



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

**COLLAGENASE CLOSTRIDIUM HISTOLYTICUM
(EN3835)**

EN3835-222

**A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-
CONTROLLED STUDY TO ASSESS THE EFFICACY, SAFETY,
AND TOLERABILITY OF EN3835 VS PLACEBO IN THE
TREATMENT OF PLANTAR FIBROMATOSIS**

Sponsor Name: Endo Pharmaceuticals Inc.

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

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Original Protocol: 09 April 2021

Amendment 01: 14 July 2021

Amendment 02: 20 October 2021

Amendment 03: 18 April 2022

Amendment 04: 10 June 2022

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.

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SUMMARY OF CHANGES

Rationale for Amendment 04

The primary purpose for this amendment was to reduce the sample size for the study based on an 85% statistical power and a lower dropout rate than expected. Major changes include:

Section Name and Number	Description of Change
Section 6.1, Participant Inclusion Criteria	Modify inclusion criterion #7, to able to read and understand the patient reported assessments in the local language of the country instead of limiting to English or Spanish
Section 2.1, Synopsis, Overall Study Design and Number of Participants (Planned) Section 2.2, Study Schema Section 5.1, Overall Study Design	Modified the expected number of participants from 216 to 172 to be enrolled in the study to account for the reduced dropout rate.
Section 2.1, Synopsis, Objectives and Endpoints Section 4, Objectives and Endpoints Section 10.3.1.2.4, Other Secondary Endpoints and Exploratory Endpoints	Changed exploratory objective and endpoint from the FFI total score to the FFI composite score
Section 3.2.2, EN3835-106	Indicated that the study is on hold.
Section 10.1, Sample Size Determination	Reduce the sample size for the study from 216 to 172 based on a statistical power of 85% (rather than 90%) and lower drop out rate (15%) than previously assumed (20%)
Section 10.3.1.1.1, Primary Estimand Section 10.3.1.1.2, Method of Analysis Section 10.3.1.2.1, Key Secondary Endpoint 1 Section 10.3.1.2.3, Key Secondary Endpoint 3	Deleted the term “after 57 days of randomization” since this was redundant.

Rationale for Amendment 03

The primary purpose for this amendment was to incorporate changes after receiving FDA feedback on 22 December 2021. These changes included modifications to the statistical method of analysis and clarification that withdrawal only refers to withdrawal of consent. Changes included in Administrative Letter 02 were also incorporated with in. The major changes include:

Section Name and Number	Description of Change
Global	Identified each study manual with better granularity.
Section 2.2, Study Schema Section 2.3, Schedule of Assessments Section 8.1, Discontinuation of Study Intervention Section 9.3.1, Time Period and Frequency for Collecting AEs and SAE Information	Added a 28-day follow-up safety visit for participants that discontinue study intervention to follow up for any ongoing adverse events (AEs) or serious adverse events (SAEs).
Section 2.2, Study Schema, footnote “a”, Section 5.1, and Section 2.1, Synopsis Section 6.2.1, Participant Inclusion Criteria – Treatment 2 Section 6.2.2, Participant Exclusion Criteria – Treatment 2	Clarified that Treatment 2 (rather than inclusion/exclusion criteria) must be met on Day 29. Added separate sections for participant inclusion and exclusion criteria for Treatment 2.
Section 2.3, Schedule of Assessments	Footnote “c” on the foot examination on Day 29 was deleted. Modified footnote “p” to specify “that the second treatment visit should be administered only if the participant has a “previously treated” palpable nodule.” Added a separate entry in the Schedule of Assessments for Treatment 2 Criteria that must be met on Day 29. Switched contents of footnote “c” and footnote “p”.
Section 3.1, Study Rationale Section 5.2, Scientific Rationale for Study Design	Modified status of Study EN3835-105 from ongoing to completed, to reflect finalized clinical study report (CSR).
Section 3.2.1, EN3835-105 Proof of Concept Section 3.2.2, EN3835-106 Section 3.2.3, EN3835-306	Updated background information to align with the current status of the development program.
Section 3.3.1, Benefits of EN3835 in Plantar Fibromatosis Section 13, References	Added reference to Mahmoud et al, 2021 .
Section 5.1, Overall Design and Section 2.1, Synopsis Section 2.3, Schedule of Assessments, footnotes “c” and “l” Section 6.1, Participant Inclusion Criteria Section 6.2.1, Participant Inclusion Criteria – Treatment 2 Section 7.1, Selection of Nodules Section 9.1.1.2, Consistency of the Selected Nodule	Modified nodule consistency scale from hard, firm, or soft to hard, firm throughout, moderately firm, or soft. For initial treatment, participants must have hard, firm throughout or moderately firm nodules. For Treatment 2, participants must have previously treated nodule(s) that remains palpable (eg, hard, moderately firm, firm throughout or soft).

Section Name and Number	Description of Change
Section 5.1, Overall Design and Section 2.1, Synopsis Section 7.1, Section of Nodules Table 2, Dose of Study Intervention per Nodule	Clarified that all hard and firm nodules on Day 1 will be treated. If all nodules on each foot are not hard or firm on Screening or Day 1, the participant will not be eligible for study inclusion.
Section 5.2.1, Changes in the Study Design Due to COVID-19 Section 6.4, Screen Failures	Harmonize rescreening procedures, including situations of COVID-19. Indicated that participants may only be rescreened once prior to randomization.
Section 5.2.4, Stopping Rules for the Study	Removed reference to “probably” or “possibly” related, since investigators are blinded to study treatment. Added anaphylaxis reactions to the stopping rule. Harmonized text with Section 11.1.4.
Section 5.3, End of Study Definition	Added a definition for the overall end of study.
Section 6.2, Participant Exclusion Criteria	In Exclusion Criterion 1, added “affected” feet for further clarification. Added Exclusion Criterion 3, 4, 5, and 18. The numbering of other exclusion criteria have changed due to these additions.
Section 7.3.1, Study Intervention Table 2	Added additional clarification to the table footnotes on criteria for treatment. Added conversion from cm to mm as caliper measurements are in mm.
Section 7.7.1, Prior Medications	To capture potential impact on immunogenicity results, added that the use of a collagenase at any point in time must be captured in the electronic case report form (eCRF).
Section 8.1, Discontinuation of Study Intervention and Discontinuation from the Study Section 2.3, Schedule of Assessments	Added a 28-day post-treatment follow-up visit and early termination (ET) visit.
Section 8.2, Participant Withdrawal from the Study	Added further clarification that withdrawal refers to withdrawal of consent.
Section 8.3, Lost to Follow-up	Removed reference to the investigator in deciding to replace participants lost to follow-up.
Section 9.1.1.2, Consistency of the Selected Nodule	Clarified text.
Section 10.3.1.1.1, Primary Estimand	To meet the FDA request, added characteristics of the primary estimand.
Section 10.3.1.1.2, Method of Analysis	To meet the FDA request, updated the method of analysis to include a sensitivity analysis.

Section Name and Number	Description of Change
Section 10.3.1.2.1, Key Secondary Endpoint Section 10.3.1.2.2, Key Secondary Endpoint 2 Section 10.3.1.2.3, Key Secondary Endpoint 3 Section 10.3.1.2.4, Other Secondary Endpoints and Exploratory Endpoints	The key secondary estimand was modified to align with the secondary endpoint defined in the protocol. To meet the FDA request, added characteristics of the key secondary endpoint 1, 2, and 3. Added characteristics of key secondary estimand 1, 2, and 3, method of calculation and sensitivity analysis. For Key Secondary Endpoint 3, removed reference to imputed data. Reorganized sections by endpoints and added exploratory analysis
Section 10.3.2.1, Adverse Events	To meet the FDA request, indicated that a confidence interval for the difference in the frequency of treatment-emergent adverse events (TEAEs) across treatments will be provided.
Section 10.5, Handling of Missing Data	Added reference to tipping point analysis.
Section 10.7, Subgroup Analysis	To meet the FDA request, added subgroup analyses.
Section 11.1.2, Informed Consent Process	Added that participants will need to sign a new informed consent form (ICF) if more than 28 days elapse between initial ICF signature and date of randomization.
Section 11.1.5, Dissemination of Clinical Study Data	Clarified that aggregate results will be disseminated for the study.

Rationale for Amendment 02

The primary purpose for this amendment was to incorporate changes after receiving FDA feedback on 22 September 2021 and 01 October 2021. The major changes include 1) limiting the dose to 1.8 mg in total per treatment visit; 2) removing pharmacokinetic (PK) assessments, PK endpoint, PK subgroups, and PK analysis; 3) removing photography subgroup and assessments; 4) including the National Institute of Allergy and Infectious Disease (NIAID) definition for assessing for anaphylaxis; 5) including the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading scale for assessing severity of adverse events (AEs); 6) including a study specific grading scale for injection site reactions; 7) modifying the Intent-to-Treat (ITT) population definition and adding a modified Intent-to-Treat (mITT) and a Full Analysis Sets (FAS) and 8) adding further details of statistical analysis to be conducted. Relevant changes included in Administrative Change Letter 01 were also incorporated into this amendment to the protocol.

Section Name and Number	Description of Change
Global	Removed all references to PK assessments, endpoints, and statistical evaluation. PK will be assessed in another study.
Global	Removed all references to photography subgroup, assessments and photography visits. Photography will be assessed in another study.

Section Name and Number	Description of Change
Global	Removed all references to high (2.7 mg) and low dose (1.8 mg) of study intervention. Capped maximum dose administered to 1.8 mg in total and removed all references to the 2.7 mg dose. Indicated that the total number of injections across all nodules present shall not exceed 3 injections (1.35 mg) in a single foot when treating participants with unilateral plantar fibromatosis. When treating participants with bilateral plantar fibromatosis, the total number of injections across all nodules present shall not exceed 4 injections (1.8 mg) in total with each foot receiving a maximum dose of 0.9 mg.
Section 2.2, Schedule of Assessments	Included assessment of the Patient Global Impression of Severity (PGIS) and Pain Numerical Rating Scale (NRS) at screening to align with analysis conducted in the psychometric testing.
Section 2.3, Schedule of Assessments, footnote “c” Section 9.2.2, Physical Examination	In the Schedule of Assessments, modified footnote “c” and Section 9.2 to indicate that a foot examination will be conducted at the time points listed in the Schedule of Assessments.
Section 2.3, Schedule of Assessments, footnote “f”	Updated footnote “f” to reflect inclusion criterion related to nodule hardness on Treatment 2.
Section 2.3, Schedule of Assessments Section 9.1.1.1, Anatomical Representation of Nodule Location	Added assessment for Anatomic Representation of Nodule(s) at Screening and Day 57. Modified footnote “m” for harmonization.
Section 2.3, Schedule of Assessments Section 6.2, Exclusion Criteria Section 9.2.5, Electrocardiogram	Removed electrocardiogram (ECG) assessments and exclusion criterion pertaining to ECGs and assessments.
Section 4, Objectives and Endpoints; Section 2.1, Synopsis	Removed the term “over time” in the endpoints being assessed on Days 15, 29, 43, and 57.
Section 4, Objectives and Endpoints; Section 2.1, Synopsis	Modified PGIS endpoints from the difference in the mean change from Baseline to Day 57 to the difference in the PGIS scores between EN3835 and placebo at the assessed time points.
Section 4, Objectives and Endpoints; Section 2.1, Synopsis Section 10.1, Sample Size Determination Section 10.3.1.1, Primary Analysis	Removed “± 5 days” in endpoints being assessed at end of study (EOS) visit.
Section 5.1, Overall Design Section 5.3, EOS Definition	Clarified that all participants are expected to remain in the study until Day 57, regardless if they receive 1 or 2 treatments.
Section 5.2.1, Changes in the Study Design due to COVID-19 Section 9.2, Safety Assessments	Updated date of the FDA COVID-19 guidance to 30 August 2021.
Section 5.2.2, Justification for Dose	Added that the maximum dose has been limited to 1.8 mg since this was the dose studied in Study EN3835-105.

Section Name and Number	Description of Change
Section 5.2.4, Stopping Rules for the Study	Per FDA recommendation, included stopping rules for enrollment into the study.
Section 6.1, Inclusion Criteria	Modified inclusion criteria to requiring ≤ 4 injections (1.8 mg maximum dose) per treatment visit. Indicated nodule configuration and maximum dose based on whether 1 or 2 feet are treated.
Section 6.3, Lifestyle Considerations	Added that participants should be encouraged to wear supportive footwear when on their feet during the study.
Section 7.3.1, Study Intervention, Table 2, Dose of Study Intervention Per Nodule	Indicated that maximum dose of study intervention is no more than 1.8 mg per foot in participants with bilateral plantar fibromatosis and no more than 1.35 mg per foot in participants with unilateral plantar fibromatosis.
Section 7.3.1, Study Intervention, Table 3 Study Intervention Group Allocation Based on Count of Nodules and Nodule Sizes and Table 4 Total Count of Injections of Study Intervention Based on Nodule Size Combinations Present in Both Feet	Removed Tables 3 and 4 since allocation to high-dose and low-dose groups were linked to PK assessments which were removed during the amendment.
Section 7.3.3, Care Procedures After Injection	Removed reference to applying a gauze bandage or an adhesive dressing after injection.
Section 7.5.1, Interactive Response Technology	Indicated that the investigator will not have access to the participant's treatment assignment.
Section 8.1, Discontinuation of Study Intervention	Indicated that participants that discontinue study intervention will be encouraged to remain in the study to complete all remaining evaluations. Indicated that participants that discontinue study intervention will not be replaced.
Section 8.2, Participant Withdrawal from the Study	Clarified procedures upon participant withdrawal from the study. Deleted text indicating that a participant can be withdrawn from the study due to AEs. Deleted text indicated that AE information must be collected after withdrawal of consent.
Section 9.1.2.5, Subject Satisfaction with Treatment Scale	Clarified instructions that the scale assessments will be completed for treated nodules on each foot, rather than per treated nodule.
Section 9.3.7, Assessment of the Severity of Local Injection Site Reactions	Per FDA recommendation, included a study specific grading scale for assessing injection site reactions.
Section 9.3.9, Anaphylaxis	Per FDA recommendation, included criteria for diagnosis of anaphylaxis according to the NIAID criteria.
Section 10.2, Populations for Analysis	Modified the definition of the ITT Population and added mITT and FAS Populations.

Section Name and Number	Description of Change
Section 10.3.1, Efficacy Analysis	Summarized approach to the conduct of the efficacy analysis.
Section 10.3.1.1, Primary Analysis	Added definitions for the primary estimands. Included statistical methods to stratify for covariates.
Section 10.3.1.2, Secondary and Exploratory Analyses	Added estimands and method of analysis for key primary endpoints.
Section 10.4, Multiplicity Adjustments	Added testing hierarchy for key secondary endpoints.
Section 10.5, Handling of Missing Data	Added text to limit missing data for key analyses.
Section 11.3.3, Intensity Assessment	Modified the definition of intensity assessment to the NCI CTCAE.

Rationale for Amendment 01

The primary purpose for this amendment was to incorporate changes after receiving FDA feedback in the Type C Written Response (received 30 April 2021). These changes included modifying the Foot Function Index (FFI) and adding additional scales to measure the severity of pain, difficulty, and activity limitation of plantar fibromatosis. Study endpoints were updated to reflect these changes. To better assess the safety of the EN3835 doses administered, an independent unblinded Data Safety Monitoring Board (DSMB) will monitor pharmacokinetics and safety. Enrollment and procedures for the Photography and Pharmacokinetic Subgroup have been separated so that participants can enroll in either or both a Photography Subgroup or Pharmacokinetic Subgroup. Additionally, throughout the protocol, it was clarified that a maximum of 1.35 mg of study intervention can be injected into each foot and all nodules present on each foot on Day 1 must be treated. Major changes to the protocol and protocol synopsis are presented. Additional changes have been made for clarity and consistency.

