NCT #: NCT05152173

SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. 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

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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, analyses of the data, and preparation of the clinical study report.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUX-I	Clostridial type I collagenase
AUX-II	Clostridial type II collagenase
BMI	Body mass index
BLA	Biologics license application
CFR	Code of Federal Regulations
CI	Confidence interval
CGIC	Clinician Global Impression of Scale Change
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcome Assessment
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
eCRF	electronic Case Report Form
EOS	End of Study
ET	Early Termination
FAS	Full Analyses Set
FFI	Foot Function Index
FFI-SF-23	Foot Function Index-Short Form-21 items
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
LSM	Least Square Mean
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	modified Intent-to-Treat
MMRM	Mixed Effect Model for Repeated Measures
MNAR	Missing Not At Random
NC	Not Calculable
NRS	Numerical Rating Scale
PCI	Potentially Clinically Important
PF	Plantar Fibromatosis
PGIC	Patient Global Impression of Change

Abbreviation	Definition
PGIS	Patient Global Impression of Severity
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analyses System
SSTS	Subject Satisfaction With Treatment Scale
SoA	Schedule of Assessments
TEAE	Treatment-Emergent Adverse Event
TPA	Tipping Point Analyses
ULN	Upper Limit of Normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to evaluate the efficacy, safety, tolerability of EN3835 vs Placebo in the treatment of adult participants with symptomatic plantar fibromatosis.

The study rationale is described in the EN3835-222 Clinical Study Protocol Amendment 4 dated June 10, 2022.(1)

2. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, and exploratory objectives and corresponding endpoints are outlined in Table 1 below:

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the improvement with EN3835 vs placebo in the Foot Function Index (FFI)[a] pain subscale.	• 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	
• To assess the improvement with EN3835 vs placebo in the FFI pain subscale over time.	• 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.
• To assess the overall improvement in the combined score of the FFI pain and difficulty subscales with EN3835 vs placebo	• 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.
• To assess investigator assessment of improvement with EN3835 treatment vs placebo.	• 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.
• To assess the change in nodule hardness after administration of EN3835 vs placebo.	• 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	
• To assess the safety and tolerability of EN3835 in participants with plantar fibromatosis.	• 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.
• To assess the immunogenicity of EN3835 in participants with plantar fibromatosis.	• 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.

Table 1: Objectives and Endpoints (Continued)

Objective	Endpoint
Exploratory	
• To assess the overall improvement in the FFI total score with EN3835 vs placebo	• The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 57 on the FFI total score of 21 items with the score of each item 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 total score with EN3835 vs placebo.
• To assess the overall improvement in severity of plantar fibromatosis on the Patient Global Impression of Severity (PGIS) PF Overall scale.	• 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.
• To assess the overall improvement in the severity of foot pain with EN3835 vs placebo in the PGIS foot pain subscale	• 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.
• To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS difficulty subscale	• 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.
• To assess the overall improvement in the severity of difficulty with EN3835 vs placebo in the PGIS activity limitation subscale	• 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.
• To assess the change in the Patient Global Impression of Change (PGIC) PF Overall with EN3835 treatment vs placebo.	• 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.
• To assess the change in the overall severity of foot pain on the Foot Pain Subscale of the PGIC.	• 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.
• To assess the change in the overall severity of difficulty on the Difficulty Subscale of the PGIC.	• 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.

Table 1: Objectives and Endpoints (Continued)

Objective	Endpoint
• To assess the change in the overall severity of activity limitation on the Activity Limitation Subscale of the PGIC.	• 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.
• To assess the overall improvement in foot pain with EN3835 vs placebo on the Pain Intensity Numerical Rating Scale (NRS).	• 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.
• To assess participant satisfaction with EN3835 treatment vs placebo.	• 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.
• To assess the improvement with EN3835 vs placebo in the FFI activity limitation subscale in participants on the activity limitation subscale at baseline.	• 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.
• To assess the improvement with EN3835 vs placebo in the FFI difficulty subscale in participants on the difficulty subscale at baseline.	• 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.
• To assess the change in nodule size after administration of EN3835 vs placebo.	• 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.
• To assess the change in nodule consistency (by palpation) after administration of EN3835 vs placebo.	• 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 the FFI.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a phase 2, double-blind, randomized, placebo-controlled study designed to assess the efficacy, safety and tolerability of EN3835 vs placebo in the treatment of plantar fibromatosis.

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 4). 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.

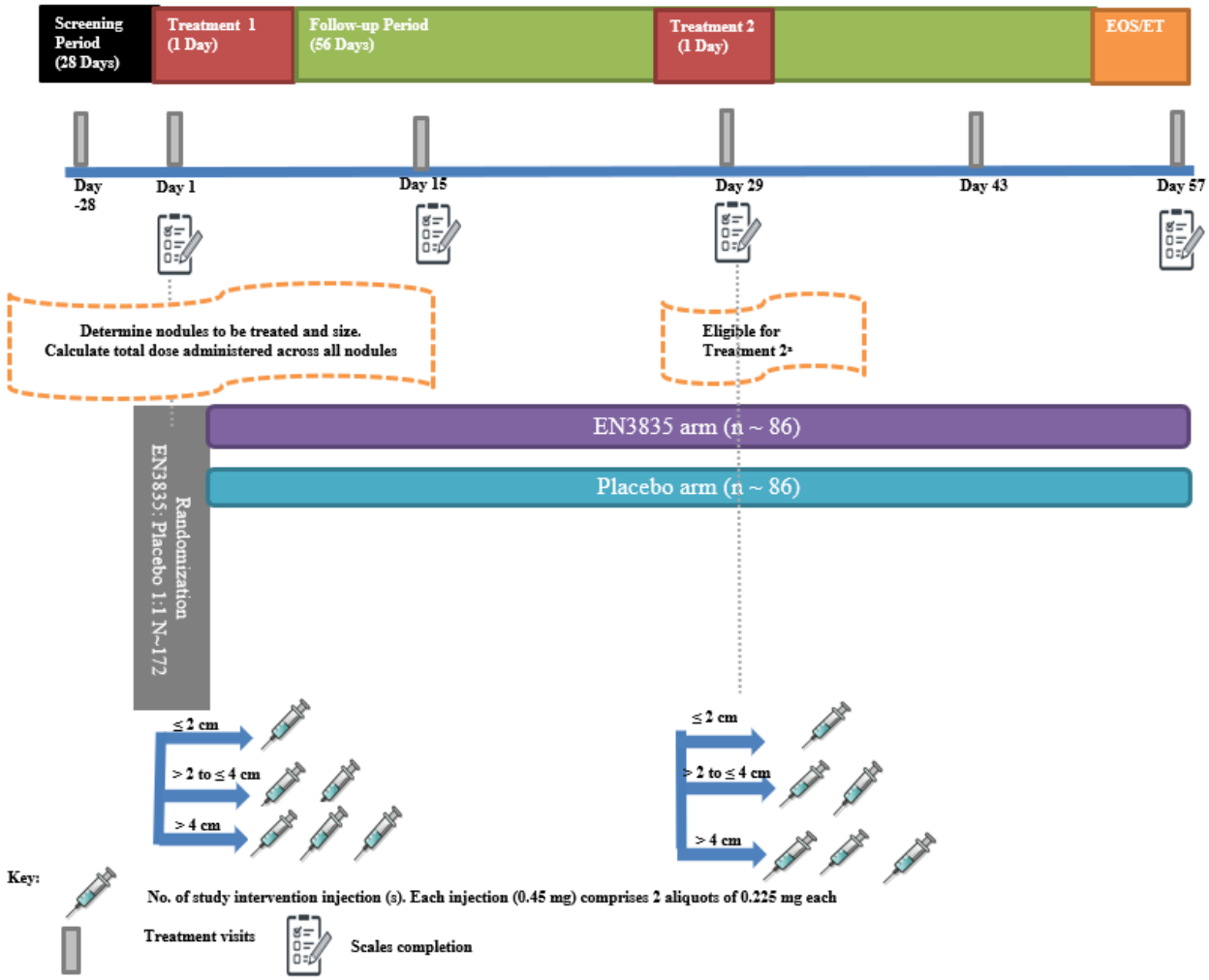
At the Day 29 visit, if the participant has any previously treated nodule(s) that remains palpable and measurable by caliper with a consistency of hard, firm throughout, moderately firm, or soft that is/are deemed appropriate for treatment by the investigator, and the Treatment 2 Criteria are met, a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

For all participants, at the time points listed in the Schedule of Assessments (SoA) Table 2, 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).

The overall study design is presented in Figure 1.

Figure 1: Overall Study Design



[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.

Table 2 describes the SoA and assessments performed throughout the study.

Table 2: 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] 28 days after the last dose (±5)
			D15 (±1)	Treatment Visit 2 D29 (±1)	D43 (±1)		
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	
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	

Table 2: Schedule of Assessments: Screening to End of Study (Continued)

	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)
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 Protocol 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 Protocol 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 and 30 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 Protocol 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 Protocol 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 Protocol Section 8.2). D = day(s); EOS = end of study; ET = early termination.

3.2. Eligibility Criteria for Participant Selection

3.2.1. Participants 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.

3.2.2. Participants Exclusion Criteria

A participant is ineligible for study participation if, the participant meets the following criteria at the Screening Visit:

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) ≥ 3 × upper limit of normal (ULN)
   b. total bilirubin (TBL) ≥ 2 × ULN (> 35% direct bilirubin)
   c. aspartate aminotransferase (AST) ≥ 3 × 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:

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

Other Considerations:

1. 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).

3.2.3. 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.

3.2.4. 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.

3.3. Selection of Nodule

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 3.

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 described in Table 3. 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 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.

3.4. Study Intervention Administration

Study intervention will be injected intralesionally directly into the nodule using a 27-gauge, 0.5-inch needle.

Table 3: Study Intervention Administration

Treatment Concentration	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.

[a] Each injection (0.45 mg) of study intervention will be administered as 2 aliquots of 0.225 mg each.

3.4.1. Study Intervention per Nodule

The dose of study intervention that will be administered per nodule based on nodule size is presented in Table 4. The total dose received by a participant is determined by size of nodule and number of injections.

Table 4: 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

3.5. Determination of Sample Size

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”).

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, 86 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.

3.6. Blinding and Randomization

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.

3.7. Nodule Assessments

Examination and evaluation of the selected nodule(s) will be performed at the time points specified in the SoA (Table 2). The description of these assessments as follows:

3.7.1. 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.

3.7.2. Consistency of the Selected Nodule

At the time points listed in the Schedule of Assessments (SoA) (Table 2), 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 0 (“Non-palpable”) to 4 (“Hard”) as follows in Table 5.

Table 5: Nodule Consistency

Rating	Description
4	Hard
3	Firm Throughout
2	Moderately Firm
1	Soft
0	Non-palpable

3.7.3. Caliper Measurements of the Selected Nodule

At the time points listed in the SoA (Table 2) 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 at each time of examination.

3.7.4. Durometer Measurements

At the time points listed in the SoA (Table 2), 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.

3.8. 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.

3.8.1. Foot Function Index

A Foot Function Index (FFI) was developed to measure the impact of foot pathology on function in terms of pain, disability and difficulty limitation. The participant will complete the scale prior to evaluation by the investigator.

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 (2) (3) 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.

At the time points included in the SoA (Table 2), each participant will be asked to complete the FFI scale, The participant will complete the scale prior to evaluation by the investigator.

The FFI will be used in this study to assess the impact of EN3835 or placebo on PF. This assessment will be completed at the Screening Visit, Treatment 1 (Day 1), Follow-up Visits (Days 15, 29, and 43) and EOS Visit (Day 57). Each item will be scored on a 5-point verbal rating scale; higher scores are indicative of greater impairment. The FFI comprises 3 subscales as follows:

- Activity limitation subscale (3 items) with a total score of 12: Each response ranges from 0 ("Never") to 4 ("Always").
- Difficulty subscale (9 items) with a total score of 36: Each response ranges from 0 ("No Difficulty") to 4 ("A lot of difficulty").
- Pain subscale with Orthotics (9 items) with a total score of 36: Each response ranges from 0 ("None") to 4 ("Extreme"). **OR**
- Pain subscale without Orthotics (7 items) with a total score of 28: Each response ranges from 0 ("None") to 4 ("Extreme"): When the participant marks "does not wear orthotics" items pertaining to orthotics are not scored and are not included in the total score.

