy summaries will be repeated using the PP Population for the sensitivity analysis.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables and data listings will be prepared using SAS version 9.3 or higher.

All statistical tests of efficacy parameters will be 2-sided with a significance level of α=0.05, unless specified otherwise. Statistical tests will be supported by presenting estimates and 95% confidence intervals (CI) for each treatment group.

Continuous data will be summarized using descriptive statistics (number of subjects [n], mean, SD, median, minimum, and maximum). Discrete data will be summarized using frequency counts and percentages. The denominator will be based on the number of subjects in the appropriate population.

For the purpose of display, the summary results will be rounded as follows:

- Minimum and maximum: Same number of decimal places as the raw data.
- Mean and Median: One more decimal place than the raw data.

- SD: Two more decimal places than the raw data.
- Percentages will be displayed with 1 decimal place precision. A zero count will be left blank.
- The standard form of a percentage change variable is 0 decimal places.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Summary tables, subject listings, graphs and any supportive SAS output will include footnotes that will indicate:

- Date of data extraction.
- Date and time of output generation.
- SAS program name, including the path that generated the output.

When calculating percentages, the denominator will be based on the number of subjects with non-missing values. If the denominator is expected to change over time, then the denominator used to calculate the percentage will be based on the number of subjects with non-missing values at each visit. Any subject removed from an analysis will be noted at the bottom of the table along with the reason the subject was removed.

Empty summary tables will be presented with a note stating that “No Subjects Met Criteria.”

Subject listings of all data from the eCRFs as well as any derived variables will be presented.

6.2. Derived Variables

Table 16 defines the derived variables for study parameters.

Table 16: Derived Variables and Definition

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Body Mass Index (BMI)	BMI will be computed using height and body weight measured at Screening as, BMI (kg/m^2) = Weight (kg) / Height $(m)^2$
Relative Day 1	The day of first injection of study drug will be considered as relative Day 1.
Study Day (for assessment on or after Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1 + 1
Study Day (for assessment before Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study drug. The assessments made in unscheduled visits will be considered in calculation of baseline, if the unscheduled assessment is the closest value preceding the first dose of study drug.
Baseline for Vital Signs on Injection Days	For vital signs on injection days, the baseline value will be the vital sign measure immediately prior to the first dose of study drug.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Last Date in Study	Last date in study is defined as: • The date of End of Study (EOS) Visit (Day 95) if the subject completes the study • The date of early termination visit if the subject is terminated early from study at a non-scheduled visit • The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up.
Duration of AE	AE end date – AE start date + 1
AE Onset Day (for AE onset date on or after date Day 1)	AE start date – Date of Day 1 + 1
AE Onset Day (for AE onset date before date of Day 1)	AE start date – Date of Day 1

6.3. Handling of Missing Data

Subjects who withdraw from the study after the initiation of the study drug will not be replaced and available data for these subjects until the point of withdrawal will be summarized.

Any missing baseline assessments (last assessment prior to initial study drug treatment) will not be imputed.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Subjects who withdraw early from study will be encouraged to have all EOS procedures and assessments completed at an early termination visit.

For ASES function subscale, if the responses to 1 or 2 items are missing, the ASES function subscale score will be calculated as = 10 × (mean of the scores for the non-missing activity items) × 5/3. If more than 2 items of the responses to the ASES function subscale are missing, then the ASES function subscale score will be considered as missing. If either of the pain subscale or function subscale score is missing, then the ASES composite score will be considered as missing.

There will be no imputation of missing values for safety data, however missing relationship between AE and study drug will be considered as related to study drug following worst case principle. Missing severity of an AE will be summarized as a severe AE. Duration of an AE will be classified in the "> 21 Days" category if an AE is ongoing for more than 21 days by the time of the last visit of the subject in the study.

Immunogenicity samples with a positive titer value will undergo a log transformation for analyses. Samples with titer level less than 10 will be assigned or imputed as a log transformed titer of 1 for analyses.

6.3.1. Handling of Missing Data for Sensitivity Analysis of Primary Endpoint

The primary endpoint is the change from baseline in the adapted ASES composite score for the affected shoulder at Day 95. This value could be missing if the subject has missing data due to discontinuation from the study prior to Day 95, due to a missed assessment, lost to follow-up, or other.