Section Name and Number	Description of Change
Section 2.1, Synopsis, Disclosure Statement	Clarified that this is a safety and efficacy study.
Section 2.2, Study Schema	<p>Harmonized the time points for scale assessments and pharmacokinetic sample collection with the Schedule of Assessments and modified for further clarification.</p> <p>Reduced syringe count in the study schema from 6 to 3 since each injection of study intervention (0.45 mg) will be administered as 2 aliquots of 0.225 mg each.</p> <p>Differentiated procedures for Pharmacokinetic and Photography Subgroup, into separate subgroups, the Pharmacokinetic Subgroup and the Photography Subgroup.</p>

Section Name and Number	Description of Change
Section 2.3, Schedule of Assessments	<p>Added PGIS - Overall Plantar Fibromatosis (PF) and its subscales, Patient Global Impression of Change (PGIC) subscales, and the Pain Intensity NRS.</p> <p>Removed the Patient Global Impression of Bother (PGIB) Scale.</p> <p>Modified the name of the Investigator Assessment of Improvement Scale to the Clinician Global Impression of Change Scale.</p> <p>Differentiated procedures for Pharmacokinetic and Photography Subgroup, into separate subgroups, the Pharmacokinetic Subgroup and the Photography Subgroup. Added footnote “n”.</p> <p>Modified text in footnotes “l”, “m”, “t”.</p> <p>Specified the order of scale completion in footnote “k”.</p>
Section 3.1, Study Rationale	Updated study rationale to reflect that an improved response in plantar fibromatosis symptoms on the FFI scale was observed with 2 injections of the higher strengths of EN3835.
Section 3.3.2, Risks of EN3835 in Plantar Fibromatosis	Included use of an independent DSMB to review safety and to mitigate risks.
Section 3.3.3, Overall Assessment of Benefit Risks	Specified a maximum dose of EN3835 1.35 mg per foot.
Section 4, Objectives and Endpoints; Section 2.1, Synopsis	<p>The PGIC and Subject Satisfaction scales were recategorized as exploratory endpoints instead of secondary endpoints.</p> <p>Added objectives and endpoints related to PGIS– Overall PF and its subscales, PGIC pain, difficulty, and activity limitation subscales, and Pain Intensity NRS.</p> <p>Modified the name of the Investigator Assessment of Improvement Scale to the Clinician Global Impression of Change Scale.</p> <p>Removed the PGIB Scale.</p> <p>Added an exploratory objective and endpoint evaluating the FFI total score.</p>
Section 5.1, Overall Study Design; Section 2.1, Synopsis	<p>Deleted 300 participants to be screened as this is unknown.</p> <p>Added that all nodules present on each foot on Day 1 must be treated.</p> <p>Clarified that PK samples will be collected after the first treatment.</p> <p>Removed photography assessments after injection.</p> <p>Added additional scales. Removed the PGIB scale. Modified the name of the Investigator Assessment of Improvement Scale to the Clinician Global Impression of Change Scale.</p> <p>Differentiated procedures for Pharmacokinetic and Photography Subgroup, into separate subgroups, the Pharmacokinetic Subgroup and the Photography Subgroup.</p> <p>Clarified maximum dose of EN3835 as 1.35 mg/foot.</p>

Section Name and Number	Description of Change
Section 5.2, Scientific Rationale for Study Design	Removed reference to placebo. Clarified maximum dose of EN3835 as 1.35 mg/foot. Indicated that PK samples will be collected after the first treatment
Section 5.2.2, Justification for Dose	Added supporting nonclinical data.
Section 5.2.3, Justification of Measures	Updated justification for the FFI-PF-May 2021 for further clarity. Added and included justification for the use of the PGIS, PGIC, and Pain Intensity NRS.
Section 6.1, Participant Inclusion Criteria	Revised Inclusion Criterion 4, to specify no more than 3 injections of EN3835 (1.35 mg) per foot.
Section 7.1, Selection of Nodules	Indicated that all nodules present on each foot on Day 1 must be treated. Given that 1 injection will be administered as 2 aliquots, the injection count was modified to from 2 to 6 injections to 1 to 3 injections per foot.
Section 7.3, Study Intervention Administration	Removed reference to the supine position and harmonized administration via the intralesional route.
Section 7.3.1, Study Intervention	In Table 1, decreased injection count from 6, 4, and 2 to 3, 2, and 1, since each injection (0.45 mg) of study intervention will be administered as 2 aliquots of 0.225 mg each. In Table 2, simplified table and added a footnote to clarify that each injection of study intervention is administered as 2 aliquots of 0.225 mg each. Table 4, simplified table and added footnote to specify no more than 3 injections (1.35 mg) of study intervention per foot. Added a footnote to clarify that each injection of study intervention is administered as 2 aliquots of 0.225 mg each.
Section 7.5, Measures to Minimize Bias	Indicated that participants will complete clinical outcome measures before the Investigator completes outcome measures. Indicated that the Investigator will be blinded to the participant's assessments.
Section 7.7.2, Concomitant Medications	Added vitamins, nutritional supplements, and vaccinations as examples of concomitant medications.
Section 9, Study Assessments and Procedures	Indicated that activities outlined in the Study Operations Manual must be followed or a protocol deviation will result. Included the order in which participant subscales should be completed. Removed the PGIB Scale. Added PGIS– Overall PF and its subscales, PGIC subscales, and Pain Intensity NRS. Modified the name of the Investigator Assessment of Improvement Scale to the Clinician Global Impression of Change Scale. Clarified text in the of the FFI Scale questions. Renamed this version FFI-PF-May-2021 (instead of FFI-PF-Feb-2021). Applies globally.

Section Name and Number	Description of Change
Section 9.1.1.2, Consistency of the Selected Nodule	Indicated that all efforts should be made to ensure the same investigator is performing these assessments for a given participant.
Section 9.1.2, Patient-Reported Outcome Assessments	Revised to include measures to limit missing data. Included order of scale completion.
Section 9.1.2.1, Foot Function Index	Modified the FFI and FFI subscales to specify pain, difficulty, and activity limitations in the past week related to the feet.
Section 9.1.2.2, Patient Global Impression of Severity	Added details for the PGIS-PF Overall and subscales for foot pain, difficulty, and activity limitation.
Section 9.1.2.3, Patient Global Impression of Change	Modified the PGIC scale to describe the change in the overall severity of PF in the past week. Added subscales for foot pain, difficulty, and activity limitation.
Section 9.1.2.4, Pain Numerical Rating Scale	Added scale to describe the severity of foot pain on a Pain Intensity NRS.
Section 9.1.2.5, Subject Satisfaction with Treatment Scale	Modified scale from capturing satisfaction with treatment of each foot to satisfaction with treatment of each nodule.
Section 9.1.3, Investigator Assessments	Added that Investigators will be trained to complete the scales in a standardized manner.
Section 9.1.3.1, Clinician Global Impression of Change Scale	Modified the name of the Investigator Assessment of Improvement Scale to the Clinician Global Impression of Change Scale.
Section 9.2.8, Foot Photography Section 9.5.1, Pharmacokinetic Sample Collection and Process Section 9.5.2, Pharmacokinetic Parameters Section 10.1, Sample Size Determination	Differentiated procedures for Pharmacokinetic and Photography Subgroup, into separate subgroups, the Pharmacokinetic Subgroup and the Photography Subgroup.
Section 9.3.5, Pregnancy	Modified text to indicate that a participant who becomes pregnant will be removed from treatment but can continue in the study.
Section 10.1, Sample Size Determination; Section 2.1, Synopsis, Number of Participants Planned	Removed reference to 300 participants screened, as this is unknown.
Section 10.2, Populations and Analysis	Updated definition of the ITT Population to account for new scales added.
Section 10.3.1.2, Secondary and Exploratory Analysis	Updated analysis section to account for additional scales. Modified analysis to account for new exploratory endpoint (FFI-total).
Section 11.1.4, Data Safety Monitoring Board Committee	Added text describing the DSMB.
Section 11.1.7, Source Documentation	Modified duration of document retention policy from 2 years to 3 years to align with Endo policy.

Section Name and Number	Description of Change
Section 11.3.1, Definitions	<p>Clarified that any medical condition or laboratory abnormality present at screening or baseline should be reported as medical history. If the medical condition present at baseline changes in severity or seriousness at any time during the study, it should be reported as an AE.</p> <p>Clarified that AEs are considered concurrent diseases or medical occurrences.</p> <p>Clarified that an SAE is a congenital anomaly/birth defect in a participant “who received a study intervention” rather than “using a study intervention.”</p>

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2. PROTOCOL SUMMARY

2.1. Synopsis

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835 (XIAFLEX)	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 2, Double-blind, Randomized, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of EN3835 vs Placebo in the Treatment of Plantar Fibromatosis	
Lead Principal Investigator: Not applicable	
Phase of development: 2	
Objectives and Endpoints:	
Objective	Endpoint
Primary	
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the Foot Function Index (FFI)^a pain subscale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the foot pain subscale (total score on 9 items) of the FFI ranging from 0 (“None”) to 4 (“Extreme”).
Secondary	
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI pain subscale over time. 	<ul style="list-style-type: none"> The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the pain subscale of the FFI (total score on 9 items), ranging from 0 (“None”) to 4 (“Extreme”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the combined score of the FFI pain and difficulty subscales with EN3835 vs placebo 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the total score of the FFI pain and difficulty subscales (combined). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the total score of the pain and difficulty subscales of the FFI with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess investigator assessment of improvement with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of EN3835-treated participants and those receiving only placebo reporting “Minimally Improved” (+1), “Much Improved” (+2), or “Very Much Improved” (+3) on the Clinician Global Impression of Change Scale, a 7-point scale ranging from –3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835 (XIAFLEX)	
Name of Active Ingredient: Collagenase clostridium histolyticum	
<ul style="list-style-type: none"> To assess the change in nodule hardness after administration of EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to the Day 57 in the nodular hardness of the treated nodules by durometer measurements. The mean change from Baseline (Day 1) to Days 15, 29, 43, 57 in the nodular hardness of the treated nodules by durometer measurements with EN3835 vs placebo
Safety	
<ul style="list-style-type: none"> To assess the safety and tolerability of EN3835 in participants with plantar fibromatosis. 	<ul style="list-style-type: none"> Safety of EN3835 as assessed by incidence, severity, and duration of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs). The change from baseline in vital signs and clinical laboratory values at each visit where these parameters are measured.
<ul style="list-style-type: none"> To assess the immunogenicity of EN3835 in participants with plantar fibromatosis. 	<ul style="list-style-type: none"> Presence of anti-AUX-I and anti-AUX-II antibody titer levels in EN3835 treated-participants at Day 1 and Day 57. Presence of neutralizing antibodies to AUX-I and AUX-II in EN3835 treated-participants at Day 1 and Day 57.
Exploratory	
<ul style="list-style-type: none"> To assess the overall improvement in the FFI composite score with EN3835 vs placebo 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the FFI composite score with the score of each of the 21 items, ranging from 0 to 4, with 4 indicating higher severity. The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the FFI composite score with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in severity of plantar fibromatosis on the Patient Global Impression of Severity (PGIS) PF Overall scale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the PGIS PF Overall score. The difference between EN3835 and placebo Days 15, 29, 43, and 57 on the PGIS PF Overall score with EN3835 vs placebo.

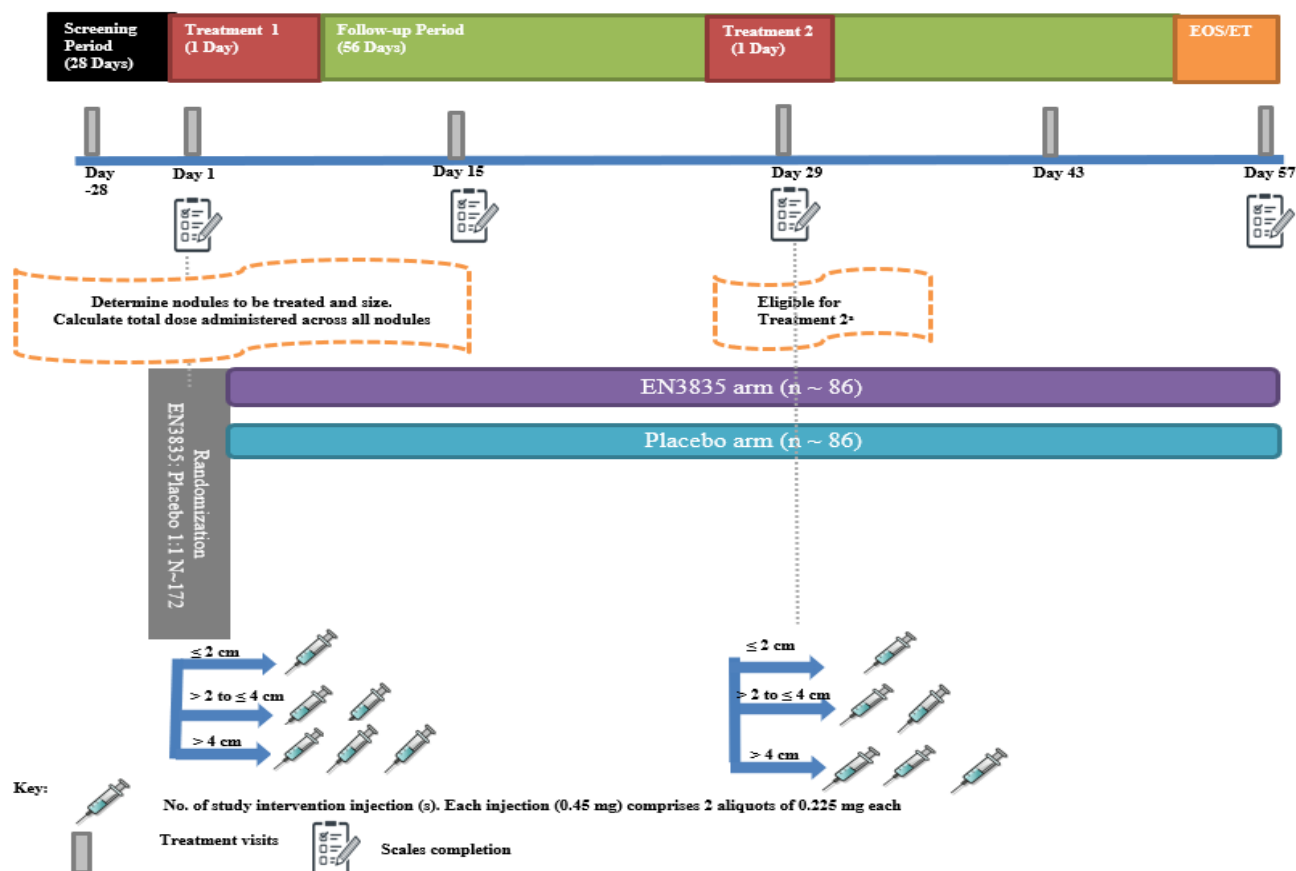
Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835 (XIAFLEX)	
Name of Active Ingredient: Collagenase clostridium histolyticum	
<ul style="list-style-type: none"> To assess the overall improvement in the severity of foot pain with EN3835 vs placebo in the PGIS foot pain subscale 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the foot pain subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS foot pain subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS difficulty subscale 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the difficulty subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS difficulty subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS activity limitation subscale 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the activity limitation subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS activity limitation subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the Patient Global Impression of Change (PGIC) PF Overall with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the PGIC scale, a 7-point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in the overall severity of foot pain on the Foot Pain Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the foot pain subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835 (XIAFLEX)	
Name of Active Ingredient: Collagenase clostridium histolyticum	
<ul style="list-style-type: none"> To assess the change in the overall severity of difficulty on the Difficulty Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the difficulty subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in the overall severity of activity limitation on the Activity Limitation Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the activity limitation subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the overall improvement in foot pain with EN3835 vs placebo on the Pain Intensity Numerical Rating Scale (NRS). 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the Pain Intensity NRS. The mean change from Baseline (Day 1) over time (Days 15, 29, 43, and 57) on the Pain Intensity NRS, ranging from 0 (“None”) to 10 (“Worst Pain Imaginable”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess participant satisfaction with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting to be “Quite Satisfied” (+1) and “Very Satisfied” (+2) on the Subject Satisfaction With Treatment Scale, a 5-point scale ranging from -2 (“Very Dissatisfied”) to +2 (“Very Satisfied”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI activity limitation subscale in participants on the activity limitation subscale at baseline. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the activity limitation subscale (total score on 3 items) of the FFI, ranging from 0 (“Never”) to 4 (“Always”). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the activity limitation subscale (total score on 3 items) of the FFI, ranging from 0 (“Never”) to 4 (“Always”) with EN3835 vs placebo.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835 (XIAFLEX)	
Name of Active Ingredient: Collagenase clostridium histolyticum	
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI difficulty subscale in participants on the difficulty subscale at baseline. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the difficulty subscale (total score on 9 items) of the FFI, ranging from 0 (“No Difficulty”) to 4 (“A Lot of Difficulty”). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the difficulty subscale (total score on 9 items) of the FFI, ranging from 0 (“No Difficulty”) to 4 (“A Lot of Difficulty”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the change in nodule size after administration of EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 in the size of the treated nodules by caliper measurements. The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in nodule size with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the change in nodule consistency (by palpation) after administration of EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the change in consistency from Baseline (Day 1) to Day 57 as determined by the number of participants with a soft or non-palpable consistency at Day 57. The change from Baseline (Day 1) to Days 15, 29, 43, and 57 in nodule consistency with EN3835 vs placebo.
<p>^a For use in this study, the Foot Function Index has been adapted for plantar fibromatosis (FFI-PF-May 2021), and will hereafter be referred to as the FFI.</p>	
<p>Overall Design: Participants will be screened to randomize approximately 172 participants into 2 groups, an EN3835 group (n ~ 86) and a placebo group (n ~ 86) in a 1:1 ratio. Study intervention will be administered intralesionally to all nodules present based on the size of each nodule at the doses described in the dosage table. All nodules present on each foot on Day 1 must be treated. (If all nodules on each foot are not hard, firm throughout, moderately firm on Screening or on Day 1, the participant will not be eligible for study inclusion). Nodules will be measured using calipers and the largest width or length will be used to determine the number of injections to be administered in each nodule. The total number of study intervention injections across all nodules present shall not exceed 3 injections (1.35 mg) of study intervention in a single foot when treating participants with unilateral plantar fibromatosis. When treating participants with bilateral plantar fibromatosis, the total number of study intervention injections across all nodules present shall not exceed 4 injections (1.8 mg) in total with each foot receiving a maximum dose of 0.9 mg.</p> <p>After receiving study intervention, participants will be encouraged to resume normal daily activities including walking and bearing weight on the treated foot/feet. All participants will return to the clinic for 3 follow-up visits, 2 weeks apart, on Days 15, 29, 43, and 57.</p>	