Subscale questions of the Foot Function Index and scoring is provided in Table 6.

Table 6: Foot Function Index (FFI)

Subscale	No.	Question	Score
Activity Limitation	1	Stay indoors most of the day because of foot problems?	0 ("Never") to 4 ("Always")
	2	Stay off one or both of my feet most of the day because of foot problems?	
	3	Limit your activities because of your foot problems?	
Difficulty	1	Walking around the house?	0 ("No Difficulty") to 4 ("A lot of difficulty")
	2	Walking outside on uneven ground?	
	3	Walking four or more blocks?	
	4	Climbing stairs?	
	5	Descending stairs?	
	6	Standing on tiptoes?	
	7	Getting out of a chair?	
	8	Climbing up or down curbs?	
	9	Walking or running fast?	
Pain	1	At its worst?	0 ("None") to 4 ("Extreme")
	2	Before you get up in the morning?	
	3	When you walk barefoot?	
	4	When you stand barefoot?	
	5	When you walk wearing shoes?	
	6	When you stand wearing shoes?	
	7	When you walk wearing orthotics? ☐ Do not wear orthotics	
	8	When you stand wearing orthotics?	
	9	At the end of the day?	

3.8.2. Patient Global Impression of Severity (PGIS) - PF Overall

At the time points included in the SoA (Table 2) (prior to evaluation by the investigator), each participant will be asked to describe the severity of plantar fibromatosis in the past week on, the PGIS-PF Overall, a 5 point scale ranging from 0 ("None") to 4 ("Severe") as follows in Table 7.

Table 7: Patient Global Impression of Severity (PGIS) - PF Overall

Rating	Description
0	None
1	Minimal
2	Mild
3	Moderate
4	Severe

3.8.3. Patient Global Impression of Severity (PGIS) - Foot Pain Subscale

At the time points included in the SoA (Table 2) (prior to evaluation by the investigator), each participant will be asked to describe the overall severity of foot pain in the past week, on the PGIS-Foot Pain, a 5 point scale ranging from 0 ("None") to 4 ("Severe") as follows in Table 8.

Table 8: Patient Global Impression of Severity (PGIS) - Foot Pain Subscale

Rating	Description
0	None
1	Minimal
2	Mild
3	Moderate
4	Severe

3.8.4. Patient Global Impression of Severity (PGIS) - Difficulty Subscale

At the time points included in the SoA (Table 2) (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 PGIS-Difficulty, a 5-point scale ranging from 0 ("None") to 4 ("Severe") as follows in Table 9.

Table 9: Patient Global Impression of Severity (PGIS) - Difficulty Subscale

Rating	Description
0	None
1	Minimal
2	Mild
3	Moderate
4	Severe

3.8.5. Patient Global Impression of Severity (PGIS) - Activity Limitation Subscale

At the time points included in the SoA (Table 2) (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 PGIS-Activity limitation, a 5-point scale ranging from 0 (“None”) to 4 (“Severe”) as follows in Table 10.

Table 10: Patient Global Impression of Severity (PGIS) - Activity Limitation Subscale

Rating	Description
0	None
1	Minimal
2	Mild
3	Moderate
4	Severe

3.8.6. Patient Global Impression of Change (PGIC) - PF Overall

At the time points included in the SoA (Table 2) (prior to evaluation by the investigator), each participant will be asked to describe the severity of plantar fibromatosis in the past week on PGIC-PF Overall, a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as follows in Table 11.

Table 11: Patient Global Impression of Change (PGIC) - PF Overall

Rating	Description
−3	Very Much Worse
−2	Much Worse
−1	Minimally Worse
0	No Change
+1	Minimal Improvement
+2	Much Improvement
+3	Very Much Improvement

3.8.7. Patient Global Impression of Change (PGIC) - Foot Pain Subscale

At the time points included in the SoA (Table 2) (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 PGIC- foot pain subscale , a 7-point scale, ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as follows in Table12.

Table 12: Patient Global Impression of Change (PGIC) - Foot Pain Subscale

Rating	Description
−3	Very Much Worse
−2	Much Worse
−1	Minimally Worse
0	No Change
+1	Minimal Improvement
+2	Much Improvement
+3	Very Much Improvement

3.8.8. Patient Global Impression of Change (PGIC) - Difficulty Subscale

At the time points included in the SoA (Table 2) (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") as follows in Table 13.

Table 13: Patient Global Impression of Change (PGIC) - Difficulty Subscale

Rating	Description
−3	Very Much Worse
−2	Much Worse
−1	Minimally Worse
0	No Change
+1	Minimal Improvement
+2	Much Improvement
+3	Very Much Improvement

3.8.9. Patient Global Impression of Change (PGIC) - Activity Limitation Subscale

At the time points included in the SoA (Table 2) (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") as follows in Table 14.

Table 14: Patient Global Impression of Change (PGIC) - Activity Limitation Subscale

Rating	Description
−3	Very Much Worse
−2	Much Worse
−1	Minimally Worse
0	No Change
+1	Minimal Improvement
+2	Much Improvement
+3	Very Much Improvement

3.8.10. Pain Intensity Numerical Rating Scale

At the time points included in the SoA (Table 2) (prior to evaluation by the investigation), 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) as follows in Table 15.

Table 15: Pain Intensity Numerical Rating Scale

Rating	Description
0	No Pain
1	
2	
3	
4	

Table 15: Pain Intensity Numerical Rating Scale (Continued)

Rating	Description
5	
6	
7	
8	
9	
10	Worst Pain imaginable

3.8.11. Subject Satisfaction with Treatment Scale

At the time points included in the SoA (Table 2) (prior to evaluation by the investigator), each participant will be asked to rate his/her satisfaction with treatment of each foot on a 5-point scale ranging from -2 ("Very Dissatisfied") to +2 ("Very Satisfied") as follows in Table 16.

Table 16: Subject Satisfaction with Treatment Scale

Rating	Description
−2	Very Dissatisfied
−1	Quite Dissatisfied
0	Neither Satisfied nor Dissatisfied
+1	Quite Satisfied
+2	Very Satisfied

3.9. Investigator Assessments

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

3.9.1. Clinician Global Impression of Scale Change

At the time points included in the SoA (Table 2), 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 in Table 17.

Table 17: Clinician Global Impression of Scale Change

Rating	Description
−3	Very Much Worse
−2	Much Worse
−1	Minimally Worse
0	No Change
+1	Minimal Improvement
+2	Much Improvement
+3	Very Much Improvement

3.10. Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit. Medical history will include relevant diagnoses and/or procedures/therapies with onset/resolutions dates.

Historical and current medical conditions including date of last menstrual period for female participants will be recorded.

Any ongoing plantar fibromatosis disease history will also be obtained from the participant during the screening period with relevant diagnoses and onset date.

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.

3.11. Substance Use

History of tobacco, alcohol use (never, current, former) and drug abuse (both illegal and prescription) will be collected during the Screening Visit. The following information will be recorded:

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

3.12. Prior/Concomitant Medications and Procedures

3.12.1. 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.

3.12.2. 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.

3.12.3. 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.

3.13. Adverse Events

All adverse events (AEs) and serious adverse events (SAEs) will be collected by the investigator from the time of signing the informed consent through the EOS Visit (Day 57), if eligible. 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.

3.13.1. Adverse Events Definition

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 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)

3.13.2. Serious Adverse Events

SAEs are AEs that meet any of the following criteria:

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

3.13.3. Adverse Events of Special Interest

AESIs are AEs that for meet any of the following criteria:

- Any severe hypersensitivity reactions.
- Plantar fascial tears.

All AESIs will be evaluated for seriousness and severity.

3.13.4. 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 18. 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 18: 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[a]	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling[b]	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	

Table 18: 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)
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental activities of daily living	Severe localized edema and intervention indicated; limiting self-care activities of daily living	
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
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.

1.1.1. Anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. To identify individuals experiencing such a reaction, use the criteria provided by Sampson et al (2006) in Table 19. Anaphylaxis will be reported as SAE in the eCRF.

Table 19: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 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) *AND AT LEAST ONE OF THE FOLLOWING* 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 to collagenase or any other excipient of EN3835 *for that participant* (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 to *collagenase or any other excipient of EN3835 for that participant* (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

3.14. Clinical Safety Laboratory Tests

Clinical laboratory tests will be performed by a designated central laboratory as per Table 20. Blood and urine samples will be collected for testing clinical laboratory parameters at Screening and the Day 57 Visit. Any new clinically significant laboratory abnormality observed, will be considered as an AE or SAE as appropriate.

Table 20: Change Clinical Safety Laboratory Parameters

Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin Hematocrit Red blood cell White blood cell (WBC) Platelets WBC Differential Prothrombin time (PT)/International Normalized Ratio (INR)	Glucose Sodium Potassium Calcium Chloride Carbon dioxide (CO_2) Blood urea nitrogen Creatinine AST ALT Gamma-glutamyl transferase (GGT) TBL (direct bilirubin reflex if elevated) Albumin Alkaline phosphatase (ALP) Total protein	Glucose Protein Specific gravity pH Ketones Bilirubin Urobilinogen Nitrite Blood[a] Leukocytes[a]

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

3.15. Pregnancy Test

All female participants of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the SoA (Table 2). Urine pregnancy tests will be provided by the central laboratory to the sites. Results must be available prior to protocol mandated study treatment.

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 treatment but will continue to be followed as described in Section 8.3.5 of the study protocol.(1)

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

3.16. Height, Body Weight and Body Mass Index

Height and body weight measurements will be collected at the Screening Visit. Body Mass Index (BMI) will be calculated using the height and weight at the Screening Visit.

3.17. Vital Signs

Vital signs measurements include systolic and diastolic blood pressure, respiratory rate, pulse, and body temperature will be collected after the participant has been sitting for 5 minutes in the seated position.

Vital signs measurements will be collected at all scheduled visits as per the SoA (Table 2). On the day that study intervention will be administered, vital signs measurements will be collected in a supine position prior to injection, at 15 (±5) and 30 (±5) minutes post injection.

The investigator will review all vital sign values for clinical significance. Any clinically significant abnormality observed in a vital sign will be considered as an AE or SAE as appropriate.

3.18. Physical Examination

A complete physical examination (by body system) will be performed at the time points outlined in the SoA (Table 2). This evaluation may include an examination of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

Physical examination findings will be recorded as normal, abnormal, or not done as not standard of care.

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

3.19. Immunogenicity

Immunogenicity variables include binding anti-AUX-I /anti-AUX-II antibodies (ie, anti-drug antibodies) and neutralizing antibody results.

Serum Samples will be collected at Day 1 and at the Day 57 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.

4. STUDY PARAMETERS

4.1. Participant Disposition

A participant is considered to have completed the study if the participant has completed the EOS Visit. The EOS Visit (Day 57) is defined as the completion of the final assessment for the last participant enrolled in the study. All participants are expected to remain in the study until Day 57, regardless of whether 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 (eg, last participant's last visit or 28-day follow-up Safety Visit). This study completion date applies whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Participants who discontinue/withdrawal from the study after dosing will be encouraged to complete all remaining study visits and evaluations and provide any additional follow-up information required by the study, unless the participant specifically indicates that they will not participate in any further evaluations.

All EOS/ET procedures will be conducted as detailed in the SoA (Table 2). The reason and date for early withdrawal will be recorded in the eCRF.

Screen failures are defined as participants who consent to participate in this study but are not randomized. A participant who is a screen failure may be rescreened with approval of the sponsor. Participants may be rescreened only once and the reason for the rescreen failure will also be recorded if any participant failed rescreening. The participant must repeat all screening procedures. The period from the start of rescreening related procedures to injection of study intervention must not exceed 28 days. Participants who were in screening (those who had completed or were in the process of screening) for the study at the time of any COVID-19 interruption, but who had not been dosed with study intervention, may be rescreened. The need to repeat screening assessments will be determined on an individual basis.