A sensitivity analysis using a mixed model with repeat measurements (MMRM) with imputation using a tipping point analysis (refer to section 7.9.4.1) will be performed on the primary endpoint to assess the impact of missing values. If the primary analysis result is not significant (p-value greater than 0.05), no sensitivity analysis (tipping point) will be completed.

6.3.2. Imputation of Partial Dates

6.3.2.1. TEAE Status for Completely Unknown Start Date

The following rules will apply in cases where start date of an AE is completely unknown:

- If the AE onset date is unknown and the end date is after first injection on Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before first injection on Day 1, then the AE will not be considered a TEAE.
- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst-case principle.

If the AE onset date is partly present and month/year is prior to the first injection on Day 1, then the AE will not be considered a TEAE.

6.3.2.2. Concomitant Status of Medication/Non-drug Therapy for Completely Unknown Start Date

The following rules will apply in cases where start date of medication is completely unknown:

- If the medication onset date is unknown and the end date is after the date of screening but before the Day 95/ET Visit or medication is ongoing, then the medication will be considered as concomitant.
- If the medication onset date is unknown and the end date is before the date of screening, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication will be considered as concomitant. This approach is considered to be the most conservative following the worst-case principle.

If the medication onset date or end date is partly present and month/year is prior to the date of screening, then the medication will not be considered as concomitant. If the medication onset date or end date is partly present and month/year is after to the date of screening or medication is ongoing, then the medication will be considered as concomitant.

6.3.2.3. Missing Last Menstrual Date

Missing date of last menstrual period will be imputed with the last day of the month and missing onset month will be imputed with December.

6.4. Interim Analysis

An interim analysis for safety and futility is planned for when approximately 86 subjects (approximately 50% of subjects) have completed the Day 95/Early Termination Visit. Enrollment will continue during this analysis. Details of the interim analysis will be provided in a separate document.

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

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group and overall. Subjects excluded from the safety, ITT, mITT, or PP populations will be listed.

The frequency counts and percentages of subjects screened, enrolled, completed and/or withdrawn from the study, as well as the reason for withdrawal from study will be summarized by treatment group and overall.

A listing of disposition data will be provided. Screen failure reasons will also be listed. In addition, a listing for inclusion/exclusion criteria will be presented.

7.2. Protocol Deviations

Protocol deviations will be summarized by deviation classification (major/minor), and by treatment group and overall. A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and overall, for the safety, mITT, and PP populations.

Age, height (at baseline), body weight (at baseline), BMI in kg/m^2, and time since last menstrual period for female subjects will be summarized as continuous variables using descriptive statistics.

Age group, gender, race, and ethnicity will be summarized as categorical variables using frequency counts and percentages.

History of tobacco and alcohol use will be summarized using frequency counts and percentages as:

- Alcohol use (Never, Current or Former).
- Tobacco use (Never, Current or Former).

All demographic and baseline characteristics will be presented in by subject listings.

7.4. Medical and Surgical History

Medical history will be coded using the MedDRA dictionary. The version to be used will be defined in the DMP. Medical and surgical history data will not be summarized; however, a subject listing for medical history will be provided for subjects in the Safety Population.

A separate listing for surgical history of the affected shoulder will also be provided.

7.5. Adhesive Capsulitis History

A listing for history of all past episodes of AC of the shoulder will be provided.

A separate listing for AC current symptomatology will also be provided.

7.6. Prior/Concomitant Medications and Nondrug Therapies

Prior and concomitant medication use will be summarized by treatment group and overall using frequency counts and percentages for subjects in the Safety Population, by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Prior and concomitant non-drug therapies (procedures) will be summarized by treatment group and overall using frequency counts and percentages with name of the procedures ordered alphabetically. Multiple use of the same medication/nondrug therapy by a subject will be counted only once.

Listings of prior and concomitant medications and nondrug therapies will be provided for all subjects in the Safety Population. Similarly, a separate listing of prior medications and non-drug therapies for AC will also be provided.

7.7. Hand Dominance

Hand dominance will be summarized by treatment group and overall using frequency count and percentages for subjects in the Safety Population.