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: EN3835 (XIAFLEX)
Name of Active Ingredient: Collagenase clostridium histolyticum
<p>At the Day 29 visit, if the participant has any previously treated nodule(s) that remains palpable and measurable by caliper with a consistency of hard, firm throughout, moderately firm, or soft that is/are deemed appropriate for treatment by the investigator, and the Treatment 2 criteria are met a second dose of the study intervention may be administered.</p> <p>For all participants, at the time points listed in the Schedule of Assessments, the efficacy of the study intervention will be assessed on the FFI (adapted for plantar fibromatosis; May 2021), the Subject Satisfaction with Treatment Scale, the PGIC PF Overall and individual PGIC subscales of pain, difficulty, and activity limitation, the Pain NRS, the PGIS PF Overall, and the individual PGIS subscales of pain, difficulty, and activity limitation, and the Clinician Global Impression of Change Scale. Safety will be assessed by evaluating the incidence and duration of TEAEs, AESIs, and SAEs, and changes in vital signs and clinical laboratory values.</p> <p>All participants will complete the study on Day 57 (EOS Visit), regardless of whether they receive 1 or 2 treatments during the study. At the EOS visit, immunogenicity samples will be collected, safety will be assessed, and nodules will be measured. The maximum duration of participation is up to 85 days (Screening Period: 28 days, Treatment Period: 1 or 2 days, and a total Follow-up Period of 56 days).</p>
Disclosure Statement: This is a placebo-controlled efficacy and safety study with 2 blinded treatment groups.
Number of Participants (planned): Participants will be screened to ensure that approximately 172 participants are randomized into 2 treatment groups, an EN3835 group and a placebo group in a 1:1 ratio.
<p>Treatment Groups and Duration: There will be an active treatment group and a placebo treatment group of participants that receive up to 2 treatments of either EN3835 or placebo.</p> <p>Duration of the study:</p> <p>Screening Phase: Up to 28 days</p> <p>Study Intervention Administration: Up to 2 days</p> <p>Follow-Up Phase: from Intervention Administration 1 (End of Day 1) until Day 57 (\pm 5 days)</p> <p>Total Duration of the Study: Up to 85 Days (\pm 5 days)</p>
Independent Data Safety Monitoring Board: An independent unblinded data monitoring committee will review safety data periodically.

2.2. Study Schema



^a Based on the Day 29 examination of the nodule(s) and review of Treatment 2 Criteria.

NOTE: The total number of injections across all nodules present shall not exceed 3 injections (1.35 mg) of study intervention in a single foot when treating participants with unilateral plantar fibromatosis. When treating participants with bilateral plantar fibromatosis, the total number of study intervention injections across all nodules present shall not exceed 4 injections (1.8 mg) in total with each foot receiving a maximum dose of 0.9 mg.

2.3. Schedule of Assessments (Screening to End-of-Study)

	Screening D -28 to D -1	Treatment Visit 1 D1	Follow-up Visits			EOS/ET D57 (±5)	Safety Follow-Up ^s
			D15 (±1)	Treatment Visit 2 D29 (±1)	D43 (±1)		28 days after the last dose (+5)
Obtain signed informed consent ^a	X						
Inclusion/exclusion criteria	X	X ^b					
Treatment 2 criteria				X ^{b,c}			
Medical and surgical history ^d	X						
Prior medications and procedures	X						
Serum pregnancy test ^e	X					X	
Urine pregnancy test ^e		X ^b		X ^{b,c}			
Physical examination	X ^f					X	
Foot examination	X	X ^b	X	X ^b	X	X	
Clinical laboratory tests	X					X	
Immunogenicity sample collection ^g		X ^b				X	
Vital signs ^h	X	X ^{b,i}	X	X ^{b,i}	X	X	
Examination and evaluation of the selected nodule(s):							
a) Caliper measurements	X	X ^b	X	X ^b	X	X	
b) Foot Function Index (FFI) ^{j,k}	X	X ^b	X	X ^b	X	X	
c) Nodular consistency (palpation) ^l	X	X ^b	X	X ^b	X	X	
d) Nodular hardness measurement using a durometer	X	X ^b	X	X ^b	X	X	

	Screening D -28 to D -1	Treatment Visit 1 D1	Follow-up Visits			EOS/ET D57 (±5)	Safety Follow-Up ^s
			D15 (±1)	Treatment Visit 2 D29 (±1)	D43 (±1)		28 days after the last dose (+5)
e) Anatomical representation of nodule(s) location ^m	X	X ^b		X		X	
Patient Global Impression of Severity (PGIS) PF Overall Scale Pain, Difficulty and Activity Limitation Subscales ^k	X	X	X	X	X	X	
Patient Global Impression of Change (PGIC) PF Overall Scale Pain, Difficulty and Activity Limitation Subscales ^k			X	X ^b	X	X	
Pain Intensity Numerical Rating Scale (NRS) ^k	X	X	X	X	X	X	
Subject Satisfaction with Treatment Scale ^k			X	X ^b	X	X	
Clinician Global Impression of Change Scale			X	X ^b	X	X	
Randomization		X ⁿ					
Study intervention administration ^o		X		X ^p			
Concomitant medications and procedures ^q		Throughout the study					
Adverse events (AEs) ^r		Throughout the study					

- ^a Performed prior to any study-required assessments.
 - ^b Before treatment.
 - ^c The second treatment should be administered only if the participant has a previously treated palpable nodule measurable by caliper and the nodule (eg, hard, firm throughout, moderately firm or soft) is appropriate for a second treatment, according to the investigator. Women of childbearing potential must also have a negative urine pregnancy test (see Section 6.2.1). The participant must not have any significant medical conditions, which in the investigator's opinion would preclude receiving a second treatment (see Section 6.2.2).
 - ^d Any diagnostic, therapeutic, or surgical procedure performed within the past 10 years before the study, including those in the treatment area, should be recorded including the date, indication for, and description of the procedure.
 - ^e For women of childbearing potential.
 - ^f A complete physical examination, including height and weight at Screening.
 - ^g Testing for neutralizing antibodies will be conducted if the participant tests positive for anti-AUX-I and anti-AUX-II antibodies.
 - ^h Vital signs (ie, blood pressure, pulse, respiratory rate, and temperature) should be collected in a seated position after the participant has been sitting for 5 minutes.
 - ⁱ Vital signs should be collected in supine position prior to treatment and at 15 (\pm 5) and 30 (\pm 5) minutes post treatment.
 - ^j Opioid analgesic use is prohibited during the study. Acetaminophen and over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) are permitted if the investigator deems it necessary.
 - ^k Participants will complete the scale prior to evaluation by the investigator. The order of scale completion by the participant is as follows: FFI, PGIS Foot Pain Subscale, PGIC Foot Pain Subscale, PGIS Difficulty Subscale, PGIC Difficulty Subscale, PGIS Activity Limitation Subscale, PGIC Activity Limitation Subscale, PGIS PF Overall, PGIC PF Overall, Pain Intensity NRS, and Subject Satisfaction with Treatment Scale.
 - ^l Palpation for nodular consistency. For Treatment 1, only hard, firm throughout, moderately firm nodules will be treated. For Treatment 2, palpable nodules that are hard, firm throughout, moderately firm, or soft on clinical examination and measurable by caliper, that were previously treated, will be treated.
 - ^m The investigator will complete a graphic representation of the foot/feet and the location of the nodule(s) that are present.
 - ⁿ Randomized in a 1:1 ratio to either EN3835 or placebo using an Interactive Response Technology (IRT) system.
 - ^o Size of the nodule(s) will be determined by caliper and the largest width or length will be used to determine number of injections to be administered.
 - ^p On Visit Day 29, urine pregnancy testing will only be performed if the participant will receive a second treatment of study intervention.
 - ^q Including concomitant surgical and medical procedures for plantar fibromatosis and for conditions other than plantar fibromatosis.
 - ^r Serious adverse events (SAEs) and adverse events (AEs) will be collected by the investigator from the time of signing the informed consent through the Day 57/EOS Visit. For participants who withdraw from the study early, SAEs and AEs will be collected for 28 days after the last dose of study intervention.
 - ^s Participants are encouraged to remain in the study for follow-up until the Day 57 Visit (see Section 8.1). Participants who discontinue from the study or study intervention and do not agree to remain in the study for follow-up until Day 57, will be asked to complete an ET visit and if applicable the 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs (see Section 8.1). At the time of withdrawing from the study (withdraw consent), if possible an ET visit should be conducted as shown in the Schedule of Assessments (see Section 8.2).
- D = day(s); EOS = end of study; ET = early termination.

3. INTRODUCTION

EN3835 is currently marketed in the United States as XIAFLEX® (collagenase clostridium histolyticum) and is indicated for the treatment of adults with Dupuytren's contracture (DC) with a palpable cord and for the treatment of adult men with Peyronie's disease (PD) with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. A biologic license application (BLA) was submitted for a different formulation of EN3835 on 06 September 2019, and approved for the treatment of cellulite as QWO® (collagenase clostridium histolyticum-aes) on 06 July 2020.

EN3835 is being investigated for the treatment of plantar fibromatosis.

3.1. Study Rationale

Plantar fibromatosis is a rare pathology of the plantar aponeurosis characterized by disordered fibrous tissue and subsequent formation of nodules of the feet (Young et al, 2018). Specifically, the disease is characterized by slow-growing nodules in the medial or central plantar fascia, which are formed by excess collagen leading to fibrotic tissue. Plantar fibromatosis presents bilaterally in 25% of patients (Gudmundsson et al, 2013) with males predominantly affected (Allen et al, 1955). Symptoms range from local pressure and distention, to tender erythematous lesions that can affect the patient's ability to bear weight and walk (Veith et al, 2013; Young et al, 2018). The primary symptom most patients experience is a slow-growing lump along the medial longitudinal arch, which becomes painful and causes swelling as it enlarges (Fuiano et al, 2019). In rare cases, the fibromatosis leads to toe contractures, which potentially can lead to shrinkage and sclerosis of the fascia (Fuiano et al, 2019; Veith et al, 2013). The condition reduces quality of life and can cause functional disability, leading to severe impairment in some patients (Syed et al, 2012).

Dupuytren's disease has been reported to coexist in patients with plantar fibromatosis (Allen et al, 1955; Aviles et al, 1971; Fausto de Souza et al, 2010; Haedicke and Sturium, 1989; Wapner et al, 1995). Similar to Dupuytren's disease, plantar fibromatosis has been reported to have a strong familial predisposition and the disease has been related to other forms of extra-palmar involvement (Gudmundsson et al, 2013).

Plantar fibromatosis is also often referred to as "Dupuytren's disease of the plantar fascia" based on immunohistological and ultrastructural analyses (Cavolo and Sherwood, 1982). The histopathology of plantar fibromatosis is the same as in the palmar fascia and the progression pattern of the disease follows the same 3 stages identified for Dupuytren's disease (de Palma, et al 1999; Veith et al, 2013):

1. A proliferative phase with increased fibroblast activity and cellular proliferation.
2. An active or involutional stage, where the nodules are formed and collagen is deposited.
3. A residual stage in which the fibroblast activity is diminished and reduced collagen maturation and contracture take place.

Based on the similar histopathology of Dupuytren's disease and plantar fibromatosis, EN3835 may be effective in the treatment of plantar fibromatosis. Furthermore, the collagenases comprising EN3835 are proteinases that can hydrolyze the triple-helical collagen polymer under physiological conditions at the site of injection (subdermal collagen as in Dupuytren's cord/Peyronie's plaque, and hypodermal septa in women with cellulite). As such, these collagenases have the potential to be effective in lysing subdermal collagen, such as that observed in the fibrous nodules of plantar fibromatosis.

To date, since there is no available therapy that addresses the pathophysiology of plantar fibromatosis, disease progression cannot be prevented. The treatment of plantar fibromatosis is aimed at symptom relief and is adapted to the severity of the disease. Nonsurgical treatment options are available for the less painful stages of the disease. If pain reduction cannot be achieved and a stage of strong fibroblast activity has been reached, other therapeutic options such as X-ray irradiation and surgery are considered. The long-term safety of radiation therapy has not been established and the risk of malignant changes at the radiation site is not known. Surgical treatment is the only indicated treatment option in cases of persistent pain, however the recurrence rate is relatively high (between 60% and 100%), and the postsurgical burden to patients is significant due to tenderness and prolonged recovery ([van der Veer et al, 2008](#)). Because of the lack of effective therapies, there is an unmet need for a less invasive and more cost-effective treatment option for patients with persistent pain from plantar fibromatosis.

Results of an interim analysis from a completed open-label Phase 1 study showed that participants who received 2 injections of either 1.2 mg/mL or 2.25 mg/mL had improvement in the severity of pain, difficulty and disability (activity limitation) in symptoms of plantar fibromatosis. A better treatment response was observed in the severity of pain, difficulty, and disability (activity limitation) in symptoms of plantar fibromatosis in participants who received 2 injections of 2.25 mg/mL compared to those receiving 2 injections of 1.2 mg/mL. Both participants and investigators saw an improvement in nodule consistency by Day 57. All AEs reported were considered mild to moderate in severity and most AEs resolved within 21 days.

The purpose of this double-blind, placebo-control Phase 2 study is to assess the efficacy, safety, tolerability, of EN3835 vs placebo.

3.2. Background

Collagenase clostridium histolyticum, or EN3835 (previously known as AA4500), comprises a mixture of 2 collagenases, Clostridial type I collagenase (AUX-I) and Clostridial type II collagenase (AUX-II) in an approximate 1:1 mass ratio. These collagenases are isolated and purified from the fermentation of the bacterium *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain consisting of approximately 1000 amino acids. It has an observed molecular weight of 114 kDa. It belongs to the Class I *Clostridium histolyticum* collagenases. Collagenase AUX-II is a single polypeptide chain consisting of approximately 1000 amino acids. It has an observed molecular weight of 113 kDa. It belongs to the Class II *Clostridium histolyticum* collagenases. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen.

Nonclinical primary pharmacology studies were conducted during the development of XIAFLEX for the DC and PD indications. The relevance of the results of these studies as applicable to plantar fibromatosis is summarized in the current edition of the investigator brochure (IB).

During clinical pharmacology studies of EN3835 conducted in participants with DC and cellulite, there were no quantifiable plasma levels of AUX-I and AUX-II after single and concurrent injections of EN3835. In participants with PD, following each of 2 intralesional injections of EN3835 0.58 mg into the penile plaque, separated by 24 hours, plasma levels of AUX-I and AUX-II in participants with quantifiable levels were minimal and short-lived. All plasma levels were below the limits of quantification within 30 minutes following dosing. There was no evidence of accumulation following 2 sequential injections of EN3835 administered 24 hours apart.

The results of 14 completed studies conducted in over 1100 participants worldwide formed the basis of the efficacy and safety data supporting the approval of XIAFLEX in adult patients with DC with a palpable cord. Since the approval of XIAFLEX for the treatment of DC, 8 additional studies have been completed in participants with DC. The safety profile of XIAFLEX in DC is summarized in the prescribing information ([XIAFLEX Prescribing Information](#)).

The efficacy and safety of EN3835 was also demonstrated in participants with palmar Dupuytren's disease nodules. The results of the study suggested that single injections of EN3835 0.60 mg and EN3835 0.40 mg may be effective in the treatment of Dupuytren's disease nodules. Most AEs reported were local to the injection site and resolved within a median of 14 days.