4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics include the following parameters in Table 21.

Table 21: Demographic and Baseline Characteristics

Continuous Parameter	Categorical Parameter
Age (years)	Gender
Height (cm)	Race
Body weight (kg)	Ethnicity
BMI in kg/m^2	Report of alcohol and tobacco use • Alcohol use (Never, Current, and Former) • Tobacco use (Never, Current, and Former)
Nodule Size (Caliper measurements)	Affected Foot • Left • Right • Both

Table 21: Demographic and Baseline Characteristics (Continued)

Continuous Parameter	Categorical Parameter
Nodule Hardness (Durometer measurements)	Nodular Consistency • Hard • Firm Throughout • Moderately Firm • Soft • Non-palpable
FFI Scores at baseline • Total Pain Subscale Score (by orthotics use and overall) • Total Difficulty Subscale Score • Total Activity Limitation Subscale Score • Total Combined (Pain & Difficulty) Score • Total Composite Score	Total Number of Nodules Treated • 1 • 2 • 3 • 4 • >4
Pain Intensity Numerical Rating Scale	Nodule Size Category • Up to 2 cm • >2 cm to ≤4 cm • >4 cm

4.3. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock. Protocol deviations will be derived from the eCRF data, electronic vendor data, and from the clinical monitoring reports. All deviations from these sources will be reconciled and duplicate deviations will be removed. When a deviation is both found in the database and in clinical monitoring reports, in most cases the text of the deviation from the database will be retained. The exception to this rule will occur if the deviation from the monitoring report provides important information not found in the database.

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

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

The Endo study team will provide final protocol deviation assignments and classify them as either important or not important during protocol deviation review meetings held throughout the study and prior to the database lock.

All study assessments conducted outside of the allowed windows outlined in the SoA (Table 2) 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.

4.4. Prior/Concomitant Medications/Procedures

All medications will be coded using the World Health Organization (WHO) Drug Dictionary, by active ingredient and WHO anatomical therapeutic chemical (ATC) classification of ingredients.

Any prior medication/procedure taken/done prior to first injection (Day 1) will be reported as prior medication/procedure.

A concomitant medication/procedure is any medication/procedure taken/done on or after first injection (Day 1) until the EOS Visit or the medication/procedure which were ongoing on Day 1.

4.5. Prior Plantar Fibromatosis Treatment

Prior plantar fibromatosis treatment will be obtained from the prior/concomitant and/or prior concomitant procedure pages of the eCRF. If on either of these pages a medication or procedure is reported with the indication 'Plantar Fibromatosis' prior to screening, then the medication or procedure will be considered a prior plantar fibromatosis treatment.

All plantar fibromatosis treatment procedures will also be classified. The classification will be reviewed and approved by the study medical monitor. Any plantar fibromatosis treatment used on or after screening will be noted and reported as a protocol deviation.

4.6. Nodule Assessments

4.6.1. Nodular Consistency of the Selected Nodule

The investigator will classify the nodule as "hard", "firm throughout", "moderately firm", "soft" or "non-palpable" at scheduled visits as per the SoA (Table 2). All nodule level assessment will be captured in the eCRF.

A participant-level responder is defined as a participant with at least 1-level reduction in nodular consistency from baseline for any treated nodule at follow-up visits. The corresponding baseline value will be used a controlling factor for the responder analyses.

A foot-level responder is defined as a participant with at least 1-level reduction in nodular consistency from baseline for any treated nodule in that foot at a follow-up visit. The corresponding baseline value will be used as a controlling factor for the responder analyses.

A nodule-level responder is defined as a treated nodule with at least 1-level reduction in nodular consistency from baseline at a follow-up visit. The corresponding baseline value will be used as a controlling factor for the responder analyses.

For participant level classification of nodule in demographic/baseline characteristics table and listing, worst case approach will be used.

4.6.2. Nodule Size by Caliper Measurement

Nodule size (ie, length and width) will be determined by handheld calipers and will be assessed for each treated nodule.

The size of nodule will be the larger of either nodule length or nodule width.

The area of nodule will be calculated as:

Area of the Nodule = (Nodule Width * Nodule Length * pi)/4 where pi=22/7

The nodule level data will be summarized by categories of nodule size, treatment group and visit. Only treated nodules will be included for data analyses and summarized at participant level. The change from Baseline (Day 1) in nodule size at EOS (Day 57) and other post baseline visits will be analyzed.

4.6.3. Nodular Hardness by Durometer Assessment

Nodule hardness will be quantified using durometer and will be assessed for each treated nodule. The nodule level data will be summarized by treatment and visit, the change from Baseline (Day 1) in nodule hardness at EOS (Day 57) and other post baseline visits of the treatment will be analyzed. The average of all treated nodule hardness will be used for data analyses and summarization at participant level.

4.6.4. Number of Nodules

The number of treated nodules will be based study intervention data from eCRF. Foot level data will be summarized by categories of nodule size, treatment group, and visit. The total number of nodules by foot will be used for data analyses and summarization at participant level. In addition, all nodules that were assessed by foot will be listed.

4.7. Participant Reported Outcome Assessments

The FFI, PGIS, PGIC and NRS assessment will be captured on a participant level. The Subject Satisfaction Scale will be captured at the foot level.

4.7.1. Foot Function Index

4.7.1.1. Pain Subscale

The participant will assess the foot pain using a 5-point scale ranging from 0 (“None”) to 4 (“Extreme”) at each visit as per the SoA (Table 2).

4.7.1.2. Difficulty Subscale

The participant will assess the difficulty of feet when performing the activities using a 5-point scale ranging from 0 (“No difficulty”) to 4 (“A lot of difficulty”) at each visit as per the SoA (Table 2).

4.7.1.3. Activity Limitation Subscale

The participant will assess the activity limitation of feet using a 5-point scale ranging from 0 (“Never”) to 4 (“Always”) at each visit as per the SoA (Table 2).

4.7.1.4. Subscale Score and Individual Item Scores on FFI

The impact of the selected nodule(s) will be assessed using the FFI, which is a foot function assessment instrument. The FFI is comprised of 21 items and is used to assess Pain, Difficulty and Activity limitation.

The subscale score (%) is calculated by adding the answered item scores and dividing by the sum of the maximum score of the items answered.

The calculation is:

$$\text{Subscale score (\%)} = \frac{\text{Sum of answered item scores}}{\text{Sum of maximum score of answered items}} \text{ x } 100$$

The maximum total score of each subscale if all items answered is given as below:

- Activity limitation subscale (3 items) with a maximum total score of 12
- Difficulty subscale (9 items) with a maximum total score of 36
- Pain subscale with Orthotics (9 items) with a maximum total score of 36 **OR**
- Pain subscale without Orthotics (7 items) with a maximum total score of 28

Total subscale score is defined as the sum of the scores of answered items in each subscale (ie, Pain subscale, Difficulty subscale, and Activity limitation subscale). In addition, the total pain subscale score will be normalized by a multiplying factor of 9/7 for participants who have answered 'No' or didn't answer the questions related to orthotics use. The normalized total pain subscale score will be utilized for analyses and for calculating the total composite score and total combined score.

4.7.1.5. Composite Score on FFI

The composite score on FFI is defined as the weighted average of **i** subscale scores (%) (ie,, Activity Limitation subscale, Difficulty subscale, and Pain subscale), with number of answered items as a weighted average.

The calculation is:

$$\text{Composite score (\%)} = \frac{\sum_{i=1}^{3}[\text{Subscale score (\%) (i) x Number of answered items in the subscale(i)}]}{\sum_{i=1}^{3} \text{Number of answered items in the subscale(i)}}$$

where, i=1, 2, 3 (for each subscale score (%)).

For participants who have answered 'No' or didn't answer the questions related to orthotics use, the number of answered items in the pain subscale will be normalized by a multiplying factor of 9/7.

The Total Composite Score is defined as the sum of all total subscale scores (Activity Limitation subscale, Difficulty subscale, and Pain subscale).

4.7.1.6. Pain and Difficulty Combined Score on FFI

The Combined score on the Pain and Difficulty subscale is defined as the weighted average of **i** subscale scores (%) (ie, Pain and Difficulty subscale), with the number of answered items used in calculating a weighted average.

The calculation is:

$$\text{Combined score (\%)} = \frac{\sum_{i=1}^{2}[\text{Subscale score (\%) (i) x Number of answered items in the subscale(i)}]}{\sum_{i=1}^{2} \text{Number of answered items in the subscale(i)}}$$

where, i=1, 2 (for each subscale score (%)). For participants who have answered 'No' or didn't answer the questions related to orthotics use, Number of answered items in the pain subscale will be normalized by a multiplying factor of 9/7.

The Total Combined (Pain and Difficulty) Score is defined as the sum of both total subscale scores.

4.7.2. Patient Global Impression of Severity (PGIS)

4.7.2.1. Patient Global Impression of Severity (PGIS)- Plantar Fibromatosis Overall

The participant will assess the overall severity of plantar fibromatosis using a 5-point scale ranging from 0 ("None") to 4 ("Severe") as per the SoA (Table 2).

4.7.2.2. Patient Global Impression of Severity (PGIS) – Foot Pain Subscale

The participant will assess the severity of foot pain using a 5-point scale ranging from 0 ("None") to 4 ("Severe") as per the SoA (Table 2).

4.7.2.3. Patient Global Impression of Severity (PGIS) – Difficulty Subscale

The participant will assess the overall difficulty for foot/feet for doing physical activities using a 5-point scale ranging from 0 ("None") to 4 ("Severe") as per the SoA (Table 2).

4.7.2.4. Patient Global Impression of Severity (PGIS) – Activity Limitation Subscale

The participant will assess the change in overall limitations in daily activities using a 5-point scale ranging from 0 ("None") to 4 ("Severe") as per the SoA (Table 2).

4.7.3. Patient Global Impression of Change (PGIC)

4.7.3.1. Patient Global Impression of Change (PGIC)- PF Overall

The participant will assess the overall severity of plantar fibromatosis using a 7-point scale ranging from −3 ("Very Much Worse") to +3 ("Very Much Improvement") as per the SoA (Table 2).

A responder is defined as a participant with a response of "Minimal Improvement", "Much Improvement" or "Very Much Improvement" in the PGIC-PF Overall. All participants who withdrew early from the study will be considered as non-responders.

4.7.3.2. Patient Global Impression of Change (PGIC) – Foot Pain Subscale

The participant will assess the overall severity of foot pain using a 7-point scale ranging from −3 ("Very Much Worse") to +3 ("Very Much Improvement") as per the SoA (Table 2).

A responder is defined as a participant with a response of "Minimal Improvement", "Much Improvement" or "Very Much Improvement" on the PGIC Foot Pain Subscale. All participants who withdraw early from the study will be considered as non-responders.

4.7.3.3. Patient Global Impression of Change (PGIC) – Difficulty Subscale

The participant will assess the overall difficulty for foot/feet for doing physical activities using a 7-point scale ranging from −3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as per the SoA (Table 2).

A responder is defined as a participant with a response of “Minimal Improvement”, “Much Improvement” or “Very Much Improvement” on the PGIC Difficulty Subscale. All participants who withdraw early from the study will be considered as non-responders.

4.7.3.4. Patient Global Impression of Change (PGIC) – Activity Limitation Subscale

The participant will assess the change in overall limitations in daily activities using a 7-point scale ranging from −3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as per the SoA (Table 2).

A responder is defined as a participant with a response of “Minimal Improvement”, “Much Improvement” or “Very Much Improvement” on the PGIC Activity Limitation. All participants who withdrew early from the study will be considered as non-responders.

4.7.4. Pain Intensity Numerical Rating Scale (NRS)

The participant will assess worst severity of overall foot pain ranging from 0 (“No Pain”) to 10 (“Worst Pain Imaginable”) as per the SoA (Table 2).