A listing for hand dominance will be provided.

7.8. Passive External Rotation

Passive external rotation at 0°, 45°, and 90° of abduction at screening will be summarized by treatment group and overall using absolute degrees, degrees and percent deficit of the affected shoulder compared to the contralateral shoulder for subjects in the Safety Population.

A listing for passive external rotation at 0°, 45°, and 90° of abduction will be provided.

7.9. Efficacy Analyses

Efficacy parameters will be summarized and analyzed by treatment group using the mITT Population.

For primary and secondary analysis, endpoints of the affected shoulder in the EN3835 treatment group will be compared to those in the placebo group.

7.9.1. Primary Analysis

7.9.1.1. Change from Baseline in Adapted ASES Composite Score

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

MMRM will be performed to estimate change from baseline treatment effect at Day 64 and Day 95 Visits comparing active to placebo for the adapted ASES composite score in the affected shoulder. MMRM will be performed to estimate the least square (LS) means of change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

Observed values and change from baseline in the adapted ASES composite score in the affected shoulder for each treatment group will be summarized at Day 22, 43, 64 and 95 Visits using descriptive statistics.

A listing of adapted ASES scores will be provided.

7.9.2. Secondary Analysis

7.9.2.1. Absolute and Percent Change from Baseline in PROM

MMRM will be performed to estimate change from baseline treatment effect at Day 22, 43, 64 and Day 95 Visits comparing active to placebo for PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder. MMRM will be performed to estimate the LS means of absolute change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be

calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

MMRM will be performed to estimate absolute and percent change from baseline treatment effect compared to baseline of the contralateral shoulder at Day 22, 43, 64 and Day 95 Visits comparing active to placebo for PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder. MMRM will be performed to estimate the LS means of absolute and percent change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

Observed values and change from baseline in PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder for each treatment group at Day 22, 43, 64, and 95 Visits compared to the affected shoulder at baseline will be summarized using descriptive statistics.

Observed values, absolute and percent change from baseline in PROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in affected shoulder for each treatment group at Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline will be summarized using descriptive statistics.

A listing of PROM will be provided.

7.9.2.2. Absolute and Percent Change from Baseline in AROM

MMRM will be performed to estimate change from baseline treatment effect at Day 22, 43, 64 and Day 95 Visits comparing active to placebo for AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder. MMRM will be performed to estimate the LS means of absolute change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

MMRM will be performed to estimate absolute and percent change from baseline treatment effect compared to baseline of the contralateral shoulder at Day 22, 43, 64 and Day 95 Visits comparing active to placebo for AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder. MMRM will be performed to estimate the LS means of absolute and percent change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

Observed values and change from baseline in AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder for each treatment

group at Day 22, 43, 64, and 95 Visits compared to the affected shoulder at baseline will be summarized using descriptive statistics.

Observed values, absolute and percent change from baseline in AROM for forward flexion, internal rotation, external rotation, abduction, and shoulder extension in the affected shoulder for each treatment group at Day 22, 43, 64, and 95 Visits compared to the contralateral shoulder at baseline will be summarized using descriptive statistics.

A Wilcoxon rank sum nonparametric test will be used to compare EN3835 to placebo for the HBB change from baseline values for active internal rotation in affected shoulder at the Day 22, 43, 64 and 95 Visits.

The null and alternative hypotheses for this test will be as below:

H_0: There is no difference in the change in baseline HBB values for active internal rotation in the 2 treatment groups.

Vs

H_1: The change in baseline HBB values for active internal rotation differs in the 2 treatment groups.

The Wilcoxon scores (Rank Sums) for treatment groups and test statistics along with *p* value for the test of significance will be presented.

Responses for HBB assessment for internal rotation will be summarized for each treatment group using frequency counts and percentages.

A listing of AROM will be provided.

7.9.2.3. Change from Baseline in Adapted Pain and Function Subscale

MMRM will be performed to estimate change from baseline treatment effect at Day 22, 43, 64 and Day 95 Visits comparing active to placebo for adapted pain subscale and adapted function subscale in the affected shoulder. MMRM will be performed to estimate the LS means of change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

Observed values and change from baseline in adapted pain subscale and adapted function subscale in the affected shoulder for each treatment group will be summarized at Day 22, 43, 64, and 95 Visits using descriptive statistics.