Because EN3835 contains foreign proteins, severe allergic reactions can occur. Anaphylaxis was reported in a postmarketing clinical study in 1 patient who had previous exposure to EN3835 in the treatment of DC.

A detailed description of the chemistry, nonclinical and clinical pharmacology, efficacy, and safety of EN3835 is provided in the current edition of the IB of EN3835 for plantar fibromatosis.

3.2.1. EN3835-105 (Proof of Concept)

Study EN3835-105 is a completed Phase 1, open-label, randomized, dose-ranging proof of concept study. The safety, immunogenicity, PK, and effect of EN3835 on nodule size in 24 participants with plantar fibromatosis were assessed. The effect of EN3835 on investigator and patient-reported outcome measures were also evaluated,

The study randomized 24 participants into 3 treatment groups (8 participants per treatment group). On Day 1, participants were randomized in a 1:1:1 ratio to 3 treatment concentrations of EN3835. Based on the maximum diameter of the nodule collected on ultrasound, participants received either 1 (for nodules ≤ 1.5 cm) or 2 (for nodules > 1.5 cm) injections of EN3835 per nodule. The total dose per nodule ranged from 0.12 to 0.45 mg for nodules ≤ 1.5 cm and 0.24 to 0.9 mg for nodules > 1.5 cm. Blood samples were drawn for PK analysis on Day 1 before dosing and at 10, 20, 30, 60 minutes and 2, 4, 8, 12, and 24 hours following injection.

During the Initial Treatment Period, participants returned to the clinic for 4 follow-up visits, 1 week apart, on Days 8, 15, 22, and 29. On each visit day, the nodules were palpated, caliper measurements of the treated nodules were collected, and an ultrasound was conducted. At each visit, the participants completed the Foot Function Index-Short Form-23 (FFI-SF-23) and the Participant Satisfaction with Treatment Scale. In addition, the Investigator Assessment of

Improvement with Treatment Scale was completed at each visit. Safety was assessed by the incidence, severity, and duration of treatment-emergent adverse events (TEAEs). Nodule size was assessed from baseline to the end of study (EOS) visit (Day 57 \pm 5 days).

A Retreatment Period was added to the EN3835-105 study to allow for retreatment of treated nodules and to assess the safety, tolerability, and efficacy of multiple doses of EN3835 in the treatment of plantar fibromatosis. Based on the result of an interim analysis, the concentration and dose of EN3835 selected for use in the Retreatment Period, was EN3835 2.25 mg/mL ranging from 0.45 mg (for nodules \leq 2 cm) to 0.9 mg per nodule (for nodules $>$ 2 cm) .

After the Initial Treatment Period, almost all (90%) nodules improved by at least 1-level in nodular consistency in the EN3835 2.25 mg/mL and 1.2 mg/mL treatment groups, and in the EN3835 0.6 mg/mL treatment group, 72.7% of nodules had at least a 1-level improvement. All (100%) participants in the EN3835 2.25 mg/mL and almost all (87.5%) participants in the 1.2 mg/mL treatment groups had at least a 1-level improvement in nodular consistency. There was an overall improvement in the FFI-SF-23 composite score in the EN3835 of -48.7%, with a negative change representing an improvement. On a nodular level, 73.3% of nodules improved by at least 1-level in nodular consistency. There was an incremental improvement of -9.3% in the FFI-SF-23 mean (SD) composite score by Day 57. On a nodular level, in all treatment groups, \geq 72.7% of nodules were responders on the Subject Satisfaction with Treatment Scale. On a participant level, in all treatment groups \geq 75% of participants were responders on the Subject Satisfaction with Treatment Rating Scale and the Investigator Assessment of Improvement Scale. There were small and inconsistent changes in nodule size (with increases and decreases) as measured by calipers, However, ultrasound measurements remained relatively unchanged and therefore did not correlate with other measures of improvement. There was no quantifiable systemic exposure of AUX-II following intralesional EN3835 injection of up to 2 injections of 0.9 mg in the foot and up to 1.8 mg per total dose

During the Retreatment Period, by Day 57, after administration of 1 or 2 treatments of EN3835 2.25 mg/mL, almost all participants (81.8%) had nodules that improved by at least 1 level in consistency. Additionally, 63.6% of participants were responders on the Subject Satisfaction with Treatment Rating Scale. On a nodular level, on, 66.7% of nodules were responders on the Subject Satisfaction with Treatment Rating Scale.

EN3835 was well tolerated. During the Initial Treatment and Retreatment Periods, there were no serious adverse events (SAEs), and no TEAEs leading to death, EN3835 discontinuation, or study withdrawal. Common TEAEs included: injection site pain, injection site swelling, and injection site bruising, with the majority resolving within 21 days. On Day 57 of the Retreatment Period, all participants tested (10/10; 100%) had detectable neutralizing AUX-I antibodies and almost all participants (8/10; 80%) tested had detectable neutralizing AUX-II antibodies. There were no clinically relevant findings in participants with detectable anti-AUX-I, anti-AUX-II, or neutralizing AUX-I and AUX-II antibodies.

3.2.2. EN3835-106

Study EN3835-106 is a Phase 1, open-label study to assess the safety, tolerability, and PK of EN3835, administered intralesionally at total doses of either 1.8 mg, 2.7 mg, or 3.6 mg in participants with complex configurations of their plantar fibromatosis nodules. The effect of EN3835 on foot function, nodule hardness, nodule consistency, and nodule size will also be

assessed. To be eligible for treatment participants must have unilateral or bilateral palpable hard or firm plantar fibromatosis nodules with a nodule configuration requiring 4 (1.8 mg), 6 (2.7 mg) or 8 (3.6 mg) injections of EN3835. Based on the total count, distribution, and size of the nodules to be treated, participants will be allocated into a low dose (1.8 mg total dose), medium dose (2.7 mg total dose), or high dose (3.6 mg total dose) cohort.

Depending on the size of the nodule, each nodule will be treated with intralesional EN3835 0.45 mg (for nodules ≤ 2 cm), 0.9 mg (for nodules $> 2 - \leq 4$ cm), 1.35 mg (for nodules $> 4 - \leq 6$ cm), or 1.8 mg (for nodules > 6 cm). PK and immunogenicity samples will be collected throughout the study.

After the first dose of EN3835, participants will return for a total of 8 outpatient follow-up visits, on Days 2 (24 hours after injection), 3 (48 hours after injection), 8 (168 hours after injection) and 22 (504 hours after injection) for collection of PK samples (collected within 10% of nominal time point). Biweekly on Days 15, 29, 43, and 57 nodules will be measured using calipers, nodule hardness will be assessed via a durometer, nodular consistency by palpation, participant assessments of foot function (pain, difficulty, and activity limitation) and treatment satisfaction, and clinician assessments of improvement. Treated feet will be photographed through Day 22 to document bruising, ecchymosis, and any other similarly related visible local reactions post injection.

Participants will complete the study on Day 57 (EOS Visit) during which immunogenicity samples will be collected, safety will be assessed and the nodules will be measured. The maximum duration of study participation is up to 85 days (Screening Period: 28 days, Dosing Period: 1 day, and a total Follow-up Period of 56 days).

To date, the study is on hold.

3.2.3. EN3835-306

Study EN3835-306 is an ongoing Phase 3, multi-center, open-label extension study to assess the long-term safety and efficacy of EN3835 in participants who have participated in a parent placebo-controlled study of EN3835. Enrolled participants will have the option of:

1. observation only,
2. treated or retreated with up to 2 treatments of EN3835, or
3. having new nodules treated with up to 2 treatments of EN3835 and agree to either be treated or retreated during this study.

EN3835 will be administered intralesionally based on the size of the nodule to all nodules present. The total number of EN3835 injections across all nodules present shall not exceed 3 injections (1.35 mg) per treatment in a single foot when treating participants with unilateral plantar fibromatosis. When treating participants with bilateral plantar fibromatosis, the total number of EN3835 injections across all nodules present shall not exceed 4 injections (1.8 mg) in total per treatment with each foot receiving a maximum dose of 0.9 mg.

Participants will include those who have been treated with EN3835 or placebo as part of a sponsored clinical study and are observed and not retreated in the study are expected to enroll in the study for approximately 15 months (Day 450).

For participants that are retreated/treated on Day 180, the study design allows for evaluation of long-term efficacy or safety of up to approximately 417 days (up to approximately 14 months). For participants retreated/treated on Day 270, the study design allows evaluation of long-term efficacy and safety for approximately 507 days (approximately 17 months).

3.3. Benefit/Risk Assessment

3.3.1. Benefit of EN3835 in Plantar Fibromatosis

There are 4 case reports of off-label use of EN3835 in patients with recurrent plantar fibromatosis. [Hammoudeh \(2014\)](#) reported unsuccessful treatment of a 72-year-old male with recurrent bilateral plantar fibromatosis after a single dose of EN3835 0.58 mg. [Lehrman et al \(2019\)](#) reported successful treatment of a 22-year-old white female with recurrent plantar fibromatosis after a single dose of EN3835 0.58 mg and foot extension and massage. [De Vitis et al \(2020\)](#) reported successful treatment of a 59-year-old male with recurrent bilateral nodules due to Ledderhose disease (a type of plantar fibromatosis) after single doses of EN3835 0.58 mg in each foot without foot extension or massage. [Mahmoud et al \(2021\)](#) reported successful treatment of plantar fibromatosis in a 13-year-old female who had recurrent plantar fibromatosis after surgical treatment. As early as 3 weeks after treatment the nodule decreased in size and there was no tenderness upon palpation. One year after treatment with EN3835 symptoms had resolved.

This study will be conducted in otherwise healthy participants with plantar fibromatosis. To date, there is no available therapy to treat the pathophysiology of plantar fibromatosis and prevent disease progression.

3.3.2. Risks of EN3835 in Plantar Fibromatosis

Safety information for EN3835 is derived from the broad experience in participants with DC, PD, and cellulite. The preponderance of evidence suggests that XIAFLEX is safe and well tolerated, but can result in AEs. In studies of participants with DC, the majority of AEs were local, mild, or moderate in severity, confined to the treated extremity, and generally resolved within 21 days. As outlined in the prescribing information and in the IB, common AEs observed in supporting clinical trials in approved indications and reported in postmarketing safety data included local injection site reactions, injection site bruising, injection site swelling, and injection site pain.

SAEs reported in studies of DC included flexor tendon ruptures that occurred after EN3835 injection into the injected finger/hand and manipulation of the tendon ([XIAFLEX Prescribing Information](#)). Other EN3835-associated serious local adverse reactions in the treatment of DC included pulley rupture, ligament injury, complex regional pain syndrome, sensory abnormality of the hand, and skin laceration (tear). There is risk that similar events may occur when EN3835 is injected into nodules of plantar fibromatosis. To mitigate these risks, participants with complicated plantar nodules (eg, encapsulating the nerves, tendons and/or vascular structures) that in the investigator's opinion would make the participant unsuitable for the study will be excluded from the study. Examination of the nodule will be conducted at the follow-up visits and can be used to assess for the risk of tendon ruptures. Investigators will be encouraged to provide necessary medical care to all participants experiencing local adverse reactions.

Additionally, investigators will be trained to inject study intervention only into the nodules resulting from plantar fibromatosis, and take precautions to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the foot. Investigators will be trained to recognize signs or symptoms that may reflect serious injury to the area injected, which should be promptly evaluated for any required surgical intervention.

Because EN3835 contains foreign proteins, severe allergic reactions to EN3835 can occur, including anaphylaxis. Participants with a known systemic allergy to collagenase or any other excipient of EN3835 will be excluded from the study. The protocol instructs healthcare providers to be prepared to address severe allergic reactions following EN3835 injections with interventions that may include epinephrine, diphenhydramine (or a suitable equivalent), and oxygen.

AEs of injection site bruising, ecchymosis/contusion, or injection site hemorrhages were commonly observed during clinical studies of EN3835 for DC and for other indications (cellulite). To mitigate this risk, participants with coagulation disorders and participants currently receiving or planning on receiving anticoagulant or antiplatelet medications (except aspirin ≤ 150 mg) within 7 days before injection of study intervention will be excluded. Use of anticoagulants and antiplatelet medications (except aspirin ≤ 150 mg) will be prohibited throughout the study.

Safety monitoring will occur throughout the study to assess the risks of treatment. An independent DSMB will periodically review safety data to mitigate risks.

3.3.3. Overall Assessment of Benefit and Risks

The assessment of the likelihood of these AEs occurring in participants with plantar fibromatosis was evaluated while taking into consideration the range of doses of EN3835 to be administered in this study. Based on the overall benefit-risk assessment and the precautions taken into account in this protocol, it is concluded that EN3835 administered as doses ranging from 0.45 mg to 1.35 mg per nodule per foot (for participants with unilateral plantar fibromatosis) for up to 2 treatment visits with a maximum total dose of 1.8 mg per treatment visit (for participants with bilateral plantar fibromatosis) has an acceptable benefit-risk ratio.

Strict inclusion and exclusion criteria, safety monitoring, and clinician training on injection technique will ensure appropriate use of EN3835. In summary, the potential risks to participants with plantar fibromatosis in this study are outweighed by the potential benefits that may result from the clinical development of EN3835 for patients with symptomatic nodules due to plantar fibromatosis.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the Foot Function Index (FFI)^a pain subscale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the foot pain subscale (total score on 9 items) of the FFI ranging from 0 (“None”) to 4 (“Extreme”).
Secondary	
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI pain subscale over time. 	<ul style="list-style-type: none"> The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the pain subscale of the FFI (total score on 9 items), ranging from 0 (“None”) to 4 (“Extreme”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the combined score of the FFI pain and difficulty subscales with EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the total score of the FFI pain and difficulty subscales (combined). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the total score of the pain and difficulty subscales of the FFI with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess investigator assessment of improvement with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of EN3835-treated participants and those receiving only placebo reporting “Minimally Improved” (+1), “Much Improved” (+2), or “Very Much Improved” (+3) on the Clinician Global Impression of Change Scale, a 7-point scale ranging from –3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in nodule hardness after administration of EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 in the nodular hardness of the treated nodules by durometer measurements. The mean change from Baseline (Day 1) to Days 15, 29, 43, 57 in the nodular hardness of the treated nodules by durometer measurements with EN3835 vs placebo

Objective	Endpoint
Safety	
<ul style="list-style-type: none"> To assess the safety and tolerability of EN3835 in participants with plantar fibromatosis. 	<ul style="list-style-type: none"> Safety of EN3835 as assessed by incidence, severity and duration of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs). The change from baseline in vital signs and clinical laboratory values at each visit where these parameters are measured.
<ul style="list-style-type: none"> To assess the immunogenicity of EN3835 in participants with plantar fibromatosis. 	<ul style="list-style-type: none"> Presence of anti-AUX-I and anti-AUX-II antibody titer levels in EN3835 treated-participants at Day 1 and Day 57. Presence of neutralizing antibodies to AUX-I and AUX-II in EN3835 treated-participants at Day 1 and Day 57.
Exploratory	
<ul style="list-style-type: none"> To assess the overall improvement in the FFI composite score with EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the FFI composite score, with the score of each of the 21 items ranging from 0 to 4, with 4 indicating higher severity. The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the FFI composite score with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in severity of plantar fibromatosis on the Patient Global Impression of Severity (PGIS) PF Overall scale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the PGIS PF Overall score. The difference between EN3835 and placebo Days 15, 29, 43, and 57 on the PGIS PF Overall score with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the severity of foot pain with EN3835 vs placebo in the PGIS foot pain subscale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the foot pain subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS foot pain subscale, ranging from 0 ("None") to 4 ("Severe") with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS difficulty subscale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the difficulty subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS difficulty subscale, ranging from 0 ("None") to 4 ("Severe") with EN3835 vs placebo.

Objective	Endpoint
<ul style="list-style-type: none"> To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS activity limitation subscale. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo at Day 57 on the activity limitation subscale of the PGIS. The difference between EN3835 and placebo at Days 15, 29, 43, and 57 on the PGIS activity limitation subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the Patient Global Impression of Change (PGIC) PF Overall with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the PGIC scale, a 7-point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in the overall severity of foot pain on the Foot Pain Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the foot pain subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in the overall severity of difficulty on the Difficulty Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the difficulty subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the change in the overall severity of activity limitation on the Activity Limitation Subscale of the PGIC. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimal Improvement” (+1), “Much Improvement” (+2), and “Very Much Improvement” (+3) on the activity limitation subscale of the PGIC scale, a 7 point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.