4.7.5. Subject Satisfaction with Treatment Scale (SSTS)

The participant will assess their satisfaction with treatment per treated foot using a 5-point scale ranging from -2 (“Very Dissatisfied”) to +2 (“Very Satisfied”) as per the SoA (Table 2).

The participant will assess the satisfaction with treatment separately for each treated foot, the assessment can be combined at participant level using worst case approach. If participant recorded a response as ‘Very Satisfied’ in one foot and ‘Quite Satisfied’ in another foot, then response will be considered as ‘Quite Satisfied’.

A responder is defined as a participant (by foot/feet) with a response of “Quite Satisfied” or “Very Satisfied” on the SSTS. All participants who withdraw early from the study will be considered as non-responders.

4.8. Investigator Assessments

4.8.1. Clinician Global Impression of Scale Change (CGIC)

The investigator will assess the degree of improvement per treated foot using a 7-point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) as per the SoA (Table 2).

As CGIC will be assessed for each treated foot. If participant is treated for both feet, then the assessment can be combined at participant level using worst case approach, if a response as ‘Minimal Improvement’ recorded in one foot and ‘Very Much Improvement’ in another foot, then response will be considered as ‘Minimal Improvement’.

A responder is defined as a participant (by foot/feet) with a response of "Minimal Improvement", "Much Improvement" or "Very Much Improvement" on the CGIC. All participants who withdraw early from the study will be considered as non-responders.

4.9. Safety Parameters

4.9.1. Adverse Events

AE verbatim terms as reported by the investigator will be mapped to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

4.9.1.1. Treatment-Emergent Adverse Events

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).

Refer to Section 6.3.4.1 to identify TEAE status when start date of an AE is unknown.

4.9.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as Grade 1 to 5 according to the CTCAE Version 5.0.

For AEs with missing grade, no imputation will be performed, and the AE will be analyzed with the missing grade. If the intensity of an AE changes, then the most severe intensity during the continuous episode will be recorded.

4.9.1.3. Relationship to Study Intervention

The causal relationship with study intervention will be classified by the investigator and will be reported as follows:

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

Related adverse events are TEAEs with the relationship described by the investigator as "probably related" or "possibly related". "not related" or "unlikely related" causality assessments are considered as not related.

Any missing relationship of an AE to study intervention will be considered as related to study intervention for the analyses, following worst case principle.

4.9.2. Clinical Laboratories and Vital Signs

4.9.2.1. Potentially Clinically Important Laboratory Values

Sponsor determined potentially clinically important (PCI) laboratory values are presented in Table 22.

Table 22: Potentially Clinically Important Laboratory Criteria

Parameter	PCI Low: ≤Or =	PCI High: ≥ Than Or =
Hemoglobin (g/L)	100	190
Hematocrit (%)	30	60
Platelets (10^9/L)	100	650
ALT (U/L)		3×ULN
AST (U/L)		3×ULN
Creatinine (µmol/L)		200
BUN (mmol/L)		14

ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; ULN=upper limit of normal

4.9.2.2. Potentially Clinically Important Vital Sign Values

Vital sign values are PCI, if they meet both the observed value criteria and the change from Baseline. The sponsor determined PCI criteria are presented in Table 23.

Table 23: Potentially Clinically Important Vital Sign Criteria

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

PCI=potentially clinically important; bpm=beats per minute; brpm=breaths per minute.

4.10. Immunogenicity

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibodies. The subset of the samples will be tested for neutralizing antibodies if the sample results are positive for anti-AUX-I or anti-AUX-II.

5. ANALYSES POPULATIONS

The study will use the following analyses populations for data summaries and analyses.

Table 24: Analyses Populations

Population	Definition	Displays
Safety Population	The Safety Population will include all participants who receive at least 1 injection of EN3835 or placebo.	All demographic, baseline characteristics, safety and immunogenicity analyses will be summarized based on this population. Participants will be included in the safety analyses based on the actual treatment received.
Intent-to-Treat (ITT) Population	The Intent-to-Treat (ITT) Population will include all randomized participants. Treatment group assignment will be based on the randomized treatment.	The ITT population will be used for analyses of the primary and secondary endpoints.
Full Analyses Set (FAS) Population	The Full Analyses Set (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.	The FAS population will be used for analyses of the primary and secondary endpoints.
Modified Intent-to-Treat (mITT) Population	The modified Intent-to-Treat (mITT) Population will include all ITT participants who receive at least 1 injection of EN3835 or Placebo and have both baseline and at least one post injection FFI pain subscale measures. The treatment group assignment will be based on the randomized treatment.	This population will be used for analyses of the primary, secondary and exploratory endpoints.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables, data listings and graphs will be prepared using SAS Version 9.4 or higher.

Continuous data will be summarized using descriptive statistics. Discrete data will be summarized using frequency and percentages. The denominator will be based on the number of participants in the appropriate population.

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

- Minimum and maximum: Same number of decimal places as the raw data
- Mean and Median: One decimal place more than the raw data
- Standard deviation (SD): Two decimal places more than the raw data
- Percentages will be displayed with one decimal place precision. A zero count will be left blank

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

Appropriate inferential statistics will be used for the primary, secondary and exploratory efficacy variables.

Tables, participant listings, graphs, and any supportive SAS output will include footnotes that will indicate:

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

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

Empty tables will be presented with a note stating that “No participants met criteria”.

Participant listings of all data from the eCRFs and/or vendor data as well as any derived variables will be presented.

6.2. Derived Variables

Table 25 defines the derived variables for study parameters:

Table 25: Derived Variables and Definition

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Body Mass Index (BMI)	BMI will be computed using height measured at screening and body weight measured at respective visits as, BMI (kg/m^2) = Weight (kg) / Height (m^2)
Relative Day	The day of first injection of study intervention will be considered as relative Day 1.
Study Day	Study Day will be computed as, Date of Assessment – Date of Day 1 + 1 for assessment on or after Day 1, else study day will be computed as Date of Assessment – Date of Day 1.
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study intervention. The assessments made in unscheduled visits will be considered in calculation of baseline, if the unscheduled assessment is the closest value preceding the study intervention injection.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Last Date in Study	Last date in study is defined as: • The date of EOS Visit (Day 57 ± 5), if the participant completes the study. • The date of early termination visits if the participant is terminated early from study at a non-scheduled visit. • The date of the latest scheduled visit if the participant is terminated early from study at a scheduled visit or lost to follow-up.
Duration (Days) of AE	AE end date - AE start date + 1
AE Onset Day	AE start date - Date of Day 1 + 1
Total Number of Nodules	Sum of all Nodules Identifier entered in Selected Nodule(s) form
Maximum of Nodule size (mm) (Caliper measurement) for participant level	Maximum of nodule size for the participant
Average Nodular Hardness (Durometer measurement) for Nodule level & Participant level	Average of nodule hardness
Area of the Nodule	(Nodule Width * Nodule Length * pi)/4 where pi=22/7
Area of Nodule for Participant level	Average of nodule area of all nodules

6.2.1. Derivation of Efficacy Parameter

Table 26 provides detailed information for the efficacy parameters as per eCRF/Vendor data collection. The derivation of these parameters is added on a participant-level, foot-level, and nodule-level.

Table 26: Efficacy Parameter Data

SN	Category	Parameter	Participant Level	Foot Level	Nodule Level	Derivation for Participant Level	Derivation for Foot Level	Derivation for Nodule Level
1	FFI	FFI Total Score	√			Section 4.7.1.4	NA	NA
2	FFI	FFI Pain Subscale Score	√			Section 4.7.1.4	NA	NA
3	FFI	FFI Difficulty Subscale Score	√			Section 4.7.1.4	NA	NA
4	FFI	FFI Pain & Difficulty combined score	√			Section 4.7.1.6	NA	NA
5	FFI	FFI Activity Limitation subscale score	√			Section 4.7.1.4	NA	NA
6	FFI	FFI Composite Score	√			Section 4.7.1.6	NA	NA
7	NRS	Pain intensity NRS	√			Section 4.7.4	NA	NA
8	Nodule	Nodule size by Caliper measurement	√		√	Section 4.6.2	NA	eCRF data
9	Nodule	Nodule Hardness by Durometer measurement	√		√	Section 4.6.3	NA	eCRF data
10	Nodule	Number of Nodules treated	√		√	Section 4.6.4	NA	eCRF data
11	Nodule	Nodular Consistency	√		√	Section 4.6.1	NA	eCRF data
12	PGIS	PGIS Overall Severity	√			Vendor data	NA	NA
13	PGIS	PGIS Pain Subscale	√			Vendor data	NA	NA
14	PGIS	PGIS Difficulty Subscale	√			Vendor data	NA	NA
15	PGIS	PGIS Activity Limitation subscale	√			Vendor data	NA	NA
16	PGIC	PGIC Overall Severity	√			Vendor data	NA	NA
17	PGIC	PGIC Pain Subscale	√			Vendor data	NA	NA
18	PGIC	PGIC Difficulty Subscale	√			Vendor data	NA	NA
19	PGIC	PGIC Activity Limitation Subscale	√			Vendor data	NA	NA
20	CGIC	Clinician Global Impression of Change Scale		√		Section 4.8.1	eCRF data	NA
21	SSTS	Subject Satisfaction with Treatment Scale		√		Section 4.8.1	eCRF data	NA

6.3. Handling of Missing Data

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables. The participants having missing value for age, race/ethnicity, height, weight, nodule consistency status will be missing.

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

6.3.1. Handling of Missing Data for the Primary Endpoint

The foot pain subscale score will be recorded at baseline and at each visit (ie, Day 15, 29, 43, and 57).

The primary endpoint will be the change from baseline at Day 57. This value will be missing if the participants have missing data due to discontinuation from the study prior to Day 57 or due to a missed assessment or lost to follow up.

The missing data at Day 57 will be imputed for the participants who withdraw from the study prior to Day 57 using multiple imputation washout model (Section 7.6.1.2) to explore the possibility of data missing not at random (MNAR). In the multiple imputation washout framework, for participants who withdraw from the study early, their missing values will be

imputed under the assumption that their outcome would be similar to those in the placebo group with similar background characteristics. Multiple imputation methods will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method.(4)

In addition, to assess the impact of missing values, sensitivity analyses using Mixed Model Repeated Measure (MMRM) (Section 7.6.1.3) without imputation and with imputation using Tipping Point Analyses (Section 7.6.1.2) will be performed on primary endpoint and key secondary endpoints. If the primary analyses of primary endpoint and key secondary endpoints result is not significant (p-value > 0.05), no sensitivity analyses (tipping point) will be performed.

6.3.2. Handling of Missing Data for Secondary and Exploratory Endpoints

Missing data at Day 57 for the key secondary endpoints of the FFI pain and difficulty combined score and nodular hardness, will be imputed using similar methods as described for primary efficacy endpoint. For the sensitivity analyses of the key secondary endpoint of the CGIC, missing data for CGIC will be imputed using the monotone logistic regression method (Section 7.6.3.2.2).

For other secondary endpoints and exploratory endpoints, missing data will not be imputed.

6.3.3. Missing Data Handling for Safety Data

There will be no imputation of missing values for safety data, however missing relationship between AE and study intervention will be considered as related to study intervention following worst case principle.

6.3.4. Imputation of Partial Dates

6.3.4.1. TEAE Status for Completely Unknown Start Date

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

- If the AE onset date is unknown and the end date is on or after study intervention injection on Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before study intervention injection on Day 1, then the AE will not be considered a TEAE.
- If both the start and end dates are unknown (or end date is ongoing), then the AE will be considered a TEAE, following the worst-case principle.
- If the AE onset date is partly present and month/year is prior to the study intervention injection on Day 1, then the AE will not be considered a TEAE.

6.3.4.2. Concomitant Status of Medications with Completely Unknown Start Date

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

- If the medication onset date is unknown and the end date is after the date of after the study intervention is administered on Day 1 or the medication is ongoing at after

study intervention is administered on Day 1, then the medication will be considered as concomitant.