In addition, score and change from baseline for each of the individual questions will be summarized for adapted function subscale for each treatment group using frequency counts and percentages with mean and SD.

7.9.2.4. Change from Baseline in PUM Scale

MMRM will be performed to estimate change from baseline treatment effect at Day 64 and Day 95 Visit comparing active to placebo for PUM scale in the affected shoulder. MMRM will be performed to estimate the LS means of change from baseline for EN3835 and placebo treatment. *P* values and 95% CIs for the treatment difference (EN3835 – Placebo) will be

calculated by MMRM for the visits with treatment, visit, and an interaction of treatment and visit as fixed effected and repeated with visit/subject. Autoregressive covariance structure will be used in the model.

Observed values and change from baseline in the PUM scale in the affected shoulder for each treatment group will be summarized at Day 64 and Day 95 Visits using descriptive statistics.

A listing of PUM scale scores will be provided.

7.9.2.5. Change from Baseline in Patient-reported Global Severity of Adhesive Capsulitis Scale

A Wilcoxon rank sum nonparametric test will be used to compare EN3835 to placebo for the change from baseline in Patient-reported Global Severity of Adhesive Capsulitis Scale in the affected shoulder at the Day 22, 43, 64 and 95 Visits.

The null and alternative hypotheses for this test will be as below:

H_0: There is no difference in the change in severity in the 2 treatment groups.

Vs

H_1: The change in severity differs in the 2 treatment groups.

The Wilcoxon scores (Rank Sums) for treatment groups and test statistics along with *p* value for the test of significance will be presented.

Observed values and change from baseline in Patient-reported Global Severity of Adhesive Capsulitis Scale in the affected shoulder for each treatment group will be summarized at the Day 22, 43, 64 and 95 Visits using descriptive statistics.

A listing of Patient-reported Global Severity of Adhesive Capsulitis Scale scores will be provided.

7.9.2.6. Patient-reported Change in Severity of Adhesive Capsulitis Scale

Reponses for Patient-reported Change in Severity of Adhesive Capsulitis Scale at the Day 22, 43, 64, and 95 Visits will be compared between EN3835 to placebo using a chi-square test (or Fisher's exact test based on expected frequencies).

The null and alternative hypotheses for this test will be as below:

H_0: The distribution of responses is independent of the treatment groups.

Vs

H_1: The distribution of responses is dependent on the treatment group (ie, there is a difference in distribution of responses among the treatment groups).

Reponses for Patient-reported Change in Severity of Adhesive Capsulitis Scale will be summarized by each treatment group using frequency counts and percentages and in addition chi-square (or Fisher's exact) test statistics along with *p* value for the test of significance will be presented.

The change in the symptoms will be summarized by each treatment group using frequency counts and percentages with mean and SD.

[redacted]

A listing of Patient-reported Change in Severity of Adhesive Capsulitis Scale scores will be provided.

7.9.2.7. Investigator Assessment of Improvement with Treatment

A Wilcoxon rank sum nonparametric test will be used to compare EN3835 to placebo for the Investigator Assessment of Improvement with Treatment in the affected shoulder at the Day 64 and 95 Visits.

The null and alternative hypotheses for this test will be as below:

H_0: There is no difference in the Investigator Assessment of Improvement with Treatment in the 2 treatment groups.

Vs

H_1: The Investigator Assessment of Improvement with Treatment differs in the 2 treatment groups.

Wilcoxon scores (Rank Sums) for treatment group and test statistics along with *p* value for the test of significance will be presented.

Reponses for Investigator Assessment of Improvement with Treatment in the affected shoulder and responders will be summarized by treatment group using frequency counts and percentages with mean and SD.

A listing of Investigator Assessment of Improvement with Treatment scores will be provided.

7.9.2.8. Subject Satisfaction with Treatment

A Wilcoxon rank sum nonparametric test will be used to compare EN3835 to placebo for all the individual questions of Subject Satisfaction prior to receiving treatment and Subject Satisfaction compared to better shoulder for the affected shoulder at the Day 64 and 95 Visits. The null and alternative hypotheses for this test will be as below:

H_0: There is no difference in the Subject Satisfaction with Treatment in the 2 treatment groups.