Objective	Endpoint
<ul style="list-style-type: none"> To assess the overall improvement in foot pain with EN3835 vs placebo on the Pain Intensity Numerical Rating Scale (NRS). 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the Pain Intensity NRS. The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the Pain Intensity NRS, ranging from 0 (“None”) to 10 (“Worst Pain Imaginable”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess participant satisfaction with EN3835 treatment vs placebo. 	<ul style="list-style-type: none"> The difference in the proportion of participants treated with EN3835 or placebo reporting to be “Satisfied” (+1) and “Very Satisfied” (+2) on the Subject Satisfaction With Treatment Scale, a 5-point scale ranging from –2 (“Very Dissatisfied”) to +2 (“Very Satisfied”) on Days 15, 29, 43, and 57.
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI activity limitation subscale in participants on the activity limitation subscale at baseline. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the activity limitation subscale (total score on 3 items) of the FFI, ranging from 0 (“Never”) to 4 (“Always”). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the activity limitation subscale (total score on 3 items) of the FFI, ranging from 0 (“Never”) to 4 (“Always”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the improvement with EN3835 vs placebo in the FFI difficulty subscale in participants on the difficulty subscale at baseline. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the difficulty subscale (total score on 9 items) of the FFI, ranging from 0 (“No Difficulty”) to 4 (“A Lot of Difficulty”). The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the difficulty subscale (total score on 9 items) of the FFI, ranging from 0 (“No Difficulty”) to 4 (“A Lot of Difficulty”) with EN3835 vs placebo.
<ul style="list-style-type: none"> To assess the change in nodule size after administration of EN3835 vs placebo. 	<ul style="list-style-type: none"> The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 in the size of the treated nodules by caliper measurements. The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in nodule size with EN3835 vs placebo.

Objective	Endpoint
<ul style="list-style-type: none">• To assess the change in nodule consistency (by palpation) after administration of EN3835 vs placebo.	<ul style="list-style-type: none">• The difference between EN3835 and placebo in the change in consistency from Baseline (Day 1) to Day 57 as determined by the number of participants with a soft or non-palpable consistency at Day 57.• The change from Baseline (Day 1) to Days 15, 29, 43, and 57 in nodule consistency with EN3835 vs placebo.

^a. For use in this study, the Foot Function Index has been adapted for plantar fibromatosis (FFI-PF-May 2021), and will hereafter be referred to as FFI.

5. STUDY DESIGN

5.1. Overall Design

Participants will be screened to randomize approximately 172 participants into 2 groups, an EN3835 group (n ~86) and a placebo group (n ~86) in a 1:1 ratio. Study intervention will be administered intralesionally to all nodules present based on the size of each nodule at the doses described in the dosage table (Table 2). All nodules present on each foot on Day 1 must be treated. (If all nodules on each foot are not hard, firm throughout, moderately firm on Screening and Day 1, the participant will not be eligible for study inclusion). Nodules will be measured using calipers and the largest width or length will be used to determine the number of injections to be administered in each nodule. The total number of study intervention injections across all nodules present, shall not exceed 3 injections (1.35 mg) in a single foot when treating participants with unilateral plantar fibromatosis. When treating participants with bilateral plantar fibromatosis, the total number of study intervention injections across all nodules present shall not exceed 4 injections (1.8 mg) in total with each foot receiving a maximum dose of 0.9 mg. After receiving study intervention, participants will be encouraged to resume normal daily activities including walking and bearing weight on the treated foot/feet. All participants will return to the clinic for 4 follow-up visits, 2 weeks apart, on Days 15, 29, 43, and 57.

At the Day 29 visit, if the participant has any previously treated nodule(s) that remains palpable and measurable by caliper with a consistency of hard, firm throughout, moderately firm, or soft that is/are deemed appropriate for treatment by the investigator, and the Treatment 2 Criteria are met, a second dose of the study intervention may be administered.

For all participants, at the time points listed in the Schedule of Assessments, the efficacy of the study intervention will be assessed on the FFI (adapted for plantar fibromatosis; May 2021), the Subject Satisfaction with Treatment Scale, the PGIC PF Overall and individual PGIC subscales of pain, difficulty, and activity limitation, the Pain Intensity NRS, the PGIS PF Overall, and the individual PGIS subscales of pain, difficulty, and activity limitation, and the Clinician Global Impression of Change Scale. Safety will be assessed by evaluating the incidence and duration of TEAEs, AESIs, SAEs, and changes in vital signs and clinical laboratory values.

All participants will complete the study on EOS (Day 57) Visit, regardless of whether they receive 1 or 2 treatments during the study. At the EOS visit, immunogenicity samples will be collected, safety will be assessed, and nodules will be measured. The maximum duration of participation is up to 85 days (Screening Period: 28 days, Treatment Periods: 1 or 2 days, and a total Follow-up Period of 56 days).

5.2. Scientific Rationale for the Study Design

Study EN3835-105 is a completed, open-label study conducted to assess the safety, tolerability, and PK of EN3835 in the treatment of plantar fibromatosis. The effect of EN3835 on nodule size was assessed and a validated assessment tool (ie, Foot Function Index-Short Form-23 [FFI-SF-23]) was used to obtain a preliminary assessment of the treatment with EN3835 on multiple functional domains (eg, foot pain, disability, and difficulty) considered representative of clinically meaningful endpoints in the treatment of plantar fibromatosis. Results of an interim analysis from this study showed that participants receiving EN3835 showed improvement in the

severity of their plantar fibromatosis symptoms of pain, difficulty, and disability (activity limitation) with improvements more prominent with the 1.2 mg/mL or 2.25 mg/mL doses. Both participants and investigators saw an improvement in nodule consistency by Day 57. All AEs in this study were considered mild to moderate in severity and most were TEAEs related to the injection site. Most AEs resolved within 21 days.

Study EN3835-222 is a randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of up to 2 doses of EN3835 vs placebo in participants with plantar fibromatosis. Participants will receive a maximum dose of up to 1.8 mg per treatment for up to 2 treatments based on the configuration of their nodules. For participants with bilateral plantar fibromatosis, no more than 2 injections (0.9 mg) per foot can be administered. For participants with unilateral plantar fibromatosis, no more than 3 injections (1.35 mg) may be administered in the single foot. Multiple nodules may be treated on the same foot.

Efficacy and safety data will be collected throughout the study.

5.2.1. Changes in the Study Design Due to COVID-19

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

To ensure participant safety and protect data integrity with Endo's approval, Endo may allow remote visits for certain safety assessments. This is aligned with the FDA Guidance on *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency* (March 2020, updated 30 August 2021).

Additionally, participants impacted by the health emergency will be allowed to continue in the study and complete assessments when the investigational sites re-open as follows:

- A participant who had received any dose of EN3835 in the study prior to an interruption will be allowed to continue in the study.

5.2.2. Justification for Dose

EN3835-105 was a randomized dose-ranging study during which in the initial phase, the safety and effectiveness of 3 different concentrations of EN3835: 0.6, 1.2, and 2.25 mg/mL, were studied. In addition, nodules which were 1.5 cm or smaller in diameter received 1 injection while nodules that exceeded 1.5 cm received 2 injections. Once all participants completed the initial study phase, an interim analysis was done to compare the 3 concentrations and select the optimal concentrations for use in the retreatment phase of EN3835-105 and EN3835-222 overall.

In EN3835-105, at the time of the interim analysis, there were an insufficient number of participants with at least a 50% score on the pain subscale to evaluate the 2.25 mg/mL cohort treatment effect. To evaluate this population participants who had a baseline total FFI-SF-23 score of at least 34 were selected to evaluate the treatment effect.

The following criteria were to be collected throughout the study and used to evaluate the dose selection: safety (incidence and severity of AEs), nodular consistency, nodule size (area), and FFI-SF-23 response in subdomains of Pain, Difficulty, and Disability.

Safety data along with a combination of observed change in nodule characteristics (size and consistency) in addition to participant-reported responses to the FFI-SF-23 were used to evaluate the response to 0.6, 1.2, and 2.25 mg/mL of EN3835.

The combination of responses to each of the 3 categories were assigned levels of treatment response (Very good, Good, Some, No, and Poor) as below:

Very good treatment response was defined as a non-palpable nodule (no measurable size or consistency) and reduction in FFI-SF-23 score.

Good treatment response was defined as a reduction in all 3 categories.

Some treatment response was defined as a reduction in 2 of the 3 categories.

No treatment response was defined as a reduction in 1 category and no change in the other 2.

Poor treatment response was defined as no reduction in any category.

Worsening (significant increase in size, increase in hardness or increase in composite FFI-SF-23 response) in any category was considered a Poor treatment response.

At the time of the interim analysis of EN3835-105 there were 24 total treatment-related AEs in the 0.6 mg/mL group, 16 treatment-related AEs in the 1.2 mg/mL group, and 15 treatment-related AEs in the 2.25 mg/mL group. All AEs were of mild to moderate intensity and most resolved within 21 days. The safety profiles, including the type (injection site reactions, including pain, bruising, swelling, and ecchymosis), intensity, and duration of the treatment related AEs were similar among treatment groups. It was concluded that all concentrations were equally safe and well tolerated.

Dose Selection

Rodent studies assessed the effects of intravenous injection of EN3835 directly into the systemic circulation. Dose-dependent liver toxicity was noted at exposures greater than or equal to 13 times the 2.7 mg of the maximum recommended human dose on a mg/kg basis (Study LAB 1007-1671). Since the proposed maximum total dose of EN3835 recommended for intralesional injection per treatment visit will be much lower than the intravenous injection administered in rodent studies, Endo considers the proposed dose will have no risk of systemic toxicity.

Based on the aforementioned data, it was concluded that in the interim analysis of Study EN3835-105, both the 1.2 and 2.25 mg/mL concentrations had a better treatment effect versus the lowest concentration, 0.6 mg/mL. Participants who received 2 injections of either 1.2 mg/mL or 2.25 mg/mL had a better treatment effect compared to those receiving 1 injection. A better treatment response on the FFI was observed in participants who received 2 injections of 2.25 mg/mL compared to those receiving 2 injections of 1.2 mg/mL. Overall, participants in the 2.25 mg/mL group had the best treatment responses as defined above. Paired with the nearly equivalent safety profile between the 2 concentrations, the 2.25 mg/mL concentration was selected to be used in the retreatment phase of Studies EN3835-105 and EN3835-222. The maximum total dose of EN3835 to be administered during this study when both feet are treated is 1.8 mg, and the maximum dose administered to a single foot is 1.35 mg when only 1 foot is treated, given that these were the maximum doses evaluated in Study EN3835-105.

5.2.3. Justification of Measures

5.2.3.1. Foot Function Index-PF-May 2021

The Foot Function Index (FFI) scale for use in Study EN3835-105 was an adapted from the Foot Function Index-Short Form-23 (FFI-SF-23) for use in plantar fibromatosis. The FFI-SF-23 is a total foot function assessment instrument ([Budiman-Mak et al, 1991](#); [Budiman-Mak et al, 2013](#)) comprising 23 items used to assess foot pain, disability, and difficulty in participants with ankle and foot disorders.

Concept elicitation and cognitive interviews were conducted with participants with plantar fibromatosis (n=19) using the FFI-SF-23 to confirm content validity and to confirm that the measure was understandable and relevant in this population. The feedback from the interviews, in combination with FDA feedback resulted in minor revisions to the instrument, which produced a 21-item version, the FFI-PF-May 2021, referred to as the FFI, which will be used in this study. This pain subscale of the FFI will be used in this study in the assessment of the primary endpoint. Additional cognitive interviews (n=7) were conducted, focused specifically on the changes present in the FFI, to confirm content validity and comprehension of the FFI. Based on the second round of cognitive interviews, participants felt that the FFI applied to them and did not recommend changes to the items or response options, therefore no additional changes were made to the FFI.

5.2.3.2. Patient Global Impression of Severity (PGIS)

A single global item PGIS scale will be used for overall severity of plantar fibromatosis. Additional PGIS subscales will measure the overall severity of foot pain, difficulty, and activity limitation

5.2.3.3. Patient Global Impression of Change (PGIC)

A single global item PGIC scale will be used for overall impression of change in plantar fibromatosis. Additional PGIC subscales will measure the overall impression of change in the severity of foot pain, difficulty with the foot/feet, and activity limitation due to the feet.

5.2.3.4. Pain Intensity Numeric Rating Scale (NRS)

A single item NRS will be used to capture the intensity for foot pain related to plantar fibromatosis.

5.2.3.5. Durometer Use

Based on the interim data available from Study EN3835-105, after administration of EN3835, most nodules become softer upon palpation and scores on the FFI-SF-23 improve during the weeks after treatment. In order to quantify nodule consistency and to standardize the interpretation of nodule consistency, a durometer will be used to measure changes in nodules during the study.

5.2.4. Stopping Rules for the Study

During the conduct of the study, AEs and SAEs will be reported to identify any safety concerns (Section 9.3.1). These events are continuously reviewed by the medical monitor at the frequency established in the medical monitoring plan.

The sponsor may decide to stop enrollment early due to recommendations from the external, independent DSMB (Section 11.1.4). The DSMB will meet at an appropriate frequency, as described in the DSMB charter. The DSMB will also convene if $\geq 3\%$ of study participants have developed a TEAE of CTCAE \geq Grade 3 due to serious injuries to the foot caused by local complications of the injection, or if $\geq 3\%$ of study participants have experienced anaphylaxis after the study treatment. In that setting, the DSMB will conduct an independent assessment and make a recommendation regarding study continuation based upon their overall assessment of risks and benefits to study participants based upon a review of unblinded data.

This study may be terminated by the sponsor for any reason at any time. This can include new safety concerns that can invalidate the earlier positive risk-benefit assessment.

5.3. End of Study Definition

A participant is considered to have completed the study if the participant has completed the EOS (Day 57) Visit.

The end of study is defined as the completion of the final assessment for the last participant. All participants are expected to remain in the study until Day 57, regardless if they receive 1 or 2 treatments.

The study completion date is defined as date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (e.g., last participant's last visit or 28-day follow-up Safety Visit), as shown in the Schedule of Assessments (Section 2.3). This study completion date applies whether the study concluded according to the pre-specified protocol or was terminated.

6. SELECTION AND WITHDRAWAL OF PARTICIPANTS

6.1. Participant Inclusion Criteria

Diagnosis and Inclusion Criteria

To be eligible to participate in the study, the participant must meet the following criteria:

Age and Sex:

1. Be an ambulatory male or female ≥ 18 years of age.

Disease Characteristics:

2. Has a diagnosis of plantar fibromatosis AND have at least 1 hard, firm throughout, or moderately firm, palpable fibrous nodule on clinical examination and measurable by caliper.

3. Has a score of at least 50% on the pain subscale of the FFI (maximum score of 28 [without orthotics] or 36 [with orthotics] as applicable).
4. Requires ≤ 4 injections (1.8 mg maximum total dose) per treatment visit.
 - a. For participants with bilateral plantar fibromatosis, has a nodule configuration requiring ≤ 2 injections per foot (0.9 mg maximum dose per foot) based on the total count and size of all plantar nodules present.
 - b. For participants with unilateral plantar fibromatosis, has a nodule configuration requiring ≤ 3 injections (1.35 mg maximum dose per foot), based on the total count and size of plantar nodules.
5. Has no significant medical history or examination findings related to the participant's plantar nodule (s), which in the investigator's opinion, would make the participant unsuitable for study intervention administration.

Type of Participant:

6. Willing and able to comply with all protocol required visits and assessments.
7. Able to read and understand the patient reported assessments in the local language of the country.
8. Agree not to use opioids (eg, codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone) during the study period and has not used opioids 2 weeks before the Screening Visit.
9. Agree to not initiate or change use of orthotics or inserts designed to relieve symptoms of plantar fibromatosis during the study period.
10. If female, be of non-childbearing 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 non-pregnant, non-lactating 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. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, 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.