- If the medication onset date is unknown and the end date is before the date of study intervention administration on Day 1, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication will be considered as concomitant. This approach is the most conservative following the worst-case principle.
- If the medication onset date is partly present and month/year is prior to date of study intervention injection on Day 1 and medication/procedure is not ongoing at after study intervention injection on Day 1, then the medication will not be considered as concomitant.
- If the medication onset date is unknown and the end date is before the date of study intervention administration on Day 1, then the medication will not be considered as prior concomitant.

6.4. Subgroup Analyses

Exploratory subgroup analyses will be performed on the primary endpoint, key secondary endpoints, and frequency of TEAE. The subgroups are:

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

6.5. Multiplicity Adjustment

Multiplicity arising from testing of secondary endpoints will be addressed by using a fixed sequence hierarchical testing procedure. A step-down testing procedure will be applied where inference for an endpoint in the predefined hierarchy is dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

The hierarchy of endpoints is defined as follows:

- Primary endpoint
- Key secondary endpoint 1
- Key secondary endpoint 2
- Key secondary endpoint 3

All the tests will be performed at the 0.05 level of significance following the pre-specified order. The testing of the first key secondary endpoint will be conducted if the result of the primary

endpoint is statistically significant and testing of the second key secondary endpoint will be conducted if the result of the first key secondary endpoint is statistically significant and so on.

The other secondary endpoints and exploratory endpoints do not fall under this hierarchical approach as no multiplicity adjustment will be made for such endpoints and only nominal p-values will be reported.

6.6. Interim Analyses

No interim analyses will be conducted for this study.

Data Safety Monitoring Board (DSMB) will be set up for the study who will review safety data to mitigate the risk. Safety monitoring will occur throughout the study to assess the risks of treatment.

A DSMB charter will be written. This charter will include the list of tables and listings to be generated for the DSMB review.

6.7. Stopping Rules for the study

During the conduct of the study, AEs and SAEs will be reported (Protocol 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 (protocol section 11.1.4). The DSMB will meet at an appropriate frequency, as described in the DSMB charter. The DSMB will also convene if ≥3% of study participants have developed a TEAE of CTCAE ≥Grade 3 due to serious injuries to the foot caused by the local complications of the injection or if ≥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.

6.8. Treatment Group

All summary tables related to ITT and Safety Population, except study intervention exposure will be presented by treatment group (“EN3835” “Placebo”) and Overall.

All efficacy analyses related to ITT population, FAS and mITT population will be presented by treatment group (“EN3835” “Placebo”).

7. STATISTICAL ANALYSES

7.1. Participant Disposition

The number of participants included in each study population will be summarized by treatment group and overall (if applicable). Participants excluded from the Safety Population, ITT Population, FAS and mITT Population will be listed.

The number and percentage of participants screened, randomized, completed, and withdrawn from the study, as well as the primary reason for withdrawal from the study will be summarized by treatment group and overall (if applicable).

A separate listing of disposition data, participants discontinued from study, and screen failure including the reasons for screen failure will be provided. In addition, a listing for exclusion from analysis populations will be provided.

7.2. Protocol Deviations

Protocol deviations will be summarized by deviation classification (important/not important), by treatment group and overall (if applicable).

A separate listing of all protocol deviations for each visit will be presented by participant.

7.3. Demographics and Baseline Characteristics

The demographic and baseline characteristics will be summarized using the Safety Population, ITT Population and FAS, by treatment group, and overall.

Separate listings by population will be provided if these populations are not identical to the Safety Population.

7.4. Medical and Surgical History

Medical history will be coded using MedDRA. Medical and surgical history data will not be summarized; however, a listing will be provided by participant using the Safety Population.

A separate listing for plantar fibromatosis history will also be provided by participant using the Safety Population.

7.5. Prior/Concomitant Medications and Procedures

Prior and concomitant medications will be summarized by treatment group and overall (if applicable) using frequency and percentages by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Prior and concomitant non-drug therapies (procedures) will be summarized by treatment group and overall (if applicable) using frequency and percentages with name of the procedures ordered alphabetically. Multiple use of the same medication/procedure by a participant will be counted only once.

A participant listing indicating prior and concomitant medications and procedures will be provided. Similarly, a separate listing of medications and procedures for plantar fibromatosis will also be presented by participant.

The prior and concomitant medications and procedures will be summarized and listed using the Safety Population.

7.6. Efficacy Analyses

For the primary and key secondary efficacy endpoints, ITT Population will be the primary analysis population. Supportive efficacy analyses will also be performed using FAS and mITT Population. If the difference between FAS and mITT is no more than 5 participants, supportive analyses using FAS will not be generated. All the efficacy listing will be provided by ITT population.

For the data collected at nodule level, analyses will be performed at participant level and nodule level.

Table 27: List of Analyses Performed on All Efficacy Endpoints

Endpoint (Primary/ Secondary /Exploratory)	Endpoint	Primary analyses	Subgroup Analyses	Sensitivity Analyses	Supportive Analyses
Primary	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”).	ANCOVA (ITT)	ANCOVA (ITT)	• MMRM based on (Observed Data) (ITT) • MMRM based on TPA (ITT)	• ANCOVA (FAS) • ANCOVA (mITT)
1st Key Secondary	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).	ANCOVA (ITT)	ANCOVA (ITT)	• MMRM based on (Observed Data) (ITT) • MMRM based on TPA (ITT)	• ANCOVA (FAS) • ANCOVA (mITT)
2nd Key Secondary	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”) at Day 57.	Cochran-Mantel-Haenszel method (ITT)	Cochran-Mantel-Haenszel method (ITT)	Cochran-Mantel-Haenszel based on TPA (ITT)	• Cochran-Mantel-Haenszel method (FAS) • Cochran-Mantel-Haenszel method (mITT)

Table 27: List of Analyses Performed on All Efficacy Endpoints (Continued)

Endpoint (Primary/ Secondary /Exploratory)	Endpoint	Primary analyses	Subgroup Analyses	Sensitivity Analyses	Supportive Analyses
3rd Key Secondary	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.	ANCOVA (ITT)- Participant level analyses	ANCOVA (ITT)- Participant level analyses	• MMRM based on (Observed Data) (ITT) • MMRM based on TPA (ITT)	• ANCOVA (FAS) • ANCOVA (mITT) • Nodule level analyses - MMRM (Observed Data) (ITT) • Nodule level analyses - MMRM (TPA) (ITT)
Secondary	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.	MMRM based on (Observed Data) (mITT)			
Secondary	The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the total combined score of the pain and difficulty subscales of the FFI with EN3835 vs placebo.	MMRM based on (Observed Data) (mITT)			
Secondary	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") at Day 15, 29, 43 and 57.	Cochran-Mantel-Haenszel method (mITT)			
Secondary	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	MMRM based on (Observed data) (mITT)			Nodule level analyses - MMRM (Observed Data) (mITT)
Exploratory	The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the FFI total score of 21 items with the score of each item ranging from 0 to 4, with 4 indicating higher severity.	MMRM based on (Observed data) (mITT)			

Table 27: List of Analyses Performed on All Efficacy Endpoints (Continued)

Endpoint (Primary/ Secondary /Exploratory)	Endpoint	Primary analyses	Subgroup Analyses	Sensitivity Analyses	Supportive Analyses
Exploratory	The difference between EN3835 and placebo at Day 57 on the PGIS PF Overall score at Days 15, 29, 43, and 57 on the PGIS PF Overall score, ranging from 0 (“None”) to 4 (“Severe”).	Wilcoxon rank-sum test & H-L estimator (mITT)			
Exploratory	The difference between EN3835 and placebo at Day 57 on the foot pain subscale of the PGIS at Days 15, 29, 43, and 57 on the PGIS foot pain subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.	Wilcoxon rank-sum test & H-L estimator (mITT)			
Exploratory	The difference between EN3835 and placebo at Day 57 on the difficulty subscale of the PGIS at Days 15, 29, 43, and 57 on the PGIS difficulty subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.	Wilcoxon rank-sum test & H-L estimator (mITT)			
Exploratory	The difference between EN3835 and placebo at Day 57 on the activity limitation subscale of the PGIS at Days 15, 29, 43, and 57 on the PGIS activity limitation subscale, ranging from 0 (“None”) to 4 (“Severe”) with EN3835 vs placebo.	Wilcoxon rank-sum test & H-L estimator (mITT)			
Exploratory	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- PF Overall, a 7-point scale ranging from -3 (“Very Much Worse”) to +3 (“Very Much Improvement”) on Days 15, 29, 43, and 57.	Cochran-Mantel-Haenszel method (mITT)			
Exploratory	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.	Cochran-Mantel-Haenszel method (mITT)			

Table 27: List of Analyses Performed on All Efficacy Endpoints (Continued)

Endpoint (Primary/ Secondary /Exploratory)	Endpoint	Primary analyses	Subgroup Analyses	Sensitivity Analyses	Supportive Analyses
Exploratory	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.	Cochran-Mantel-Haenszel method (mITT)			
Exploratory	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.	Cochran-Mantel-Haenszel method (mITT)			
Exploratory	The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day Days 15, 29, 43, and 57 on the Pain Intensity NRS, ranging from 0 (“None”) to 10 (“Worst Pain Imaginable”) with EN3835 vs placebo.	MMRM based on (Observed Data) (mITT)			
Exploratory	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.	Cochran-Mantel-Haenszel method (mITT)			
Exploratory	The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Day 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”).	MMRM based on (Observed Data) (mITT)			
Exploratory	The difference between EN3835 and placebo in 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”).	MMRM based on (Observed Data) (mITT)			

Table 27: List of Analyses Performed on All Efficacy Endpoints (Continued)

Endpoint (Primary/ Secondary /Exploratory)	Endpoint	Primary analyses	Subgroup Analyses	Sensitivity Analyses	Supportive Analyses
Exploratory	The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in the nodule size of the treated nodules by caliper measurements.	MMRM based on (Observed Data) (mITT)			Nodule level analyses - MMRM (Observed Data) (mITT)
Exploratory	The difference between EN3835 and placebo in the change in nodule consistency from Baseline (Day 1) to Days 15, 29, 43, and 57 as determined by the number of participants with a soft or non-palpable consistency at Day 57.	Cochran-Mantel-Haenszel method (mITT)			Nodule level analyses: Cochran-Mantel-Haenszel method (mITT)
Exploratory	The difference between EN3835 and placebo in the mean change from Baseline (Day 1) to Days 15, 29, 43, and 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.	MMRM based on (Observed Data) (mITT)			

7.6.1. Primary Analyses

7.6.1.1. Mean Change from Baseline to EOS Visit on the Foot Pain Subscale

The primary estimand is defined by the following:

- **The *primary* clinical question of interest is:** In participants with plantar fibromatosis, what is the difference in mean change from Baseline (Day 1) to Day 57 in the total foot pain score (as measured with the FFI pain subscale) between EN3835 and placebo regardless of discontinuation of study intervention?
- **Treatment condition:** Randomized study intervention (EN3835 or placebo)
- **Target Population:** Adult participants with plantar fibromatosis included in the ITT Population.
- **Variable (Endpoint) of interest:** Mean change from baseline (Day 1) to Day 57 in FFI total foot pain subscale score.
- **Treatments being compared:** The mean change from baseline (Day 1) to Day 57 in FFI total foot pain subscale score will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for the analyses.
  - Any new or change in concomitant treatment will not be adjusted for primary analyses.
  - Early discontinuation from the study is the potential intercurrent event that could occur. If participants do not have FFI total pain subscale score at Day 57 due to early discontinuation, the missing values will be imputed before the analyses

using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered (Section 7.6.1.2 for details on imputation).