Vs

H_1: Subject Satisfaction with Treatment differs in the 2 treatment groups.

Wilcoxon scores (Rank Sums) for treatment group and test statistics along with *p* value for the test of significance will be presented.

Reponses for Subject Satisfaction with Treatment in the affected shoulder and responders will be summarized by treatment group using frequency counts and percentages with mean and SD.

A listing of Subject Satisfaction with Treatment scores will be provided.

7.9.3. Exploratory/Tertiary Analyses

7.9.3.1. [redacted]

[redacted]

[redacted]

[redacted]

7.9.4. Sensitivity Analysis

7.9.4.1. Primary Endpoint Sensitivity Analysis with MMRM using Tipping Point Analysis (TPA)

A sensivity analysis will be performed to assess the impact of missing data with MMRM using tipping point analysis as described in section 7.9.1. Note that if the primary analysis result is not significant (p-value greater than 0.05), no sensitivity analysis will be perfomed.

To evaluate the impact of deviations from the missing at random (MAR) assumption, a delta-adjustment multiple imputation (MI) method will be used to find the tipping point where the result is no longer statistically significant.

There are three steps to be followed for this sensivity analysis.

Step 1: Generate Pattern of Missing Data

Before various MI methods are applied, the different types of missing data patterns will be checked using NIMPUTE=0 in SAS PROC MI. This will generate the pattern of missing data and will not generate any imputed values for missing data.

PROC MI DATA=*INPUT* NIMPUTE=0;
VAR *VAR1 VAR2 VAR3...(variables in order the missing patterns are created for)*;
RUN;

Step 2: Imputation of data for non-monotone and monotone missing data

- Intermittent missing values: If there are subjects with intermittent missing values (ie. non-monotone missing data), the intermittent missing values will be imputed based on Markov Chain Monte Carlo (MCMC) methods. SAS PROC MI will be utilized with MCMC to generate datasets with monotone missing pattern. The number of imputations will be set to *n* (20 is the default value).

  PROC MI DATA=*INPUT* NIMPUTE=*n* SEED=234 OUT=*IN_MCMC*;
  VAR …; (*treatment group, baseline covariates, and the preceding non-missing values in the order of clinical visits: baseline, Visit X, ..., Visit Y*)
  MCMC CHAIN=SINGLE NBITER=1000 NITER=1000 IMPUTE=MONOTONE;
  RUN;

[redacted]

- If all subjects have a monotone missing data pattern (either directly from the study or created by the previous step), the MAR-based multiple imputation with the regression option will be used to impute missing values, the imputed values will then be adjusted accordingly. Delta-adjustment will be generated for different combinations of δ_P an δ_A values as defined below:
    - Active-only adjustment analysis: $\delta_P = 0$ and $\delta_A = 0$ to Δ_1 (Δ_1 is the effect size reported in the primary analysis)
    - Analysis with a control adjustment that is half of the active adjustment: $\delta_P = \delta_A /2$ and $\delta_A = 0$ to Δ_1
    - All arms with identical adjustment: $\delta_P = \delta_A$ and $\delta_A = 0$ to Δ_1

- The imputation will be performed using SAS PROC MI with the MONOTONE statement and the REGRESSION option with the following specifications:

  PROC MI DATA=*IN_MCMC* NIMPUTE=*1* (*see note*) SEED=234 OUT=*OUTPUT*;
  VAR …; (*treatment group, baseline covariates, and the preceding non-missing values in the order of clinical visits: baseline, Visit X, ..., Visit Y*)
  CLASS…; (*treatment group*)
  MONOTONE REG (/details);
  MNAR ADJUST (*Visit X* / SHIFT=*delta_a* ADJUSTOBS=(TRT01PN ='1'));
  MNAR ADJUST (*Visit Y* / SHIFT=*delta_a* ADJUSTOBS=(TRT01PN ='1'));
  MNAR ADJUST (… / SHIFT=*delta_a* ADJUSTOBS=(TRT01PN ='1'));
  MNAR ADJUST (*Visit X* / SHIFT=*delta_p* ADJUSTOBS=(TRT01PN ='0'));
  MNAR ADJUST (*Visit Y* / SHIFT=*delta_p* ADJUSTOBS=(TRT01PN ='0'));
  MNAR ADJUST (… / SHIFT=*delta_p* ADJUSTOBS=(TRT01PN ='0'));
  RUN;

  Note: NIMPUTE=n if MCMC was NOT applied at the previous step.