Informed Consent:

11. Capable of providing consent, are adequately informed, and understand the nature and risks of the study.

6.2. Participant Exclusion Criteria

A participant is ineligible for study participation if the participant meets any of the following criteria:

Medical Conditions:

1. Has the presence of non-plantar fibromatosis-related nodules on the affected foot/feet (eg, neurofibroma, rhabdomyosarcoma, liposarcoma, neurilemmomas, rheumatoid nodules, desmoid tumors, or malignant soft tissue lesions of the foot or ankle).
2. Has any musculoskeletal, neuromuscular, neurosensory, other neurological or related disorder that affects the participant's use of his or her feet and/or would impair his/her completion of study assessments as determined by the investigator.
3. Has the presence of soft (or not hard/firm) plantar fibromatosis nodule on either foot.
4. Has ≥ 5 plantar fibromatosis nodules (for bilateral and unilateral plantar fibromatosis).
5. For bilateral plantar fibromatosis:
 - Has > 2 nodules per foot OR
 - Has any nodules > 4 cm
6. For unilateral plantar fibromatosis:
 - Has > 3 nodules OR
 - Has ≥ 2 nodule that are > 2 cm each.
7. Has a known systemic allergy to collagenase or any other excipient of EN3835.
8. Has a known bleeding disorder which would make the participant unsuitable for enrollment in the study (see Exclusion Criterion #16).
9. Has a clinically significant laboratory abnormality or any laboratory test results meeting any of the following criteria:
 - a. alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN)
 - b. total bilirubin (TBL) $\geq 2 \times$ ULN ($> 35\%$ direct bilirubin)
 - c. aspartate aminotransferase (AST) $\geq 3 \times$ ULN
 - d. international normalized ratio (INR) > 1.5
10. Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the participant's well-being, (eg, evidence or history of malignancy other than excised basal-cell carcinoma) or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, or gastrointestinal disease). If there is a history of such disease but the condition has been stable (defined as not requiring significant change in therapy or hospitalization for worsening disease) for more than 1 year and is judged by the investigator not to interfere with participation in the study, the participant may be included, with the documented approval of the medical monitor.
11. Any other significant medical condition(s), which in the investigator's opinion would make the participant unsuitable for enrollment in the study.
12. Is pregnant or plans to become pregnant.
13. Is breastfeeding, or is providing or plans to provide breast milk in any manner during the study.

Prior/Concomitant Therapy:

14. Received surgical or non-surgical treatment(s) (eg, steroid injection, transdermal/intralesional verapamil, radiation therapy, extracorporeal shock wave therapy) on the foot or nodule(s) to be treated within 3 months before administration of study intervention.
15. Has received any collagenase treatment (eg, Santyl[®] ointment, XIAFLEX[®]/XIAPEX[®], EN3835, or CCH) within 30 days prior to Day 1.
16. Is currently receiving, has received (within 7 days of the first treatment of study intervention, or plans to receive any anticoagulant or antiplatelet medication (except for ≤ 150 mg aspirin daily) that would increase the risk of bleeding during the study.

Prior/Concurrent Clinical Study Experience:

17. Participation in other studies involving an investigational drug within 30 days before treatment with study intervention and/or during study participation.
18. Has previously participated in clinical studies of EN3835 in plantar fibromatosis.

Other Considerations:

19. 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 Institutional Review Board (IRB).

6.2.1. Participant Inclusion Criteria – Treatment 2

To be eligible to receive the second treatment, on Day 29, the participant must meet the following criteria:

Disease Characteristics:

1. The participant may receive additional treatment if the participant has a previously treated nodule(s) that remains palpable (eg, hard, moderately firm, firm throughout or soft) on clinical examination and measurable by caliper.
2. Women of childbearing potential must have a negative urine pregnancy test.

6.2.2. Participant Exclusion Criteria – Treatment 2

Medical Conditions:

1. The participant must not have any significant medical conditions, which in the investigator's opinion would preclude receiving a second treatment.

6.3. Lifestyle Considerations

After receiving study intervention, participants will be encouraged to resume normal daily activities including weight bearing and walking on the treated foot/feet. Participants should be

encouraged to wear supportive footwear (such as sneakers or tennis shoes) when on their feet during the study. Participants must agree to not initiate or change the use of orthotics or inserts designed to relieve symptoms of plantar fibromatosis during the study period.

6.4. Screen Failures

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

A participant who is a screen failure at the Screening Visit or Day 1 may be rescreened with approval of the sponsor. The period from the start of rescreening related procedures to injection of study intervention must not exceed 28 days. Participants may be rescreened only once; this includes any rescreening due to COVID-19 interruption.

If the day of rescreening is > 28 days from the day the participant was initially screened, the participant will need to repeat all procedures and be reconsented. If the day of rescreening is < 28 days from the day the participant was initially screened, the need to repeat other screening assessments will be determined on an individual basis.

Participants who do not meet all of the eligibility criteria at the Screening and Day 1 visits will be deemed a screen failure and the following information must be recorded for all participants who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which inclusion criteria not met or exclusion criteria met.
- Any AE/SAE experienced by the participant.

7. STUDY INTERVENTION

Study intervention is defined as any investigational treatment, marketed products, placebo, or device intended to be administered to a study participant according to the study protocol. In this protocol, study intervention refers to EN3835 and placebo.

7.1. Selection of Nodules

During the Screening and Day 1 Visits, the investigator will examine and evaluate the nodules on the affected foot/feet, by conducting caliper measurements, measuring nodule hardness using a durometer, palpating the nodule for consistency, and assessing the FFI. Only hard, firm throughout, moderately firm fibrous nodules that are palpable on clinical examination and measurable on calipers are eligible for treatment on Day 1. All hard, firm throughout, moderately firm nodules present on each foot on Day 1 must be treated. (If all nodules on each foot are not hard, moderately firm or firm throughout on Screening and Day 1, the participant will not be eligible for study inclusion). Study intervention will be administered intralesionally to nodules present meeting eligibility criteria based on the size of each nodule at the doses described in [Table 2](#).

Based on the largest diameter of width or length of the nodule determined by calipers, participants will receive 1 to 3 injections of study intervention per foot. Participants with nodules of ≤ 2 cm will receive 1 intralesional injection of study intervention per nodule. Participants with nodules of > 2 cm to ≤ 4 cm will receive 2 intralesional injections of study intervention per nodule. Participants with nodules of > 4 cm will receive 3 intralesional injections of study intervention per nodule.

Nodules treated on Day 1 that remain palpable on Day 29 clinical examination and have consistency of hard, firm throughout, moderately firm, or soft are eligible for a second treatment on Day 29.

7.2. Topical Anesthetic

Topical anesthetics (ie, cream, ointment, gel, spray) may be administered before intralesional injection of study intervention provided it does not interfere with proper identification of the nodule or with administration of the study intervention. The topical anesthetic used should be captured as a concomitant medication.

7.3. Study Intervention Administration

Details of the study intervention and administration are presented in Table 1. Specific instructions for EN3835/placebo reconstitution and preparation of administration syringes will be provided in the Pharmacy Manual. Study intervention will be injected intralesionally. Specific instructions outlining the injection techniques will be provided in the Study Operations Manual.

Table 1: Study Intervention Administration

Treatment Concentrations	EN3835	Placebo
Product Name	EN3835 (0.9 mg of collagenase clostridium histolyticum with 0.5 mg of hydrochloric acid, 18.5 mg of sucrose and 1.1 mg of tromethamine) plus diluent	Placebo (0.5 mg of hydrochloric acid, 18.5 mg of sucrose and 1.1 mg of tromethamine) plus diluent
Type	Biologic	NA
Dose Formulation	Injectable liquid	Injectable liquid
Unit Dose Strengths	2.25 mg/mL	NA
Dose Amount and Frequency ^a	0.45 mg administered as 1 injection 0.9 mg administered as 2 injections 1.35 mg administered as 3 injections	Volume matched placebo administered as 1 injection, 2 injections, or 3 injections per nodule depending on nodule size
Route of Administration	Intralesional injection	Intralesional injection
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Product will be provided in vials. Each vial will be labeled per country requirement.	Product will be provided in vials. Each vial will be labeled per country requirement.

^aEach injection (0.45 mg) of study intervention will be administered as 2 aliquots of 0.225 mg each.

7.3.1. Study Intervention

The dose of study intervention that will be administered per nodule based on nodule size is presented in Table 2. The total dose received by a participant is determined by size of nodule and number of injections. Each injection (0.45 mg) of study intervention will be administered as 2 aliquots of 0.225 mg each.

Table 2: Dose of Study Intervention per Nodule

Palpable Nodule Size	Injections	Total Volume (mL)	Total Dose Administered/ Nodule (mg)
Up to 2 cm	1	0.2	0.45
>2 cm to ≤4 cm	2	0.4	0.9
>4 cm	3	0.6	1.35

- Size of each nodule will be determined by caliper and the largest width or length will be used to determine number of injections/aliquots to be administered.
- Each injection of study intervention (0.45 mg) is administered as 2 aliquots of 0.225 mg each.
- Maximum dose at 1 treatment visit not to exceed 1.8 mg in total (with maximum of 0.9 mg/per foot) when treating bilateral plantar fibromatosis. When treating unilateral plantar fibromatosis, the maximum dose at 1 treatment should not exceed 1.35 mg in the affected foot. All hard, firm throughout, or moderately firm nodules present on each foot on Day 1 must be treated. If all nodules on each foot are not hard, firm throughout, moderately firm on Screening and on Day 1, the participants are not eligible for inclusion.
- 1 cm = 10 mm

7.3.2. Injection of Study Intervention

Study intervention will be injected intralesionally directly into the nodule using a 27-gauge, 0.5-inch needle. Instructions are provided in the Injection Guide in the Study Operations Manual.

NOTE: As EN3835 is a foreign protein, investigators must be prepared to address a severe allergic reaction should it occur. At the time of injection, a 1:1000 solution of epinephrine for injection, 50 mg diphenhydramine injection or a suitable equivalent, and oxygen should be available to the investigator and site staff familiar with their use.

7.3.3. Care Procedures After Injection

Care procedures after the injection are provided in the Study Operations Manual.

To evaluate the participant for possible immediate immunological AEs, the participant will remain in direct observation of medical personnel who are skilled in the management of acute allergic reactions for the first 30 minutes after receiving an injection of study intervention (see Section 7.3.2). Participants may leave direct observation after the 30-minute period provided:

- The participant exhibits no sign of an immunological or other clinically significant systemic or local AE.
- The participant's vital signs have remained stable throughout the 30-minute observation period (see Section 9.2.4).

Participants will be instructed when to inspect the treated foot for edema, sensation, movement, and when they will be allowed to walk bearing their full weight as tolerable.

7.4. Study Intervention Preparation/Handling/Storage/Accountability

EN3835, placebo, and the diluent will be supplied in glass vials, which will be shipped and stored at 2°C to 8°C.

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

The study intervention will be maintained in a monitored, environmentally controlled (in accordance with treatment labeling), secure, locked area with restricted access at the study site.

Only participants enrolled in the study will receive study intervention and only authorized study staff will dispense study intervention.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study intervention furnished to the study site. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study intervention received, to whom it was administered (participant-by-participant accounting) and accounts of any study intervention accidentally or deliberately destroyed. All unused study intervention not involved in immediate participant treatment will be maintained under locked, temperature-controlled storage at the study site. Please refer to the Pharmacy Manual for complete information regarding preparation, handling, storage, and accountability of study intervention.

7.5. Measures to Minimize Bias

This is a double-blind, placebo-controlled study. Participants will be randomized according to a validated, computer generated allocation scheme to receive the study interventions described in a 1:1 ratio. Participants will complete their assessment scales before the investigator scales will be completed to avoid bias. Precautions will be in place to ensure that investigators are blinded to participant assessments on the COA scales.

7.5.1. Interactive Response Technology

The investigator or designee will utilize interactive response technology (IRT) system to register participants at screening. Each participant's unique identification (ID) number will be assigned by the IRT system and will be used to identify the participant for the duration of the study within all systems and documentation. If the participant is not eligible to receive study intervention, or should discontinue from the study, the participant ID number will not be reassigned to another participant. Specific instructions for the use of the IRT system will be included in the IRT User Manual.

The investigator must maintain a participant master log linking the participant ID to the participant's name. The investigator will not have access to the participant's treatment assignment. The investigator must follow all applicable privacy laws in order to protect a participant's privacy and confidentiality. Information that could identify a participant will be masked on material received by the sponsor.

7.5.2. Emergency Identification of Study Intervention

The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study intervention assignment. The sponsor must be notified before the blind is broken unless identification of the study intervention is required for a medical emergency in which the knowledge of the specific blinded treatment will affect the immediate management of the participant's condition (eg, antidote available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and time that the blind was broken must be recorded in the source documentation.

7.6. Treatment Compliance

All participants will receive study intervention administered by a qualified health care professional at the study site. Study intervention will be administered according to the instructions provided in the Study Operations Manual.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 9.4).

7.7. Prior and Concomitant Medications and Procedures

7.7.1. Prior Medications

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior medications (taken within the 30 days prior to the Screening Visit) and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

In addition, all prior treatments administered for the disease/condition under study will be recorded with start and stop date, dose, unit, frequency and route of administration. The use of a collagenase at any point in time must be captured in the electronic case report form (eCRF).

7.7.2. Concomitant Medications

The start and stop date, dose, unit, frequency, route of administration, and indication for all concomitant medications taken from the Screening Visit through the EOS (Day 57) Visit, including oral and topical analgesics/anesthetics before study intervention injection, and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, nutritional supplements, vitamins, vaccinations, etc) received will be recorded.

7.7.3. Prohibited Medications

The following medications are prohibited during the study:

- Opioids (eg, codeine, heroin, hydrocodone, hydromorphone, morphine, oxycodone) 2 weeks prior to the screening visit and during the study period.
- Anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor Xa inhibitors) and antiplatelet agents (aspirin > 150 mg/day and P2Y12 inhibitors, such as clopidogrel) from 7 days before the Day 1 Visit through the EOS (Day 57) Visit as

these medications can cause additional bruising. However, the use of aspirin ≤ 150 mg per day will be permitted.

- Injectable anesthetic use in or around the plantar nodule targeted for treatment is prohibited from the Day 1 Visit through the EOS (Day 57) Visit.
- Use of an investigational drug during the study

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

7.8. COVID-19-Related Protocol Deviations

All study assessments conducted outside of the allowed windows outlined in the Schedule of Assessments due to a COVID-19 interruption will be documented as a protocol deviation. COVID-19 will be recorded as the reason for these out-of-window assessments.

8. DISCONTINUATION FROM STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

8.1. Discontinuation of Study Intervention or from the Study

In rare instances, it may be necessary for a participant to be permanently discontinued from study intervention by the investigator or the sponsor for safety, behavioral, or compliance reasons. Participants who request to discontinue from the study intervention or discontinue from the study prior to the Day 57 visit will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study. Participants who discontinue from the study intervention and do not agree to remain in the study for follow-up until Day 57, will be requested to complete an ET visit and if applicable the 28-day post-treatment Safety Follow-up Visit (or phone call if a visit is not possible) to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The date of and reason for discontinuation of study intervention will be recorded.

Discontinuation of study intervention for abnormal liver function will be considered by the investigator when a participant meets one of the conditions outlined in Section [11.5](#).

If a clinically significant finding is identified after the start of study intervention, the investigator or a qualified designee will discuss with the sponsor to determine if the participant can continue in the study and if any change in management is needed.

Participants who discontinue study intervention will not be replaced according to the discretion of the sponsor and discussion as needed with investigator.

8.2. Participant Withdrawal from the Study

A participant may withdraw from the study (withdraw consent) at any time at his/her own request.

- At the time of withdrawing from the study, if possible, an ET visit should be conducted, as shown in the Schedule of Assessments
- The participant will be permanently discontinued from the study intervention, and the study, at the time of withdrawal of consent.
- If the participant withdraws consent for the sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The date a participant withdraws and the reason for withdrawal will be recorded in the source documentation and the electronic case report form (eCRF). When a participant withdraws consent and does not agree to an ET visit, then no procedures are required.

8.3. Lost to Follow-up

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

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

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

Participants who have been lost to follow-up may be replaced according to the discretion of the sponsor.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Section 2.3). Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. Activities outlined in the Study Operations Manual must be followed or a protocol deviation will result.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue study intervention and/or be discontinued from the study.

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

9.1. Efficacy Assessments

Examination and evaluation of the selected nodule(s) will be performed at the time points specified in the Schedule of Assessments. A general description of each of these assessments follows. Specific instructions and questionnaires/forms (where appropriate) will be provided in the Study Operations Manual.

9.1.1. Nodule Assessments

9.1.1.1. Anatomical Representation of Nodule Location

At Screening, Days 1, 29, and 57 Visits, the investigator will complete a graphic representation of the foot/feet and the location(s) of the nodule(s) treated.

Additional information is provided in the Study Operations Manual.

9.1.1.2. Consistency of the Selected Nodule

At the time points listed in the Schedule of Assessments, the investigator or qualified designee will palpate the selected nodule, determine the consistency of the nodule, and classify the nodule. For the first treatment, only hard, firm throughout, or moderately firm, palpable fibrous nodules will be treated. For the second treatment, nodules previously treated on Day 1 that remain palpable and are either hard, firm throughout, moderately firm, or soft) are eligible for Treatment 2. All efforts should be made to ensure the same investigator is performing these assessments for each participant. The nodule consistency scale is classified as,

4: Hard

3: Firm Throughout

2: Moderately Firm

1: Soft

0: Non-palpable.

Additional information on the classification of the nodule is provided in the Study Operations Manual.

9.1.1.3. Caliper Measurements of the Selected Module

At the time points listed in the Schedule of Assessments, the investigator or qualified designee will use a surgical marker to outline the circumference of the selected nodule.