- **Population Level-Summary measure:** Least square mean (LSM) estimate for treatment difference between EN3835 and placebo.
- **Method of Analyses:** The change from Baseline (Day 1) to Day 57 in the total foot pain subscale score will be calculated after the missing data imputation has been performed and will be analyzed using an Analysis of Covariance (ANCOVA) model on each multiply imputed dataset. The model will include the fixed effect of treatment group and FFI pain subscale score at baseline, the maximum of Nodule length/Nodule width, and the total number of nodules as covariates. Treatment effects from these ANCOVA analyses will then be combined using Rubin's Method via the SAS PROC MIANALYZE procedure. The LSM estimate for each treatment, the LSM of treatment difference, their corresponding 95% confidence interval (CI) and associated p-value will be provided (Section 7.6.1.2 for more details on this analyses).
- **Sensitivity analyses to primary endpoint:** The following sensitivity analyses will be performed on primary efficacy endpoint to assess the impact of missing data:
  - A sensitivity analyses will be performed based on all observed data up to Day 57. The change from Baseline (Day 1) to Day 57 will be analyzed using an MMRM (Section 7.6.1.3).
  - Another sensitivity analyses will be performed using MMRM with imputation of missing values for participant who discontinue treatment or who are withdrawn from the study. The imputed missing values will be adjusted using a TPA (Section 7.6.2).
- **Supportive analyses to primary endpoint:** The primary efficacy endpoint will also be analyzed using ANCOVA by FAS and mITT population.

7.6.1.2. Multiple Imputation Method

Multiple imputation will be used to account for uncertainty in the imputation process and results from the imputed datasets will be combined using Rubin's method. ANCOVA will be used as the analyses method. The main steps of the implementation of the washout imputation are described below.

[redacted]

[redacted]

In addition, the observed and change from Baseline in individual item score, subscale score (%), and Total Pain Subscale Score on Day 15, 29, 43, and EOS (Day 57) will be summarized descriptively by treatment group.

The change from Baseline in the Total Foot Pain Subscale Score in the ANCOVA derived LSM at Day 57, will be presented using a bar graph with error bars depicting the SE (on the y-axis) and treatment group along the x-axis by ITT, FAS and mITT population.

The mean change from Baseline in the Total Foot Pain Subscale Score with observed data by treatment group will be presented using a line graph with error bars depicting the SE (on the y-axis) and visit along the x-axis by ITT, FAS and mITT population.

A listing of FFI individual item scores, subscale score (%), composite score (%), total subscale score, and total score by participant will be provided.

7.6.1.3. Sensitivity Analyses using MMRM (Observed Data)

Sensitivity analyses will be performed on observed data using MMRM. The mean change in Total Pain Subscale Score from Baseline to Day 57 in EN3835 compared to placebo will be analyzed using a MMRM. An unstructured covariance matrix will be used to model the covariance of within-participant values. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the convergent criteria are not met then other covariance matrix structure, ie., autoregressive (1) (AR (1)) will be used for model. The MMRM model will include:

[redacted]

The least square mean (LSM) estimate for each treatment at EOS, the LSM of treatment difference, their corresponding 95% confidence interval (CI) and associated p-value will be provided.

7.6.2. Sensitivity Analyses using MMRM using Tipping Point Analyses (TPA)

The analyses in Section 7.6.1.2 is based on the MAR assumption, to evaluate the impact of deviations from the MAR assumption, a delta adjustment multiple imputation method will be used here to find the tipping point where the result is no longer statistically significant.

There are 3 different steps which will be followed for sensitivity analyses. The following steps will be performed to impute the missing data using the methods described in Section 6.3.1:

[redacted]

[redacted]

All steps above are repeated with different values of the shift parameter until the tipping point is reached or all possible values are explored. The tipping point can be identified when the result is no longer statistically significant (one p-value >0.025). It is possible a tipping point is not reached if little to no data is missing.

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

7.6.3. Secondary Analyses

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

7.6.3.1. Key Secondary Endpoint 1: Mean Change from baseline to Day 57 for FFI Pain and Difficulty combined score between EN3835 and placebo

The 1st key secondary estimand is defined by the following:

- **The *secondary* clinical question of interest is:** In participants with plantar fibromatosis, what is the difference in mean change from Baseline (Day 1) to Day 57 in foot pain and difficulty combined score (as measured with total combined score of the FFI pain subscale and the FFI difficulty subscale) between EN3835 and placebo, regardless of discontinuation of study intervention?
- **Treatment condition:** Randomized study intervention (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 foot pain and difficulty combined score.
- **Treatments being compared:** The change from Baseline (Day 1) to Day 57 in the Total Combined (Pain and Difficulty) Subscale Score will be compared between EN3835 and placebo.

- **Intercurrent Event:** The treatment policy strategy will be adopted for the analyses.
  - Any new or change in concomitant treatment will not be adjusted for primary analyses.
  - Early discontinuation from the study is the potential intercurrent event that could occur. If participants do not have FFI Total Combined (Pain and Difficulty) subscale score at Day 57 due to early discontinuation, the missing values will be imputed before the analyses using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered (Section 7.6.1.2 for more details on imputation).
- **Population Level-Summary measure:** Least square mean (LSM) estimate for treatment difference between EN3835 and placebo.
- **Method of Analyses:** The change from Baseline (Day 1) to Day 57 in Total Combined (Pain and Difficulty) subscale score will be calculated after the missing data imputation has been performed and will be analyzed using ANCOVA model on each multiply imputed dataset. The model will include the fixed effect of treatment group and FFI pain and difficulty subscale combined score at baseline, the maximum of Nodule length/Nodule width, and the total number of nodules as covariates. Treatment effects from these ANCOVA analyses will then be combined using Rubin's Method via the SAS PROC MIANALYZE procedure. The LSM estimate for each treatment, the LSM of treatment difference, their corresponding 95% confidence interval (CI) and associated p-value will be provided. Refer Section 7.6.1.2 for more details on this analyses.
- **Sensitivity analyses to secondary endpoint:** The following sensitivity analyses will be performed on secondary efficacy endpoint to assess the impact of missing data:
  - A sensitivity analyses will be performed based all observed data up to Day 57. The change from Baseline (Day 1) to Day 57 will be analyzed using an MMRM (Section 7.6.1.3).
  - Another sensitivity analyses will be performed using MMRM with imputation of missing values for participant who discontinue treatment or who are withdrawn from the study. The imputed missing values will be adjusted using TPA (Section 7.6.2).
- **Supportive analyses to secondary endpoint:** The secondary efficacy endpoint will also be analyzed using ANCOVA by FAS and mITT population.

The descriptive statistics for observed and change from baseline at each visit of the Total Combined (Pain and Difficulty) subscale score by treatment group will be provided.

The mean change from Baseline in the Total Combined (Pain and Difficulty) subscale score with observed data by treatment group will be presented using a line graph with error bars depicting the SE (on the y-axis) and visit along the x-axis using ITT, FAS and mITT population.

7.6.3.2. Key Secondary Endpoint 2: Clinician Global Impression of Change Scale

7.6.3.2.1. Key Secondary Endpoint 2: Primary Analyses

The 2nd key secondary estimand is defined by the following:

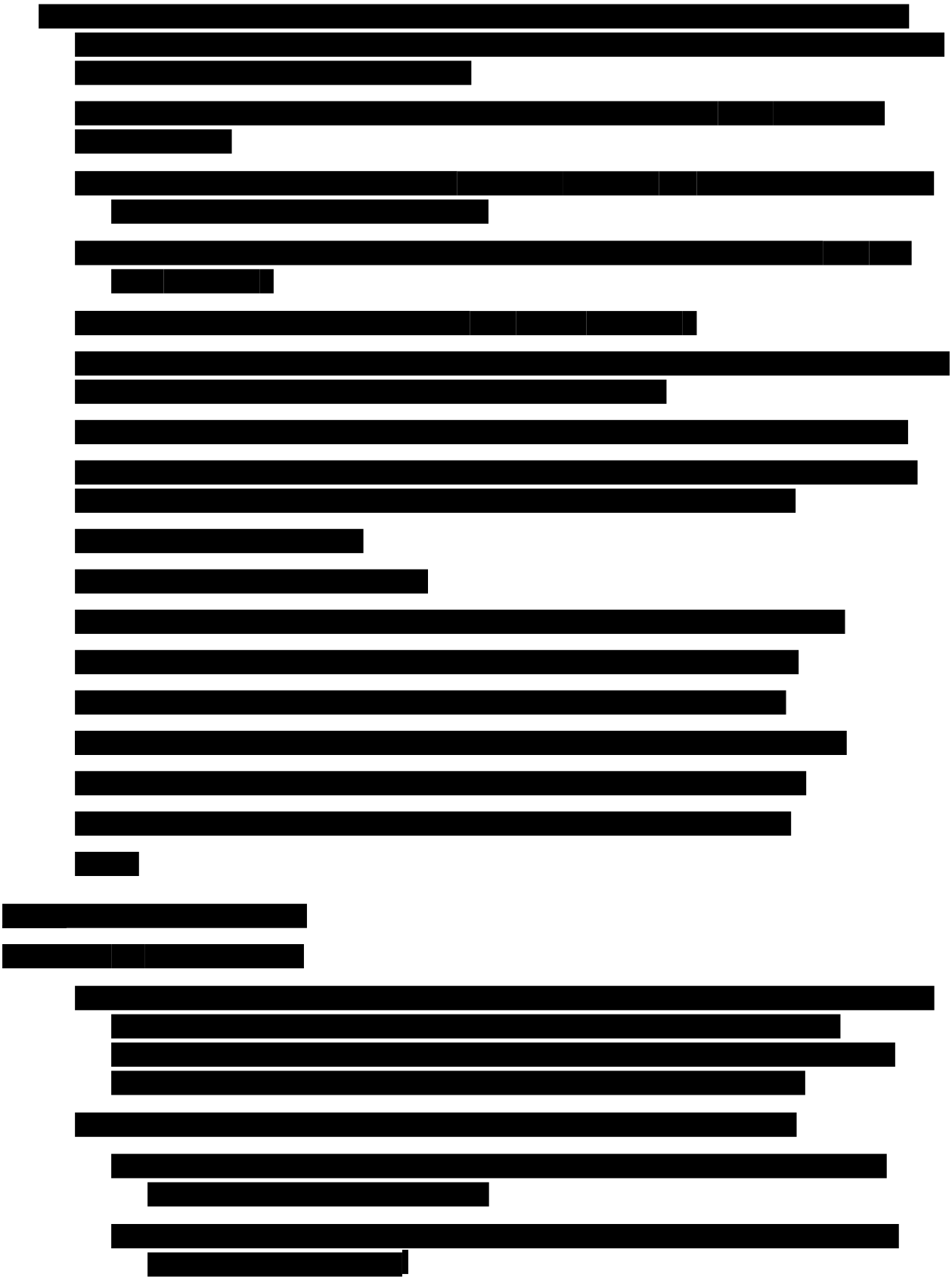
- **The *secondary* clinical question of interest is:** In participants with plantar fibromatosis, what is the difference in the proportion of EN3835-treated participants and those receiving only placebo reporting "Minimally Improved" (+1) "Much Improved" (+2) or "Very Much Improved" (+3) on CGIC, a 7-point scale ranging from −3 ("Very Much Worse") to +3 ("Very Much Improvement") at Day 57 between EN3835 and placebo, regardless of discontinuation of study intervention?
- **Treatment condition:** Randomized study intervention (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 participants reporting a response on the 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 of participants reporting a response on the CGIC at Day 57 will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for the analyses.
  - Any new or change in concomitant treatment will not be adjusted for primary analyses.
  - Early withdrawal from the study is the potential intercurrent event that could occur. All participants who withdraw early from the study will be considered as non-responders. The responder is defined as a participant who reports a score to be "Minimal Improvement", "Much Improvement" or "Very Much Improvement" on the CGIC at Day 57.
- **Population Level-Summary measure:** The stratum adjusted risk difference, associated 95% CI and p-value will be presented.
- **Method of Analyses:** The difference in proportion of responders between EN3835 and placebo will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by total number of nodules at baseline. The stratum adjusted risk difference, associated 95% CI and p-value will be presented using CMH test. The frequency and percentage of responders and 95% CI will be provided based on the Wilson (Score) by treatment group.
- **Sensitivity analyses to secondary endpoint:** Sensitivity analyses will be performed using CMH with imputation of missing values for participant who discontinue treatment or discontinue/withdrawn from the study. The imputed missing values will be adjusted using TPA (Section 7.6.3.2.2).
- **Supportive analyses to secondary endpoint:** The secondary efficacy endpoint will also be analyzed using FAS and mITT population.