<u>Step 3</u>: Analysis and Pooling

For each value of δ_P and δ_A, MMRM described in section 7.9.1 will be performed for each of the n adjusted fully imputed datasets. The analysis results obtained will be combined into a single estimation using PROC MIANALYZE to produce final inferences.

The following estimates will be presented in the sensitivity analysis table:

1. LSM estimate for the mean change from baseline at the visit where primary endpoint is measured for each treatment.
2. LSM estimate for treatment difference of the mean change from baseline at the visit where primary endpoint is measured and the corresponding 2-sided 95% CI and p-value for change from baseline in the primary endpoint will be provided.

Shift parameters will begin with active-only adjustment, followed by a control adjustment that is half of the active adjustment, followed by all arms with identical shift adjustments, as stated in Step 2.

All steps above are repeated with different values of the shift parameter until the tipping point is reached or all possible values are explored. The tipping point can be identified when the result is no longer statistically significant (p-value >0.05). It is possible a tipping point is not reached if little to no data is missing.

Once tipping point is reached, if implausible departure from MAR is needed to change the results from statistically significant to insignificance, the results of the primary endpoint are considered to be robust. If the tipping point obtained for overturning the primary endpoint result is clinically plausible, the conclusion can be questioned and viewed with caution.

7.9.5. Supportive Analysis

7.9.5.1. Per-Protocol Population Analysis

If more than 10% of the mITT Population is excluded from the PP Population, then select efficacy summaries will be repeated using the PP Population for the supportive analysis.

7.10. Safety Analyses

Safety data will be summarized by each treatment group and overall using the Safety Population. Subjects will be included in the safety analyses based on the actual treatment received.

7.10.1. Study Drug Exposure

The study drug exposure will be summarized at each treatment visit and by each treatment group. The following will be summarized descriptively:

- Number of injections received.
- Total dose administered (mg).

A subject listing of overall exposure will be provided.

7.10.2. Adverse Events

Proportion of subjects reporting at least 1 adverse event, treatment-emergent adverse event, adverse event of special interest, and serious adverse event will be compared for EN3835 to placebo treatment group using Fisher's exact test.

The null and alternative hypotheses for this test will be as below:

H_0: p1 = p2 (Proportion of subjects having an adverse event are equal in treatment groups)

Vs

H_1: p1 ≠ p2 (Proportion of subjects having an adverse event are unequal in treatment groups)

Where,

p1: Proportion of subjects having adverse event in EN3835 treatment group.

p2: Proportion of subjects having adverse event in placebo treatment group.

Number and proportion of subjects with at least 1 adverse event, treatment-emergent adverse event, adverse event of special interest, and serious adverse will be summarized by treatment groups and in addition *p* value for treatment comparison will also be presented.

All AE summary tables will include only TEAEs, unless otherwise specified.

AEs will be summarized by SOC and PT. A subject will only be counted once per SOC and PT.

For AEs by severity grade (mild, moderate, severe), if a subject has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (ie, severe) will be counted.

For AEs by relationship to study drug, if a subject has multiple events occurring in the same SOC or same PT, the event with the highest association (ie, related) to study drug will be summarized.

AEs will be presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the PT level.

An overall summary of AEs and AEs related to study drug will be presented and will include:

- Total number of TEAEs reported.
- Total number of TEAEs reported by severity.
- Total number of TEAEs of special interest.
- Subjects with any TEAE.
- Subjects with any TEAE of special interest.
- Subjects with any serious TEAE.
- Subjects with any severe TEAE.
- Subjects with no severe TEAEs, but at least 1 moderate TEAE.
- Subjects with no severe TEAEs, but at least 1 mild TEAE.
- Subjects with any TEAEs leading to drug interruption/withdrawal.
- Subjects with any TEAEs leading to study discontinuation.
- Subjects with any TEAEs resulting in death.