After the nodule has been marked, the investigator or qualified designee will use handheld calipers to measure the length and width of the selected nodule, and nodule measurements will be recorded.

Gross observations will be solicited from the investigator from the investigator at each time of examination.

Additional information is provided in the Study Operations Manual.

9.1.1.4. Durometer Measurements

At the time points listed in the Schedule of Assessments, the investigator or qualified designee will use the Type OO Shore Durometer provided to measure the hardness of each of the selected nodule, on a scale ranging from 0 to 100, and the nodule hardness measurements will be recorded.

Additional information is provided in the Study Operations Manual.

9.1.2. Patient-Reported Outcome Assessments

To limit missing data from the clinical outcome assessments (COA) scales the following measures will be implemented:

- Participants and site staff will be trained on the purpose of collecting COAs to encourage compliance with completing these assessments.
- COA scales will be completed electronically. Furthermore, completion of each COA scale will be required to proceed to the subsequent COA scale.

The order of scale completion by the participant is as follows: FFI-PF-May 2021, PGIS Foot Pain Subscale, PGIC Foot Pain Subscale, PGIS Difficulty Subscale, PGIC Difficulty Subscale, PGIS Activity Limitation Subscale, PGIC Activity Limitation Subscale, PGIS-PF Overall, PGIC PF Overall, Pain Intensity NRS, and Subject Satisfaction with Treatment Scale.

9.1.2.1. Foot Function Index

At the time points included in the Schedule of Assessments, each participant will be asked to complete the FFI-PF-May 2021, otherwise known as the FFI, which assesses the impact of foot pathology on 3 domains of pain, difficulty, and activity limitation. The participant will complete the scale prior to evaluation by the investigator.

The activity limitation subscale consists of 3 items and measures limitations in activities because of your feet in the past week, such as staying off one foot or both feet. It is scored on a 5-point verbal rating scale as follows:

- 0 - Never
- 1 - Rarely
- 2 - Sometimes
- 3 - Often
- 4 - Always

The difficulty subscale consists of 9 items and measures difficulty performing various functional activities because of your feet in the past week, such as difficulty climbing stairs. It is scored on a 5-point verbal rating scale as follows:

- 0 - No difficulty
- 1 - A little difficulty
- 2 - Some difficulty
- 3 - Much difficulty
- 4 - A lot of difficulty

The pain subscale consists of 9 items and measures the severity of foot pain during the past week in different situations, such as walking barefoot versus walking with shoes. For the pain subscale, if the participant marks “does not wear orthotics” items pertaining to orthotics are not scored and are not included in the total score. It is scored on a 5-point verbal rating scale as follows:

- 0 - None
- 1 - Mild
- 2 - Moderate
- 3 - Severe
- 4 - Extreme

9.1.2.2. Patient Global Impression of Severity- Plantar Fibromatosis Overall

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the severity of plantar fibromatosis in the past week on a 5 point scale ranging from 0 (“None”) to 4 (“Severe”).

- 0 None
- 1 Minimal
- 2 Mild
- 3 Moderate
- 4 Severe

9.1.2.2.1. Patient Global Impression of Severity – Foot Pain

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the overall severity of foot pain in the past week on a 5 point scale ranging from 0 (“None”) to 4 (“Severe”).

9.1.2.2.2. Patient Global Impression of Severity -Difficulty

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the overall difficulty had with your foot or feet doing physical activities (eg, walking, running, going up and down stairs and curbs) in the past week on a 5 point scale ranging from 0 (“None”) to 4 (“Severe”).

9.1.2.2.3. Patient Global Impression of Severity- Activity Limitation Subscale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the activity limitation had with your foot or feet doing physical activities (eg. staying off one foot or both feet) in the past week on a 5 point scale ranging from 0 (“None”) to 4 (“Severe”).

9.1.2.3. Patient Global Impression of Change- PF Overall

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the change in the overall severity of plantar fibromatosis in the past week on a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as follows:

- 3 Very Much Worse
- 2 Much Worse
- 1 Minimally Worse
- 0 No Change
- +1 Minimal Improvement
- +2 Much Improvement
- +3 Very Much Improvement

9.1.2.3.1. Patient Global Impression of Change- Foot Pain Subscale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the change in the overall severity of foot pain experienced in the past week on a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”).

9.1.2.3.2. Patient Global Impression of Change- Difficulty Subscale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the change in the overall difficulty with the foot or feet doing physical activities (eg, walking, running, going up and down stairs and curbs) in the past week on a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”).

9.1.2.3.3. Patient Global Impression of Change- Activity Limitation Subscale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the change in the overall limitations in the daily activities experienced in the past week on a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”).

9.1.2.4. Pain Intensity Numerical Rating Scale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to describe the worst severity of foot pain in the past week, ranging from 0 (No Pain) to 10 (Worst Pain Imaginable).

9.1.2.5. Subject Satisfaction with Treatment Scale

At the time points included in the Schedule of Assessments (prior to evaluation by the investigator), each participant will be asked to rate his/her satisfaction with treatment of their nodule(s) per treated foot on a 5-point scale ranging from -2 (“Very Dissatisfied”) to +2 (“Very Satisfied”) as follows:

- 2 Very Dissatisfied
- 1 Quite Dissatisfied
- 0 Neither Satisfied nor Dissatisfied
- +1 Quite Satisfied
- +2 Very Satisfied

9.1.3. Investigator Assessments

Training will be provided to ensure that investigators complete the Clinician Global Impression of Change Scale in a standardized manner.

9.1.3.1. Clinician Global Impression of Change Scale

At the time points included in the Schedule of Assessments, the investigator will determine the degree of improvement with treatment per each foot on a 7-point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as follows:

- 3 Very Much Worse
- 2 Much Worse
- 1 Minimally Worse
- 0 No Change
- +1 Minimal Improvement
- +2 Much Improvement
- +3 Very Much Improvement

9.2. Safety Assessments

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

To ensure participant safety and protect data integrity, Endo, in accordance with the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (March 2020, updated 30 August 2021), will allow remote visits for certain safety assessments. Additionally, participants impacted by the health emergency will be allowed to continue in the study and complete remaining assessments when the investigational sites re-open.

9.2.1. Medical and Surgical History

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

History of tobacco use, and alcohol use (never, current, former) and drug abuse (both illegal and prescription) will be collected.

Any diagnostic, therapeutic, or surgical procedure performed ≤ 10 years before the study, including those in the treatment area, should be recorded including the date, indication for, and description of the procedure.

Note: Any medical condition or laboratory abnormality already present at screening or baseline should be reported as medical history. If the medical condition present at baseline changes in severity or seriousness at any time during the study, it should be reported as an AE.

9.2.2. Physical Examination

At the time points listed in the Schedule of Assessments, a physical examination will be conducted. The physical examination should be conducted per standard of care and may 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, particularly of the feet, and other conditions of note.

At the time points listed in the Schedule of Assessments, a foot examination will be conducted.

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical exam findings for clinical significance. Any physical examination finding meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

9.2.3. Height and Weight

Height and weight will be evaluated at Screening.

9.2.4. Vital Signs

At the time points listed in the Schedule of Assessments, vital signs will be obtained after the participant has been sitting for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded. On the day that study intervention will be administered, vital signs should be collected in supine position prior to injection and at 15 (± 5) and 30 (± 5) minutes post injection.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

9.2.5. Clinical Laboratory Determinations

At the time points listed in the Schedule of Assessments, clinical laboratory tests will be conducted. Required clinical laboratory tests are outlined in Section 11.2. Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging, and transport. The results of the tests will be returned to the investigational sites.

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

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory if needed to ensure participant safety.

Urine dipsticks will be provided by the central laboratory to the sites.

9.2.6. Pregnancy Testing

All female participants of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the Schedule of Assessments. Results must be available prior to protocol mandated study intervention. Participants with positive results at the Screening Visit will be ineligible for study entry. A positive urine pregnancy test at any time will be confirmed with a serum pregnancy test. Any female participant that becomes pregnant during the study will immediately be discontinued from study intervention but may continue in the study. Pregnancy will be reported as described in Section 9.3.5.

For all female participants of childbearing potential, the participant's agreement to use contraception throughout their study participation (Screening Visit through the Day 57/EOS Visit), if eligible, will be documented.

9.3. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs are provided in Section 11.3.

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded, regardless of whether associated with the use of study intervention. 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 intervention will be captured as an AE; the onset date will

be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

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

The investigator will collect all SAEs and AEs from the time of signing the informed consent form (ICF) through the EOS (Day 57) Visit. This will include any AEs that are ongoing at the time of completion/termination of the study. Participants who request to discontinue from the study will be asked to complete the 28-day post treatment Safety Follow-up Visit (or phone call if a visit is not possible) to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Investigators are not obligated to actively seek AEs and SAEs after conclusion of participant study participation. However, if the investigator learns of any SAE, including death, at any time after the participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must notify the sponsor within 24 hours as described in Section [11.3.4.2](#).

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and submitting SAE reports are provided in Section [11.3](#).

9.3.2. Method of Detecting Adverse Events and Serious Adverse Events

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

At each visit, participants will be queried regarding any AEs that have occurred since the last visit. Study site personnel will then record all pertinent information. The study medication compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

9.3.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All ongoing AEs must be followed until they have resolved, or for 28 days after the participant's last study intervention, whichever comes first. All SAEs will be followed until they resolved or the condition stabilizes, the event is otherwise explained, or until follow-up is no longer possible. Further information on follow-up procedures is provided in Section [11.3](#).

9.3.4. Regulatory Reporting Requirements for Serious Adverse Events

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study intervention under clinical investigation. The

sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, IRBs, and investigators.

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

An investigator who receives a SUSAR (IND) safety report describing an SAE or other specific safety information (ie, summary or listing of SAEs) from the sponsor will review and then file it with the IB, and will notify the IRB, if appropriate according to local requirements.

9.3.5. Pregnancy

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

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects, or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form (see Section 11.3). Spontaneous miscarriages should also be reported and handled as SAEs.

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

A participant who becomes pregnant while participating in the study will discontinue study intervention, but can continue in the study. Should a participant discontinue study intervention due to pregnancy, alternative treatment (if available) should be arranged according to standard of care, as determined by the investigator. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a participant discontinues study intervention because of pregnancy.

9.3.6. AEs/SAEs Experienced by Nonparticipants Exposed to Study Intervention

Nonparticipants are persons who are not enrolled in the study but have been exposed to study intervention, including instances of diversion of study intervention. All AEs/SAEs occurring in nonparticipants from such exposure will be reported to the Endo Pharmacovigilance and Risk Management Department on the Serious Adverse Event (SAE)/ Reportable Event Form regardless of whether the event is serious or not. Instructions for completing the form for events experienced by nonparticipants will be provided. SAEs occurring in nonparticipants exposed to study intervention will be processed within the same SAE reporting timelines as described

in Section 11.3. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

9.3.7. Assessment of the Severity of Local Injection Site Reactions

Based on clinical assessments, investigators should classify and assess the severity of local injection site reactions during the study according to Table 3. The table does not comprise a comprehensive list of injection site reactions. For TEAEs not included, refer to the CTCAE Version 5 for a more comprehensive list of events. Local injection site reactions will be reported as TEAEs in the eCRF.

Table 3: Assessment and Grading of the Severity of Injection Site Reactions

Local Reaction to Study Intervention	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain/Pain in extremity	Mild Pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	
Erythema/Redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Pruritus, itchiness	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL	
Bruising, Contusion, Ecchymosis	Localized or in a dependent area	Generalized		
Hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated

Table 3: Assessment and Grading of the Severity of Injection Site Reactions (Continued)

Local Reaction to Study Intervention	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated
Skin laceration	Observation only; topical intervention indicated	Bedside local care indicated	Operative intervention indicated	Life-threatening consequences
Injection site lymphadenopathy	Local lymph node enlargement	Localized ulceration; generalized lymph node enlargement		
Injection site reaction	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Plantar fascial tear/rupture	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; Minimal or noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; Invasive intervention indicated	

Source: Adapted from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5 and FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials September 1997.

ADL = activities of daily living

9.3.8. Adverse Events of Special Interest

AESIs for this study include:

- Any severe hypersensitivity reactions.
- Plantar fascial tears.

These events will be reported as AEs in the eCRF. All AESIs will be evaluated for seriousness and severity. If any of these events meet the criteria for an SAE, they will also be reported as such using the procedure outlined in Section 11.3.

9.3.9. Anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. To identify participants experiencing such a reaction, use the criteria provided by [Sampson et al \(2006\)](#) in [Table 4](#). Anaphylaxis will be reported as an SAE in the eCRF.

Table 4: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>1</u> of the following 3 criteria are fulfilled:	
1.	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) <i>AND AT LEAST ONE OF THE FOLLOWING</i>
a.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b.	Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2.	Two or more of the following that occur rapidly after exposure <i>to collagenase or any other excipient of EN3835 for that participant</i> (minutes to several hours):
a.	Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
c.	Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d.	Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3.	Reduced blood pressure after exposure <i>to collagenase or any other excipient of EN3835 for that participant</i> (minutes to several hours):
a.	Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

9.4. Treatment Overdose

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

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

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the AE eCRF and reported using the procedures detailed in Section 11.3, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/ Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the AE eCRF.

9.4.1. Treatment Abuse/Misuse

Not applicable.

9.5. Pharmacodynamics

Not applicable.

9.6. Genetics

Not applicable.

9.7. Biomarkers

Not applicable.

9.8. Immunogenicity Assessments

Serum samples will be collected at the time points listed in the Schedule of Assessments and will be tested for binding anti-AUX-I and anti-AUX-II antibodies. If the participant tests positive for anti-AUX-I and anti-AUX-II antibodies, testing for neutralizing antibodies will be conducted.

The serum samples obtained will be processed, stored, and then shipped frozen on dry ice to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies.

Specific instructions for the collection, processing, storage, handling, and shipment of the immunogenicity samples will be provided in the Laboratory Manual.

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

10. STATISTICAL CONSIDERATIONS AND METHODS

10.1. Sample Size Determination

The primary endpoint is the difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the foot pain subscale (total score on 9 items) of the FFI ranging from 0 ("None") to 4 ("Extreme").

The sample size was estimated based on an interim analysis of the Day 57 data from Study EN3835-105, a dose-finding Phase 1 study. Assuming a difference in the mean change from Baseline to Day 57 in the pain subscale of FFI between EN3835 and placebo of 5.0 with a 10 standard deviation and 85% statistical power using a 2-sided test ($\alpha = 0.05$), 73 participants per treatment group (146 in total) will be needed to detect this difference between the 2 treatment groups. Assuming a dropout rate of 15%, the total sample size will be 172, eighty-six per treatment group for the study.

Participants will be screened to ensure that approximately 172 participants are randomized into 2 treatment groups, an EN3835 group and a placebo group in a 1:1 ratio.

10.2. Populations for Analysis

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

- The Safety Population will include all participants who receive at least 1 injection of EN3835 or placebo. All safety and immunogenicity analyses will be based on the Safety Population.
- The ITT Population will include all randomized participants. Treatment group assignment will be based on the randomized treatment. The ITT population will be used for analysis of the primary and secondary endpoints.
- The FAS Population will include all ITT participants who receive at least 1 injection of EN3835 or placebo and have at least 1 post injection FFI pain subscale measures. Treatment group assignment will be based on the randomized treatment. This population will be used for analysis of the primary and secondary endpoints.
- The mITT Population will include all ITT participants who receive at least 1 injection of EN3835 or placebo and have both baseline and at least 1 post injection FFI pain subscale measures. The treatment group assignment will be based on the randomized treatment. This population will be used for analysis of the primary, secondary, and exploratory endpoints.

10.3. Statistical Hypotheses and Analyses

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

10.3.1. Efficacy Analysis

The ITT population will be the primary population for the efficacy analysis. Efficacy analyses will also be performed for the FAS and mITT populations as supportive analyses.

For the data collected at nodule level, the analyses will be performed at participant level and nodule level. The data interpretation will be based on participant level results. The nodule level results will be supportive. The details of how to map the data from nodule level to participant level will be specified in the SAP.

10.3.1.1. Primary Analysis

10.3.1.1.1. Primary Estimand

Primary Endpoint:

The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the foot pain subscale (total score on 9 items) of the FFI ranging from 0 (“None”) to 4 (“Extreme”).

The primary estimand is defined as follows:

In participants with plantar fibromatosis, what is the difference in mean change from baseline (Day 1) to Day 57 in foot pain score (as measured with the FFI pain subscale) between EN3835 and placebo regardless of discontinuation of study intervention?