The degree of improvement in the 7-point scale as determined by the Investigator using CGIC Scale will be summarized using frequency and percentages with mean and SD by each treatment group and visit (ie, Days 15, 29, 43, and 57) for each foot.

A listing of CGIC Scale ratings by participant will be provided.

7.6.3.2.2. Sensitivity Analyses using CMH using Tipping Point Analyses (TPA)

The sensitivity analyses will be performed to assess the impact of missing data with CMH using delta adjustment for TPA as described in Section 7.6.3.2.2. The following 3 steps will be performed to impute the missing data based on Section 6.3.1 for sensitivity analyses:



[redacted]

The tipping point can be identified when the result is no longer statistically significant.

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

All steps above are repeated with different values of the shift parameter until the tipping point is reached or all possible values are explored. The tipping point can be identified when the result is no longer statistically significant (one p-value >0.025). It is possible a tipping point is not reached if little to no data is missing.

7.6.3.3. Key Secondary Endpoint 3: Difference of Mean Changes from Baseline to Day 57 for Nodular Hardness Measurements between EN3835 and Placebo

7.6.3.3.1. Participant Level Analyses:

The 3rd key secondary estimand is defined by the following:

- **The *secondary* clinical question of interest is:** In participants with plantar fibromatosis, what is the difference in mean change from Baseline (Day 1) to Day 57 in nodular hardness measurements (as measured by durometer) between EN3835 and placebo, regardless of discontinuation of study intervention?
- **Treatment condition:** Randomized study intervention (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 in Nodular Hardness measurements will be compared between EN3835 and placebo.
- **Intercurrent Event:** The treatment policy strategy will be adopted for the analyses.
  - Any new or change in concomitant treatment will not be adjusted for primary analyses.
  - Early withdrawal from the study is the potential intercurrent event that could occur. If participants do not have nodular hardness at Day 57 due to early withdrawal, the missing values will be imputed before the analyses using a multiple imputation washout model. In multiple imputation washout model, all participants who are randomized and have a baseline assessment will be considered (Section 7.6.1.2 for details on imputation).
- **Population Level-Summary measure:** Least square mean (LSM) estimate for treatment difference between EN3835 and placebo.
- **Method of Analyses:** The change from baseline (Day 1) to Day 57 in nodular hardness will be calculated after the missing data imputation has been performed and will be analyzed using ANCOVA model on each imputed dataset. The model will

include the fixed effect of treatment group and average nodular hardness at baseline, the maximum of Nodule length/Nodule width, and the total number of nodules as covariates. Treatment effects from these ANCOVA analyses will then be combined using Rubin's Method via the SAS PROC MIANALYZE procedure. The LSM estimate for each treatment, the LSM of treatment difference, their corresponding 95% confidence interval (CI) and associated p-value will be provided (Section 7.6.1.2 for more details on this analyses).

- **Sensitivity analyses to secondary endpoint:** Following sensitivity analyses will be performed on secondary efficacy endpoint to assess the impact of missing data:
  - A sensitivity analyses will be performed based all observed data up to Day 57. The change from baseline (Day 1) to Day 57 will be analyzed using a MMRM (Section 7.6.1.3).
  - Another sensitivity analyses will be performed using MMRM with imputation of missing values for participant who discontinue treatment or who are withdrawn from the study. The imputed missing values will be adjusted using a TPA (Section 7.6.2).
- **Supportive analyses to secondary endpoint:** The secondary efficacy endpoint will also be analyzed using ANCOVA by FAS and mITT population..

The descriptive statistics for observed and change from baseline at each visit of the hardness measurements (as measured by durometer) by treatment group will be provided for participant level and nodule level.

A listing of nodular hardness by participant will be provided.

7.6.3.3.2. Nodule Level Analyses:

Nodule level analyses will be performed on observed data using MMRM (Section 7.6.1.3) and to assess the impact of missing data using MMRM of missing values for participant who discontinue treatment or who are withdrawn from the study. The imputed missing values will be adjusted using a TPA (Section 7.6.2).

The mean change in nodular hardness from Baseline to Day 57 for EN3835 compared to placebo will be analyzed using a MMRM. An unstructured covariance matrix will be used to model the covariance of within-participant values. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the convergent criteria are not met then other covariance matrix structure, ie., autoregressive (1) (AR (1)) will be used for model. The MMRM model will include:

- The dependent variable, the change from the Baseline to each visit (ie, change from baseline score to day 15, day 29, day 43, and day 57)
- The fixed effect, treatment group, study visit, treatment by visit interaction.
- The covariate, the Baseline Nodular Hardness at Day 1, maximum of nodule length/nodule width for the respective nodule.
- The repeated measures will be the study visit and nodules.

7.6.3.4. Other Secondary Endpoints: FFI

7.6.3.4.1. Mean Change from Baseline to Days 15, 29, 43, and 57 on the Pain Subscale

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the Total Pain Subscale Score of the FFI ranging from 0 ("None") to 4 ("Extreme") with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM for the mITT population(Section 7.6.1.3).

7.6.3.4.2. Mean Change from Baseline to Days 15, 29, 43 and 57 on the FFI – Pain and Difficulty Combined Score

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the Total Combined (Pain and Difficulty) Subscale Score with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM for the mITT population (Section 7.6.1.3).

7.6.3.5. Other Secondary Endpoints: Clinician Global Impression of Scale Change and Nodular Hardness

7.6.3.5.1. Proportion of Participants Reporting a Response on the CGIC at Day 15, 29, and 43

The proportion of participants reporting a response on the CGIC will be summarized by visit and compared between EN3835 and placebo using the mITT population. The analysis will follow the primary analysis approach in Section 7.6.3.2.

7.6.3.5.2. Mean Change from Baseline to Day 15, 29, 43 and 57 for Hardness Measurements between EN3835 and Placebo

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in average nodular hardness of the treated nodules by durometer measurements with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM for the mITT population (Section 7.6.1.3).

Refer to Section 7.6.3.3.2 for nodule level analyses.

7.6.4. Exploratory Analyses

7.6.4.1. FFI Composite Score

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on FFI total composite score with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM (Section 7.6.1.3).

The LSM estimate for the mean change from baseline on FFI total composite score at each visit for each treatment group and the LSM for treatment difference at each visit and their 95% confidence interval (CI) will be presented.

The descriptive statistics for observed and change from baseline on the composite score on FFI by visit and treatment group will be provided.

A listing of the FFI total score (derived) by participant will be provided.

7.6.4.2. Patient Global Impression of Severity

A listing will be provided for PGIS PF Overall scores, PGIS foot pain subscale scores, PGIS difficulty subscale scores and PGIS activity limitation subscale scores by participant.

7.6.4.2.1. Difference between EN3835 and Placebo at Day 15, 29, 43 and 57 in the PGIS PF Overall Score

The differences in the PGIS PF Overall scores at Day 15, 29, 43 and 57 between EN3835 and placebo will be tested using the Wilcoxon rank-sum test; corresponding p-values will be provided. In addition, the median difference/location shift between the treatment groups at each visit and corresponding 95% CIs using the Hodges-Lehmann estimator will be provided.

PGIS PF overall scores will be summarized using frequency and percentages of participant with mean and SD by treatment group and visits.

7.6.4.2.2. Difference between EN3835 and Placebo at Day 15, 29, 43 and 57 on the PGIS Foot Pain Subscale Score.

The change in PGIS foot pain subscale scores at Day 15, 29, 43 and 57 between EN3835 and Placebo will be tested using the Wilcoxon rank-sum test and the p-value will be provided. In addition, the Hodges-Lehmann estimator and its 95% CIs will be provided to represent the median difference/location shift between the treatment groups at each visit.

PGIS foot pain subscale scores will be summarized using frequency and percentages of participant with mean and SD by treatment group and visits.

7.6.4.2.3. Difference between EN3835 and Placebo at Day 15, 29, 43 and 57 on the PGIS Difficulty Subscale Score.

The change in PGIS difficulty subscale scores at Day 15, 29, 43 and 57 between EN3835 and Placebo will be tested using the Wilcoxon rank-sum test and the p-value will be provided. In addition, the Hodges-Lehmann estimator and its 95% CIs will be provided to represent the median difference/location shift between the treatment groups at each visit.

PGIS difficulty subscale scores will be summarized using frequency and percentages of participant with mean and SD by treatment group and visits.

7.6.4.2.4. Difference between EN3835 and Placebo at Day 15, 29, 43 and 57 on the PGIS Activity Limitation subscale score.

The change in PGIS activity limitation subscale score at Day 15, 29, 43 and 57 between EN3835 and Placebo will be tested using the Wilcoxon rank-sum test and the p-value will be provided. In addition, the Hodges-Lehmann estimator and its 95% CIs will be provided to represent the median difference/location shift between the treatment groups at each visit.

PGIS activity limitation subscale scores will be summarized using frequency and percentages of participant with mean and SD by treatment group and visits.

7.6.4.3. Patient Global Impression of Change

A listing will be provided for PGIC PF Overall scores, PGIC foot pain subscale scores, PGIC difficulty subscale scores and PGIC activity limitation subscale scores by participant.

7.6.4.3.1. Patient Global Impression of Change - PF Overall Score

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline severity score (ie, PGIS-PF Overall) separately for each visit.

The stratum adjusted risk difference (RR) from the CMH test, associated 95% CI and p-value will be presented separately for each visit. The frequency and percentage of responders (Section 4.7.3.1) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit.

The degree of improvement in the 7-point scale as determined by the investigator using PGIC – PF overall will be summarized using frequency and percentages with mean and SD by each treatment group and visit.

7.6.4.3.2. Patient Global Impression of Change - Foot Pain Subscale Score

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline severity score (ie, PGIS – Foot Pain Subscale Score) separately for each visit.

The stratum adjusted risk difference, associated 95% CI and p-value will be presented separately for each visit. The frequency and percentage of responders (Section 4.7.3.2) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit (ie, Days 15, 29, 43, and 57).

The degree of improvement in the 7-point scale as determined by the investigator using PGIC – Foot Pain Subscale will be summarized using frequency and percentages with mean and SD by each treatment group and visit.

7.6.4.3.3. Patient Global Impression of Change - Difficulty Subscale Score

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline severity score (ie, PGIS – Difficulty Subscale Score) separately for each visit.

The risk difference, associated 95% CI and p-value will be presented separately for each visit. The frequency and percentage of responders (Section 4.7.3.3) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit.

The degree of improvement in the 7-point scale as determined by the investigator using PGIC – Difficulty Subscale will be summarized using frequency and percentages with mean and SD by each treatment group and visit.

7.6.4.3.4. Patient Global Impression of Change - Activity Limitation Subscale Score

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline severity score (ie, PGIS – Activity Limitation Subscale Score) separately for each visit.

The stratum adjusted risk difference, associated 95% CI and p-value will also be presented separately for each visit. The frequency and percentage of responders (Section 4.7.3.4) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit.

The degree of improvement in the 7-point scale as determined by the investigator using PGIC – Activity Limitation Subscale will be summarized using frequency and percentages with mean and SD by each treatment group and visit.

7.6.4.4. Pain Intensity Numerical Rating Scale

7.6.4.4.1. Mean Change from Baseline to Day 15, 29, 43 and 57 on the Pain Intensity NRS

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in Pain Intensity NRS with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM (Section 7.6.1.3).

The LSM estimate for the mean change from baseline at each visit for each treatment group and the LSM for treatment difference at each visit and their 95% confidence interval (CI) will be presented.

The descriptive statistics for observed and change from baseline on the Pain Intensity NRS by visit and treatment group will be provided.

A listing for Pain Intensity NRS will be provided by participant.

7.6.4.5. Subject Satisfaction with Treatment Scale

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline severity score (ie, PGIS – PF Overall Score) separately for each visit.

The stratum adjusted risk difference, associated 95% CI and p-value will also be presented separately for each visit. The frequency and percentage of responders (Section 4.7.5) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit (ie, Days 15, 29, 43, and 57).