The following summary tables will be presented by SOC and PT:

- All TEAEs.
- Study drug related TEAEs.
- TEAEs by severity.
- Study drug related TEAEs by severity.
- Study drug related TEAEs by treatment session
- Duration (1-7 days, 8-14 days, 15-21 days, > 21 days) of study drug related TEAEs.
- Serious TEAEs.

- TEAE of special interest.
- TEAE of special interest by severity.

Most common non-serious TEAEs by order of frequency (Most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. Most common non-serious AEs are those that at least 5% of the subjects reported at least once (using PT).

The following listings will be presented by subject:

- All AEs.
- AEs resulting in death.
- Non-fatal serious AEs.
- AEs resulting in drug interruption/withdrawal.
- AEs resulting in study discontinuation.

Refer to Table 16 for computation of duration of AEs.

7.10.3. Clinical Laboratory

Student *t* test (2-sample *t* test) will be used to compare EN3835 to placebo for change from baseline in the laboratory parameters (hematology and chemistry) at the Day 95 Visit.

The null and alternative hypotheses for this test will be as below:

H_0: There is no significant difference in mean change in laboratory parameters for 2 treatment groups.

Vs

H_1: There is significant difference in mean change in laboratory parameters for 2 treatment groups.

Hematology and chemistry results will be summarized by each treatment group using descriptive statistics for observed and change from baseline values along with *p* value at Day 95/EOS Visit.

Proportion of subjects reporting with PCI laboratory values will be compared for EN3835 to the placebo treatment group using Fisher's exact test. Refer to Table 13 for PCI criteria.

The null and alternative hypotheses for this test will be as below:

H_0: $p1 = p2$ (Proportion of subjects having PCI laboratory values are equal in treatment groups)

Vs

H_1: $p1 \neq p2$ (Proportion of subjects having PCI laboratory values are unequal in treatment groups)

Where,

p1: Proportion of subjects having PCI laboratory values in EN3835 treatment group.

P2: Proportion of subjects having PCI laboratory values in placebo treatment group.

The PCI laboratory values will be summarized by treatment groups. In addition, the *p* value for treatment comparison will be presented.

A subject listing will be presented for all laboratory parameters (hematology, biochemistry, urinalysis, TSH and HbA1c). Serum and urine pregnancy test results will be listed separately.

7.10.4. Vital Signs

Student *t* test (2-sample *t* test) will be used to compare EN3835 to placebo for change from baseline in the vital signs (SBP, DBP, pulse rate, respiratory rate, body temperature, and body weight) at Day 1, 22, 43, 64, and 95 Visits.

The null and alternative hypotheses for this test will be as below:

H_0: There is no significant difference in mean change in vital sign parameters between the 2 treatment groups.

Vs

H_1: There is a significant difference in mean change in vital sign parameters between the 2 treatment groups.

Vital signs (SBP, DBP, pulse rate, respiratory rate, body temperature) taken on the injection days will be summarized across the required measurement time points (15 minutes and 30 minutes post injection) for each treatment group using descriptive statistics for observed and change from baseline values.

Vital signs taken at each visit will be summarized across study visits not including the post injection time points for each treatment group and overall using descriptive statistics for observed and change from baseline values along with *p* value.

Proportion of subjects reporting with PCI vital sign values will be compared for EN3835 to the placebo treatment group using Fisher's exact test. Refer to Table 14 for PCI criteria.

The null and alternative hypotheses for this test will be as below:

H_0: p1 = p2 (Proportion of subjects having PCI vital sign values are equal in treatment groups)

Vs

H_1: p1 ≠ p2 (Proportion of subjects having PCI vital sign values are unequal in treatment groups)

Where,

p1: Proportion of subjects having PCI vital sign values in EN3835 treatment group.

p2: Proportion of subjects having PCI vital sign values in placebo treatment group.

The PCI vital sign values will be summarized by treatment groups. In addition, the *p* value for treatment comparison will be presented.

A listing will be presented for vital signs results.

7.10.5. 12-Lead ECG

The investigator interpretation of ECG results (normal, abnormal not clinically significant, or abnormal clinically significant) will be summarized by each treatment group and overall using frequency counts and percentages.