The primary estimand includes the following components:

- Treatment of interest: The randomized study intervention (EN3835 or placebo)
- **Target Population:** Adult participants with plantar fibromatosis who are included in the ITT Population.
- **Variable (Endpoint) of interest:** Change from Baseline (Day 1) to Day 57 in FFI pain subscale score.
- **Treatments being compared:** The mean change from Baseline (Day 1) to Day 57 in FFI pain subscale score will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for primary analysis.
 - Any new or change in concomitant treatment will not be adjusted for in the primary analysis.
 - Early discontinuation from the study or loss to follow up: If participants do not have a FFI pain subscale score at Day 57, the missing values will be imputed before the analysis using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered.
- **Population Level-Summary measure:** Least square mean (LSM) estimates for treatment difference between EN3835 and placebo.

10.3.1.1.2. Method of Analysis

The primary estimand will be based on the data at Baseline and Day 57. Therefore participants who discontinue study intervention or discontinue from the study will be encouraged to complete the remaining study visits and evaluations, and provide any additional follow-up information as required by the study. In cases where the participants do not have an FFI pain subscale score at Day 57 due to early study discontinuation, the missing values will be imputed before the analysis using a multiple imputation washout model. The details of the model will be specified in the SAP.

After imputation, the changes from Baseline to Day 57 will be analyzed using an ANCOVA model with treatment group as fixed effect, FFI pain subscale at baseline, the nodule size and the number of nodules as covariates. The summary measure, least squares (LS) mean estimate for treatment difference between EN3835 and placebo and their corresponding 95% confidence intervals (CIs) will be reported.

A sensitivity analysis with tipping-point approach will be implemented, the details of this approach will be specified in the SAP. In addition, another sensitivity analysis will be performed based all observed data up to Day 57. The changes from Baseline will be analyzed using a mixed

effect model for repeated measures (MMRM). This MMRM model will include treatment group, study visit, treatment by visit interaction as fixed effects, and the covariates of the baseline score, nodule size and the number of nodules. The repeated measure is the participant visits. The dependent variable will be the change from the Baseline at each visit. The summary measure, LSM estimate for treatment difference at Day 57 between EN3835 and placebo and their corresponding 95% CIs will be reported.

The FFI pain subscales, and their changes from Baseline will be summarized by study visit (if applicable) and treatment group using appropriate descriptive statistics.

10.3.1.2. Secondary and Exploratory Analysis

All secondary and exploratory endpoints will be summarized by study visit (if applicable) and treatment group using appropriate descriptive statistics.

10.3.1.2.1. Key Secondary Endpoint 1

Key Secondary Endpoint 1:

The difference of mean change from baseline to Day 57 for FFI Pain and Difficulty combined score between EN3835 and placebo

Key Secondary Estimand 1: In participants with plantar fibromatosis, what is the difference in mean change from baseline to Day 57 in foot pain and difficulty combined score (as measured with combined score of the FFI pain subscale and the FFI difficulty subscale) between EN3835 and placebo, regardless of discontinuation of study intervention?

The key secondary estimand 1 includes the following components:

- Treatment of interest: The randomized study treatment (EN3835 or placebo)
- **Target Population:** Adult participants with plantar fibromatosis who are included in the ITT Population.
- **Variable (Endpoint) of interest:** Change from Baseline (Day 1) to Day 57 in FFI pain and difficulty combined score.
- **Treatments being compared:** The mean change from Baseline (Day 1) to Day 57 FFI pain and difficulty combined score will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for primary analysis.
 - Any new or change in concomitant treatment will not be adjusted for primary analysis.
 - Early discontinuation from the study or loss to follow up: If participants do not have FFI pain and difficulty combined score at Day 57, the missing values will be imputed before the analysis using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered.

- **Population Level-Summary measure:** LSM estimate for treatment difference between EN3835 and placebo.

The method of analysis (including sensitivity analysis) for key secondary endpoint #1 will follow the same method of analysis for primary endpoint.

10.3.1.2.2. Key Secondary Endpoint 2

Key Secondary Endpoint 2: The difference in the proportion of participants treated with EN3835 or placebo reporting “Minimally Improved” (+1), “Much Improved” (+2), or “Very Much Improved” (+3) on the Clinician Global Impression of Change Scale at Day 57.

Key Secondary Estimand 2: In participants with plantar fibromatosis, what is the difference in the proportion of participants with an improvement (as assessed by the investigators with rating of “Minimally Improved” (+1), “Much Improved” (+2), or “Very Much Improved” (+3) on the Clinician Global Impression of Change Scale) between EN3835 and placebo at Day 57, regardless of study withdrawal?

The key secondary estimand 2: includes the following components:

- Treatment of interest: The randomized study treatment (EN3835 or placebo)
- **Target Population:** Adult participants with plantar fibromatosis who are included in the ITT Population.
- **Variable (Endpoint) of interest:** Difference in the proportion of Clinician Global Impression of Change (CGIC), a 7-point scale ranging from –3 (“Very Much Worse”) to +3 (“Very Much Improvement”) at Day 57.
- **Treatments being compared:** The difference in proportion at Day 57 in CGIC will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for primary analysis.
 - Any new or change in concomitant treatment will not be adjusted for primary analysis.
 - Early discontinuation from the study or loss to follow up: All participants with early discontinuation or loss to follow up will be considered as non-responders. The responder is defined as a participant for whom the investigator reports a score to be “Minimal Improvement”, “Much Improvement” or “Very Much Improvement” on the Clinician Global Impression of Change Scale at Day 57.
- **Population Level-Summary measure:** The stratum adjusted risk difference, associated 95% CI and *p* value will be presented separately for each visit between EN3835 and placebo.

The proportions (response rates) will be compared between treatment groups using the Cochran-Mantel-Haenszel method.

A sensitivity analysis with tipping-point approach will be implemented for key secondary endpoint #2. The details of this approach will be specified in the SAP.

10.3.1.2.3. Key Secondary Endpoint 3

Key Secondary Endpoint 3: The difference of mean changes from Baseline to Day 57 for hardness measurements between EN3835 and placebo.

Key Secondary Estimand 3: In participants with plantar fibromatosis, what is the difference in mean change from baseline to Day 57 in hardness measurements (as measured by durometer) between EN3835 and placebo, regardless of discontinuation of study intervention?

The key secondary estimand 3: includes the following components:

- Treatment of interest: The randomized study treatment (EN3835 or placebo)
- **Target Population:** Adult participants with plantar fibromatosis who are included in the ITT Population.
- **Variable (Endpoint) of interest:** Mean change from Baseline (Day 1) to Day 57 in nodular hardness.
- **Treatments being compared:** The mean change from Baseline (Day 1) to Day 57 nodular hardness will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for primary analysis.
 - Any new or change in concomitant treatment will not be adjusted for primary analysis.
 - Early discontinuation from the study or loss to follow up. If participants do not have nodular hardness at Day 57, the missing values will be imputed before the analysis using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered.
- **Population Level-Summary measure:** LSM estimate for treatment difference between EN3835 and placebo.

This estimand will be based on the data at Baseline and Day 57. The imputation and the analysis methods (including sensitivity analysis) are similar to the primary estimand. The summary measure, LSM estimates for treatment difference between EN3835 and placebo, and the corresponding 95% CIs will be reported.

10.3.1.2.4. Other Secondary Endpoints and Exploratory Endpoints

The other secondary endpoints and exploratory endpoints including the mean changes from Baseline (Day 1) to study visits (Days 15, 29, 43 and 57) for FFI- Pain and Difficulty combined score, FFI- pain subscale, FFI- difficulty subscale, and FFI-activity limitation subscale, FFI-composite score, Pain intensity NRS, nodule size, and hardness measurement will be analyzed using the MMRM method based on observed data. The LSM estimates for the treatment difference at each visit and their corresponding 95% CIs will be reported.

The PGIS (overall, pain, difficulty, and activity limitation subscales) scores at each study visit (Days 15, 29, 43, and 57) will be compared between treatment groups using a rank based

analysis. The Hodges-Lehmann estimator and its 95% CIs will be provided to represent the median difference/location shift between the treatment groups.

In addition, response rates for the PGIC for PF overall and each individual subscale, participant satisfaction with treatments, Clinician Global Impression of Change Scale, and nodule consistency will be compared between treatment groups using the Cochran-Mantel-Haenszel method. The responder definition for each assessment will be detailed in the SAP.

Psychometric properties of the FFI will be assessed under a separate SAP. A series of tests are proposed to validate the FFI in the plantar fibromatosis patient population. Upon completion of the analyses, an overall impression and conclusion regarding the psychometric properties of the FFI instrument will be made, based on the analysis results.

10.3.2. Safety Analyses

All participants who receive at least 1 injection of study intervention will be included in the safety analyses. Participants will be included in the safety analyses based on the actual treatment received.

10.3.2.1. Adverse Events

AE analysis by treatment group will include the incidence of AEs, AEs resulting in drug discontinuation, AEs leading to study discontinuation, SAEs, and AESIs. Summaries of AEs will be provided including the number and percentage of participants who experienced at least 1 AE. These summaries will be presented by system organ class (SOC) and preferred term (PT). The occurrence of AEs will also be tabulated by severity. A confidence interval for the difference in frequency of TEAEs across treatment groups will be provided. SAEs and AEs resulting in study discontinuation will be summarized separately by treatment group.

10.3.2.2. Vital Sign, Laboratory Tests, and Other Safety Measures

All vital sign measurements, laboratory tests, and other safety variables and their changes (if applicable) from Baseline will be summarized by treatment group, study visit/days using appropriate descriptive statistics.

10.3.2.3. Immunogenicity Analysis

Anti-AUX-I and anti-AUX-II antibody results (titer levels) and neutralizing antibodies to AUX-I and AUX-II will be summarized using descriptive statistics.

10.4. Multiplicity Adjustment

The significance tests for key secondary endpoints will be conducted in sequential order to preserve the overall type-I error rate < 0.05 according to the following order:

1. Key secondary endpoint 1
2. Key secondary endpoint 2
3. Key secondary endpoint 3

Testing of the first key secondary endpoint will be conducted if the results of the primary endpoint are statistically significant. Testing of these key secondary endpoints will be conducted in a hierarchical manner until p value > 0.05 .

No multiplicity adjustment will be made on other secondary endpoints and exploratory endpoints. The nominal p values will be reported for those endpoints.

10.5. Handling of Missing Data

Before the primary efficacy analysis, the missing values due to participant discontinuation from the study or loss to follow up will be imputed using a multiple imputation washout model. The washout model will be performed on actual values, ie, FFI pain subscale. The changes from baseline are calculated after the imputation. The full details of the multiple imputation washout model will be provided in the SAP.

In addition, sensitivity analyses using MMRM without multiple imputation and tipping point analysis (see details in the SAP) will be performed on the primary and key secondary efficacy endpoints (if applicable) to assess the impact of missing values.

No imputation will be performed for all non-specified secondary and exploratory endpoints. The analyses for those endpoints will be based on observed data.

10.6. Interim Analysis

Not applicable.

10.7. Subgroup Analysis

Analysis for primary endpoint, key secondary endpoints, and frequency of TEAEs will be performed in the following subgroups.

1. Number of injections (1 vs 2 vs 3 vs 4)
2. Baseline FFI pain subscale score: Group 1 vs Group 2
 - a. Group 1: subscale score ≤ 20 for participants without orthotics or subscale score ≤ 26 for participants with orthotics
 - b. Group 2: subscale score ≥ 21 for participants without orthotics or subscale score ≥ 27 for participants with orthotics

Subgroups maybe be combined with adjacent groups if the number of participants in that group is less than 10.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

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

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

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

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

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

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

11.1.1. Financial Disclosure

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

11.1.2. Informed Consent Process

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

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

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

At the Screening Visit (and at other time as may be required by the study or when changes are made to the consent form), participants will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), participants will have an opportunity to ask questions about the study and discuss the contents of these forms with study site personnel. The consent/assent process shall be recorded in source documents. Participants will need to sign a new ICF if more than 28 days elapse between initial ICF signature and date of randomization.

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

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

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

11.1.3. Data Protection

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

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

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

11.1.4. Data Safety Monitoring Board Committee

To supplement the routine study monitoring outlined in this protocol, an independent, unblinded DSMB will be used to monitor safety data on an ongoing basis. The voting members of the DSMB are external to the Sponsor. The members of the DSMB must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DSMB will make recommendations to the Sponsor regarding steps to ensure participant safety and the continued ethical integrity of the study. The DSMB will evaluate the accumulated safety data, consider the overall risk and benefit to study participants, and provide recommendations for continuation of dosing and any necessary steps to ensure participant safety.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DSMB reports, minutes and recommendations will be described in a separate charter that is reviewed and approved by the DSMB. The DSMB will monitor the study at an appropriate frequency, as described in the detailed DSMB charter. The DSMB will also provide recommendations to the Sponsor regarding steps to ensure participant safety and the continued ethical integrity of the study.

11.1.5. Dissemination of Clinical Study Data

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

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

11.1.6. Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the sponsor or sponsor representative. Significant and/or repeated noncompliance will be

investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

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

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

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

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

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

11.1.7. Source Documents

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

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

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained for at least 3 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region, or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

11.1.8. Study and Site Closure

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

11.1.9. Publication Policy

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

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

11.2. Appendix 2: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	Carbon dioxide (CO ₂)	Bilirubin
Prothrombin Time (PT)/	Blood urea nitrogen	Urobilinogen
International Normalized	Creatinine	Nitrite
Ratio (INR)	AST	Blood ^a
	ALT	Leukocytes ^a
	Gamma-glutamyl transferase (GGT)	
	TBL (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Total protein	

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

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

11.3.1. Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a preexisting condition associated temporally with the use of the study intervention whether or not considered related to the study intervention. Note: Any medical condition or laboratory abnormality already present at screening or baseline should be reported as medical history. If the medical condition present at baseline changes in severity or seriousness at any time during the study, it should be reported as an AE. AEs will be captured once a participant has signed the informed consent. AEs include:

- Changes in the general condition of the participant.
- Subjective symptoms offered by or elicited from the participant.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases and/or medical occurrences that occur after the start of the study, including any change in severity or frequency of pre-existing disease.
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

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

An SAE is defined as an AE that:

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

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include any cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias

or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.3.2. Relationship to Study Intervention

The degree of “relatedness” of the AE to study intervention must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to study intervention.
- **Unlikely related** indicates that there are other, more likely causes and study intervention is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study intervention and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by study intervention
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and EN3835.

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

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

11.3.3. Intensity Assessment

The intensity (or severity) of AEs is characterized as Grades 1 to 5 according to the CTCAE Version 5.0. For the AEs not directly referenced in CTCAE, the investigator should use clinical judgment in assessing the intensity of such events using the below categories as a guide:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).*
- **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.†
- **Grade 4** Life-threatening consequences; urgent intervention indicated
- **Grade 5** Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

† Self-care-ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.3.4. Method of Reporting Adverse Events and Serious Adverse Events

11.3.4.1. Method of Reporting Adverse Events

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

11.3.4.2. Method of Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any participant participating in this study, must be reported via email or fax by the investigator using the Endo Serious Adverse Event (SAE)/Reportable Event Form within 24 hours of first becoming aware of the SAE. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

All Endo Serious Adverse Event (SAE)/Reportable Event Forms should be sent to safety@endo.com or faxed to 610-968-7135.

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

11.3.4.3. Follow-up Procedures for Serious Adverse Events

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

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

See Section 6, Section 9.2.6, and Section 9.3.5.

11.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

All events, which may indicate severe liver injury (possible Hy's Law), meeting the following criteria:

- $ALT \geq 3 \times ULN$ or $AST \geq 3 \times ULN$ and $TBL \geq 2 \times ULN$ ($> 35\%$ direct bilirubin),
OR
- $ALT \geq 3 \times ULN$ or $AST \geq 3 \times ULN$ and $INR > 1.5$

must be reported as an SAE as outlined in Section [11.3.4](#).

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

11.6. Appendix 6: Abbreviations

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUX-I	Clostridial type I collagenase
AUX-II	Clostridial type II collagenase
BLA	Biologics license application
CFR	Code of Federal Regulations
CI	Confidence interval
COA	Clinical Outcome Assessment
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dupuytren's contracture
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
FAS	Full Analysis Set
FFI	Foot Function Index
FFI-SF-23	Foot Function Index-Short Form
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LS	Least squares
LSM	Least squares mean

Abbreviation	Definition
mITT	Modified Intent-to-Treat Population
MMRM	Mixed effect model for repeated measures
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Disease
NRS	Numerical Rating Scale
PD	Peyronie's disease
PF	Plantar fibromatosis
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected, unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

12. INVESTIGATOR'S STATEMENT

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

_____/_____/_____
Investigator's Signature Date

Typed Name of Investigator

13. REFERENCES

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