The degree of improvement in the 5-point scale as determined by the investigator using Subject Satisfaction with Treatment Scale will be summarized using frequency and percentages with Mean and SD by each treatment group and visit (ie, Days 15, 29, 43, and 57) for each foot.

A listing of Subject Satisfaction with Treatment Scale will be provided by participant.

7.6.4.6. FFI Individual Subscales Scores

7.6.4.6.1. Mean Change from Baseline to Days 15, 29, 43 and 57 on the FFI- Activity Limitation Subscale

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 on the FFI-Activity Limitation Subscale for EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM (Section 7.6.1.3).

The LSM estimate for the mean change from baseline at each visit for each treatment group and the LSM for treatment difference at each visit and the corresponding 95% CI will be presented.

The descriptive statistics for observed and change from baseline on the activity limitation subscale by visit and treatment group will be provided.

The listing of FFI will include the activity limitation score by participant.

7.6.4.6.2. Mean Change from Baseline to Days 15, 29, 43 and 57 on the FFI - Difficulty Subscale Score

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 and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM (Section 7.6.1.3).

The LSM estimate for the mean change from baseline at each visit for each treatment group and the LSM for treatment difference at each visit and their 95% confidence interval (CI) will be presented.

The descriptive statistics for observed and change from baseline at each visit on the difficulty subscale score by treatment group will be provided.

The listing of FFI will include the difficulty subscale score by participant.

7.6.4.7. Nodule Size by Caliper Measurement

7.6.4.7.1. Participant Level Analyses: Mean change from Baseline to Days 15, 29, 43 and 57 in the size of the treated nodules

The mean change from Baseline (Day 1) to Days 15, 29, 43, and 57 in the size of the treated nodules with EN3835 vs placebo and their treatment differences will be estimated using the similar statistical model based on observed data using MMRM (Section 7.6.1.3).

The LSM estimate for the mean change from baseline at each visit for each treatment group and the LSM for treatment difference at each visit and their 95% confidence interval (CI) will be presented.

The descriptive statistics for observed and change from baseline at each visit by treatment group will be provided. The nodule size (up to 2 cm, > 2 cm to ≤4 cm and > 4 cm) will also be summarized by each treated nodule.

A listing for nodule size will be provided by participant.

7.6.4.7.2. Nodule Level Analyses: Mean change from Baseline to Days 15, 29, 43 and 57 in the size of the treated nodules

Nodule level analyses will be performed on observed data using MMRM (Section 7.6.1.3).

The mean change in nodule size from baseline to Days 15, 29, 43, and 57 in EN3835 compared to placebo will be analyzed using a MMRM. An unstructured covariance matrix will be used to model the covariance of within-participant values. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the convergent criteria are not met then

other covariance matrix structure, ie., autoregressive (1) (AR (1)) will be used for model. The MMRM model will include:

- The dependent variable, the change from the Baseline to each visit (ie, change from baseline score to day 15, day 29, day 43, and day 57)
- The fixed effect, treatment group, study visit, treatment by visit interaction.
- The covariate, the baseline maximum of Nodule length/Nodule width for respective nodule at Day 1, maximum of Nodule length/Nodule width for respective nodule.
- The repeated measures will be the study visit and nodules.

The least square mean (LSM) estimate for each treatment at EOS, the LSM of treatment difference, their corresponding 95% confidence interval (CI) and associated p-value will be provided.

7.6.4.8. Nodule Consistency – Responder Analyses

7.6.4.8.1. Participant Level Analyses: Change in consistency from Baseline to Day 15, 29, 43 and 57 in the Nodule Consistency

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline nodule consistency separately for each visit.

The stratum adjusted risk difference, associated 95% CI and p-value will be presented separately for each visit. The frequency and percentage of responders (Section 4.6.1) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit (ie, Days 15, 29, 43, and 57).

The degree of improvement in nodular consistency will be summarized using frequency and percentages with mean and SD by each treatment group and visit (ie, Days 15, 29, 43, and 57).

A listing of nodule consistency will be provided by participant.

7.6.4.8.2. Nodule Level Analyses: Change in consistency from Baseline to Day 15, 29, 43 and 57 in the Nodule Consistency

The difference in proportion of responders between EN3835 and placebo will be analyzed using CMH test stratified by baseline nodule consistency separately for each visit and each nodule.

The stratum adjusted risk difference, associated 95% CI and p-value will be presented separately for each visit. The frequency and percentage of responders (Section 4.6.1) and 95% CI will be provided based on the Wilson (Score) by treatment group and visit (ie, Days 15, 29, 43, and 57).

The degree of improvement in nodular consistency will be summarized using frequency and percentages with mean and SD by each treatment group and visit (ie, Days 15, 29, 43, and 57) for each treated nodule.

7.6.5. Subgroup Analysis

The primary, key secondary, and frequency of TEAEs will be performed for the following subgroups:

1. Number of injections (1 vs 2 vs 3 vs 4) at Day 1

2. Baseline FFI Total Pain Subscale Score: Group 1 vs Group 2
    a. Group 1: FFI total pain subscale score ≤20 for participants without orthotics or FFI total pain subscale score ≤ 26 for participants with orthotics
    b. Group 2: FFI total pain subscale score ≥21 for participants without orthotics or FFI total pain subscale score ≥ 27 for participants with orthotics

Subgroups may be combined with adjacent groups (which have less number of participants until count of participant exceeds 10). if the number of participants in that group is less than 10.

The subgroup analyses will be tabulated similar to primary analyses for primary endpoint and key secondary endpoints (Section 7.6.1.2 for 1st and 3rd Key secondary endpoints and Section 7.6.3.2.1 for 2nd key secondary endpoint).

Incidence of TEAEs will be tabulated with risk difference and confidence interval using subgroups (Section 7.7.2).

7.7. Safety Analyses

7.7.1. Study Intervention Exposure

The number of injections will be summarized using frequency and percentage by the treatment group, and by single foot treated or both feet treated using Safety Population. Summary using ITT Population, mITT population and FAS Population will be provided, only if these populations are not identical to the Safety Population.

A separate listing of study intervention exposure for each treatment group will be provided using ITT Population, mITT population and FAS Population, only if these populations are not identical to the Safety Population.

7.7.2. Safety by Incidence of TEAEs, AESIs, SAEs

The safety of treatment groups is assessed by incidence, severity and duration of treatment emergent adverse events (TEAEs), adverse events of special interest (AESIs), AEs resulting in study discontinuation and serious adverse events (SAEs).

The risk difference and associated 95% CI using the exact method will be presented for incidence of TEAEs, TEAEs resulting in drug discontinuation, and TEAEs leading to study discontinuation across treatments.

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

TEAEs will be summarized by SOC and PT. A participant will only be counted once per SOC and PT.

For TEAEs by severity grade (Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5), if a participant has multiple events occurring in the same SOC or same PT, then the event with the highest grade will be counted.

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

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

An overall summary of TEAEs and TEAEs related to study intervention will be presented and will include:

- Total number of TEAEs reported
- Total number of TEAEs reported by severity
- Participants with any TEAE
- Participants with any serious TEAE
- Participants with any TEAE of special interest
- Participants with any Grade 3+ TEAE
- Participants with no Grade 3+ TEAEs, but at least one Grade 2 TEAE
- Participants with no Grade 3+/Grade 2 TEAEs, but at least one Grade 1 TEAE
- Participants with any TEAEs leading to drug interruption/discontinuation
- Participants with any TEAEs leading to withdrawal from study
- Participants with any TEAEs resulting in death

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

- All TEAEs
- TEAEs by severity
- TEAEs by special interest
- Treatment related TEAEs
- Treatment related TEAEs by severity
- Serious TEAEs
- Serious treatment related TEAEs
- TEAEs resulting in death
- Study intervention related TEAEs resulting in death
- Duration of treatment related TEAEs (Duration of treatment related TEAEs (<14 days, 14 – 21 days and >21 days) (Refer to Table 25 for computation of duration of AEs.)

The most common serious and non-serious TEAEs by order of frequency (most frequent, 2nd most frequent, 3rd most frequent and so on) will be summarized by PT. The most common serious and non-serious AEs are those with any PT that at least 5% of the Participants reported at least once.

The following listings will be presented by participant:

- All AEs

- Serious AEs
- AEs of special interest
- AEs resulting in drug interruption/discontinuation
- AEs resulting in study withdrawal
- AEs resulting in death

7.7.3. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be summarized by treatment group and overall (if applicable) using descriptive statistics for observed and change from Baseline values for all post-baseline assessment visits.

The PCI vital signs values will be summarized by treatment group and overall using frequency and percentages separately for each treatment. Refer to Table 23 for PCI criteria.

A separate listing will be presented for vital sign results by participant.

7.7.4. Clinical Laboratory

Hematology and chemistry results will be summarized by treatment group and overall (if applicable) using descriptive statistics for observed and change from Baseline values at each visit.

The PCI laboratory values will be summarized by treatment group and overall (if applicable) using frequency and percentages. The participants with treatment-emergent PCI values will be summarized. The pre-treatment PCI values can be found in individual listings. Refer to Table 22 for PCI criteria.

Additionally, shift tables will be produced by treatment group and overall. The shift tables will be based on the classification of laboratory results (ie, low, normal, high) at Day 57/EOS compared to the classification of baseline results.

A listing for hematology, chemistry and urinalysis results will be presented for all laboratory parameters by participant. Serum and urine pregnancy test and urine drug screen results will be listed separately by participant.

7.7.5. Physical Examination

Physical examination results (by body system) at Baseline, at Day 29, and Day 57/EOS will be presented by treatment group and overall (if applicable) using frequency and percentages separately by treatment.

A listing will be presented for physical examination results (by body system) for each visit as per the SoA (Table 2) by participant.

7.7.6. Foot Examination

Foot examination results will be presented by visit, treatment group and overall (if applicable) using frequency and percentages separately by treatment.

A listing will be presented for foot examination results for each visit as per the SoA (Table 2) by participant.

7.7.7. Immunogenicity

7.7.7.1. Presence of anti-AUX-I and anti-AUX-II antibody titer levels

The following will be summarized: the number of participants with an immunogenicity sample collected, the percentage of participants with positive and negative anti-AUX-I and anti-AUX-II antibodies, the titer level of the positive samples at Screening and Day57/EOS.

The titer levels will be logarithmically transformed prior to being summarized. Samples from Screening and Day 57/EOS will be analyzed for anti-AUX-I and anti-AUX-II antibodies.

7.7.7.2. Presence neutralizing antibodies to AUX-I and AUX-II

A subset of positive samples of AUX-I or AUX-II will be analyzed for neutralizing antibodies. Neutralizing antibody results will be summarized as percentage of positive/negative results by visit and treatment group if applicable.

A listing of immunogenicity results by participant will be provided.

8. CHANGE FROM PROTOCOL

This SAP is based on Clinical Study Protocol Amendment 04, dated 10 June 2022.

Table 28: Changes from Protocol

Text in Protocol	Text in SAP	Justification
Section 7.7.1: 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.	Any medication/procedure taken/done prior to first injection (Day 1) will be reported as prior medication/procedure.	It was observed in the proof-of-concept study EN3835-105 that there were medications which remain unclassified because the medications were taken > 30 days prior to screening visit. This change is intended to ensure that all prior medications taken, even if > 30 days are classified.

9. REFERENCES

1. Clinical Study Protocol Amendment 04: 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; Dated: 10 June 2022.
2. Budiman-Mak E, Conrad KJ, Mazza J, Stuck RM. A review of the foot function index and the foot function index - revised. *J Foot Ankle Res*. 2013;6(1):5. Published 01 Feb 2013. doi:10.1186/1757-1146-6-5
3. Budiman-Mak E, Conrad KJ, Roach KE. The Foot Function Index: a measure of foot pain and disability. *J Clin Epidemiol*. 1991;44(6):561-570. doi:10.1016/0895-4356(91)90220-4
4. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons, Inc, 1987

10. APPENDIX

All the SAS codes will be provided in Module 2.

11. TABLES, LISTINGS, AND GRAPH SHELLS

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