A listing of investigator interpretation of ECG results will be presented.

7.10.6. Physical Examination

Physical examination results (by body system) at baseline and at Day 95/ET will be presented by each treatment group and overall using frequency counts and percentages.

A listing will be presented for the physical examination results (by body system).

7.10.7. Immunogenicity

The immunogenicity analysis of binding and neutralizing anti-AUX-I and anti-AUX-II antibodies will be summarized by the number of subjects with an immunogenicity sample, the percentage of subjects with a positive sample, and the average titer level of the positive samples at Screening and Day 95/ET along with summary statistics if antibody assays are conducted.

The titer levels will be logarithmically transformed prior to being summarized. Samples from Screening and Day 95/ET will be analyzed for anti-AUX-I and anti-AUX-II antibodies and only positive samples will be analyzed for neutralizing antibodies. Neutralizing antibody results will be summarized as percentage of samples tested by positive/negative results.

A listing of immunogenicity results by subject will be provided.

7.11. Other Analyses

7.11.1. X-Ray

A listing for x-ray will be provided.

7.11.2. Physical Therapy

A listing for physical therapy will be provided.

7.11.3. Home Exercise

The compliance of home exercises at all study days (starting 3 days after each study treatment up to the Day 95/ET Visit) will be summarized for each treatment group and overall using descriptive statistics.

A listing for home exercise will be provided.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on the study protocol; original version dated April 06, 2020, Amendment 1 dated July 10, 2020, Amendment 2 dated July 31, 2020, Amendment 3 on November 06, 2020, and Amendment 4 on October 22, 2021.

Table 17 lists any significant changes in the SAP from what is proposed in the protocol.

Table 17: Changes from Protocol

Text in Protocol	Change in SAP	Justification
The Per-Protocol (PP) Population is defined as those subjects in the mITT Population who do not have any major protocol deviations.	The PP Population is defined as those subjects in the mITT Population who do not have any major protocol deviations which have a significant effect on the primary endpoint.	Change the PP Population to emphasize only subjects with major PDs that effect the primary endpoint to be excluded. This allows subjects with major PDs related to safety only (and no effect on primary endpoint) to be included in PP Population.
N/A	Added a tipping point sensitivity analysis (section 7.9.4)	Tipping point analysis checks if the missing data effects the primary analysis conclusions by checking severity of missing data. Identify the tipping poing where treatment effect in subjects with missing data overturns the significant treatment effect otbtained in the missing at random primary analysis.

9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP will be recorded in Table 18.

Table 18: Revision History

Version	Date	Revision Author	Comments
v1.0	Aug 12, 2020	[redacted]	Original version
v2.0	April 25, 2022	[redacted]	Protocol amendment updates, prior/concomitant definition, adverse events of special interest, tipping point sensitivity analysis

10. REFERENCES

1. Endo Pharmaceuticals Inc. 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 [EN3835-210 Clinical Study Protocol, Amendment 2]. Malvern, PA; 31 July 2020.
2. McClure P, Michener L. Measures of adult shoulder function: the American Shoulder and Elbow Surgeons Standardized Shoulder Form patient self-reported section (ASES), Disabilities of the Arm, Shoulder, and Hand (DASH), Shoulder Disability Questionnaire, Shoulder Pain and Disability Index (SPADI), and Simple Shoulder Test. *Arthritis Rheum*. 2003;49(5S):S50-S58. doi:10.1002/art.11404
3. Michener LA, McClure PW, Sennett BJ. American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form, patient self-report section: reliability, validity, and responsiveness. *J Shoulder Elbow Surg*. 2002;11(6):587-594. doi:10.1067/mse.2002.127096
4. Evidera. Evaluation of Test-Retest Reliability of the Standardized Shoulder Assessment Form Adapted from the ASES and a Pain Upon Movement Question. Version 1.0. Bethesda, MD; 22 January 2016.

11. TABLES, LISTINGS, AND GRAPH SHELLS

The layouts of the summary tables, subject listings, and graphs are presented in SAP Module 2. These layouts incorporate all the appropriate table titles, table numbers, and footnotes.

[redacted]