Protocol Title:	**An Adaptive, Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of Engensis in Participants with Painful Diabetic Peripheral Neuropathy**
Protocol Number:	VMDN-003-2
Version Number:	6.0
Approval Date:	28 Jan 2022
Compound:	Engensis
Study Phase:	3
Short Title:	Phase 3 Study to Assess Safety and Efficacy of Engensis in Painful Diabetic Peripheral Neuropathy
Acronym:	REGAiN-1A

[redacted]

[redacted]

DISCLOSURE STATEMENT

This study will be conducted in compliance with the protocol, US Code of Federal Regulations applicable to clinical studies, principles of ICH Good Clinical Practice, the Declaration of Helsinki, and all applicable regulatory requirements. This protocol is the confidential information of Helixmith and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of Helixmith.

Protocol Amendment Summary of Changes Table

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Overall Rationales for the Amendment (Version 5.0 to 6.0):

Changes implemented in this amendment clarified that only severe (Grade 3) and potentially life-threatening (Grade 4) Injection Site Reactions will be considered Adverse Events of Special Interest (AESI) and that the Average Daily Pain Score is based on questions in the Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), whether using the full or partial questionnaire.

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1. Protocol Summary

The following sections present an overview of the study, the study schema, and the schedule of activities. A list of abbreviations is presented in Section 10.5, Appendix 5.

1.1. Synopsis

Protocol Title: An Adaptive, Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Engensis in Participants with Painful Diabetic Peripheral Neuropathy

Short Title: Phase 3 Study to Assess Safety and Efficacy of Engensis in Painful Diabetic Peripheral Neuropathy

Rationale:

The purpose of this study is to evaluate the efficacy and safety of intramuscular (IM) administration of Engensis on pain in Participants with painful diabetic peripheral neuropathy (DPN) in the feet and lower legs, as compared to Placebo, as a second Phase 3, well-controlled study, sufficient in supporting the efficacy and safety of Engensis.

Engensis contains the active pharmaceutical ingredient VM202, a novel genomic complementary deoxyribonucleic acid (cDNA) hybrid human hepatocyte growth factor (HGF) coding sequence (HGF-X7) expressing two isoforms of HGF, HGF_{728} and HGF_{723}, being developed for treatment of painful DPN.

Diabetic peripheral neuropathy, by definition, is a bilateral neuropathy. Based on the safety profile of Engensis observed in the Phase 1 and Phase 2 critical limb ischemia (CLI) studies and the Phase 1/2, 2, and 3 DPN studies in addition to the preliminary efficacy data from the Phase 1/2 and 2 studies of Engensis injections in Participants with DPN, we propose continued bilateral treatment in this Phase 3 study, as treating only one leg may confound patient-reported pain levels and quality-of-life measures.

Engensis will be tested against Placebo. The total dose of Engensis plasmid DNA to be delivered per leg uses the same dosing schedule of administration as was conducted in a Phase 2 and one Phase 3 DPN study: 16 mg per leg (total of 32 mg) per Participant. As in the prior Phase 3 study (Protocol VMDN-003), Participants will receive Engensis or Placebo by IM injections in both legs (in the calf gastrocnemius muscles) in the first Treatment Cycle on Day 0 and Day 14, followed by a second Treatment Cycle on Day 90 and Day 104.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of IM administration of Engensis on pain in participants with painful DPN in the feet and lower legs as compared to Placebo	• Change in the means of the Average Daily Pain Scores (ADPSs) from the Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo in the intent-to-treat (ITT) population
Secondary Efficacy	
• To evaluate the efficacy of IM administration of Engensis on the worst pain in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Change in the means of the Worst Pain scores from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
• To evaluate the efficacy of IM administration of Engensis on reducing pain in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Proportion of Responders (≥ 50% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
Secondary Safety	
• To evaluate the safety of IM administration of Engensis in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) for Engensis compared to Placebo • Incidence of injection site reactions for Engensis compared to Placebo • Incidence of clinically significant laboratory values for Engensis compared to Placebo
• To evaluate the possibility of cellular and/or humoral responses to Engensis compared to Placebo in Participants with painful DPN in the feet and lower legs	• Change from Baseline in the cytokine profile through post-dose on Day 104 for Engensis compared to Placebo

Objectives	Endpoints
	• Presence of anti-hepatocyte growth factor (HGF) antibodies following Engensis administration compared to Placebo
Exploratory Efficacy	
• To evaluate the efficacy of IM administration of Engensis on Quality of Life and Patient Reported Outcomes in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Patient Global Impression of Change (PGIC) on Day 90 and on Day 180 for Engensis compared to Placebo
• To evaluate the durability of the analgesic response to IM administration of Engensis in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Proportion of Responders (≥ 50% reduction in the means of ADPSs) from the 7 days prior to the Day 180 Visit who were Responders on Day 104 (final injection visit) for Engensis compared to Placebo
• To determine whether IM administration of Engensis has a positive effect (reverses/reduces pain, improves neurological function and quality of life) on painful DPN as compared to Placebo	• Change in the Bedside Sensory Testing (BST) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Proportion of Responders (≥20, 30, 40, 60, and 70% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo • Change in the means of the ADPSs from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit for Engensis compared to Placebo • Changes in the severity scores (Average Pain, Worst Pain, Least Pain, and Pain Right Now) from the full BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo

Objectives	Endpoints
	• Changes in Michigan Neuropathy Screening Instrument (MNSI) assessments from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the 36-Item Short Form Health Survey (SF-36) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the EuroQol Health Utilities Index (EQ-5D) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the means of the daily use of rescue medication from Day 0 to Day 90, from Day 0 to Day 180, and from Day 90 to Day 180 for Engensis compared to Placebo

Overall Design

VMDN-003-2 is an adaptive Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to assess the efficacy and safety of Engensis (containing the active pharmaceutical ingredient VM202) in Participants with painful DPN.

Following completion of the informed consent process, Screening activities (during 45 days [from Day -52 to Day -7] prior to Day 0) will determine which Participants meet all-but-one eligibility criteria, which are assessed by an adjudication procedure, followed by completion of a 7-day eDiary prior to Day 0. Eligible participants will be enrolled and randomly assigned in a double-blind fashion and in a 1:1 ratio on Day 0 to either Engensis or Placebo.

During Screening, medical history and familial cancer history, demographics, vital signs, height, body mass index (BMI), waist size, physical examination, retinal fundoscopy (by an ophthalmologist or experienced optometrist), 12-lead electrocardiogram (ECG), ultrasound of the right and left gastrocnemius muscles (to guide IM Study Injections), laboratory assessments, estimated glomerular filtration rate (eGFR), HBA1c levels, viral screening, a record of all concomitant medications and procedures, urine drug analysis, and urine pregnancy test for females of childbearing potential will be conducted.

In addition, the following procedures will be conducted during Screening: Hospital Anxiety and Depression Scale (HADS), Accurate Pain Reporting (APR) and Placebo Response Reduction (PRR), Michigan Neuropathy Screening Instrument (MNSI), and cancer screening tests.

During 7 days before Day 0 and randomization, Participants must complete the full Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) on an electronic diary (eDiary) for determining the Average Daily Pain Scores (ADPSs) for at least 5 out of the 7 days. Adverse event (AE) assessments will start upon completion of the consent process at the start of Screening.

At any time prior to dosing on Day 0, Bedside Sensory Testing (BST) should be administered. Following randomization, and prior to the first IM injections of Engensis or Placebo on Day 0, the partial BPI-DPN, and quality of life instruments will be completed. Blood will be collected for testing of selected cytokines, anti-HGF antibodies, and laboratory assessments.

All Participants will receive sixteen (16) 0.5-mL IM injections of Engensis or Placebo in each calf gastrocnemius muscle at each of two Visits during two Treatment Cycles: Treatment Cycle 1 on Day 0 and Day 14, and Treatment Cycle 2 on Day 90 and Day 104. At 2 hours (± 1 hour) after completion of IM injections of Engensis or Placebo on Days 0 and 14 and Days 90 and 104, vital signs and blood draw for cytokine levels will be performed.

Treatment-emergent adverse event (TEAE) assessment, including injection site reactions, will start as of randomization (Day 0) and continue throughout the study.

Follow-up Study Visits will be conducted on Days 28, 60, 150, and 180 or early termination (ET). Vital signs will be recorded at all Study Visits. At the Day 180 Visit (end of study), the following assessments will be conducted: the full BPI-DPN (performed for 7 days prior to the Day 180 Visit), MNSI, BST, Patient Global Impression of Change (PGIC), and the quality of life assessments (36-item Short Form Health Survey [SF-36] and EuroQol Health Utilities Index [EQ-5D]), urine drug analysis, urine pregnancy status (females only), retinal fundoscopy, physical examination, concomitant medications and procedures, and anti-HGF antibodies. Blood will be drawn for determination of serum chemistry, lipid profile, hematology, and HbA1c levels.

The purpose of this study is to assess the efficacy and safety of Engensis compared to Placebo as measured by changes in the means of the Average Daily Pain Scores (ADPSs) of the BPI-DPN, selected blood cytokines, BST, and assessments of injection site reactions, physical examination, laboratory assessments, vital signs, TEAEs, and treatment-emergent serious adverse events (TESAEs).

Study and Treatment Duration:

Screening will occur up to 52 days prior to Baseline (Day 0) and Participants will be followed from Day 0, the day of first Study Injections, to Day 180/ET.

Visit Frequency:

Consented Participants will be seen and evaluated for enrollment during Screening (up to 52 days prior to Baseline, Day 0). There are 8 visits to the Clinical Site during the study from Day 0 to Day 180 for Study Injections and follow-up.

Intervention Groups and Duration:

Two treatment groups of Participants (Engensis or Placebo) will be in the study for 180 days.

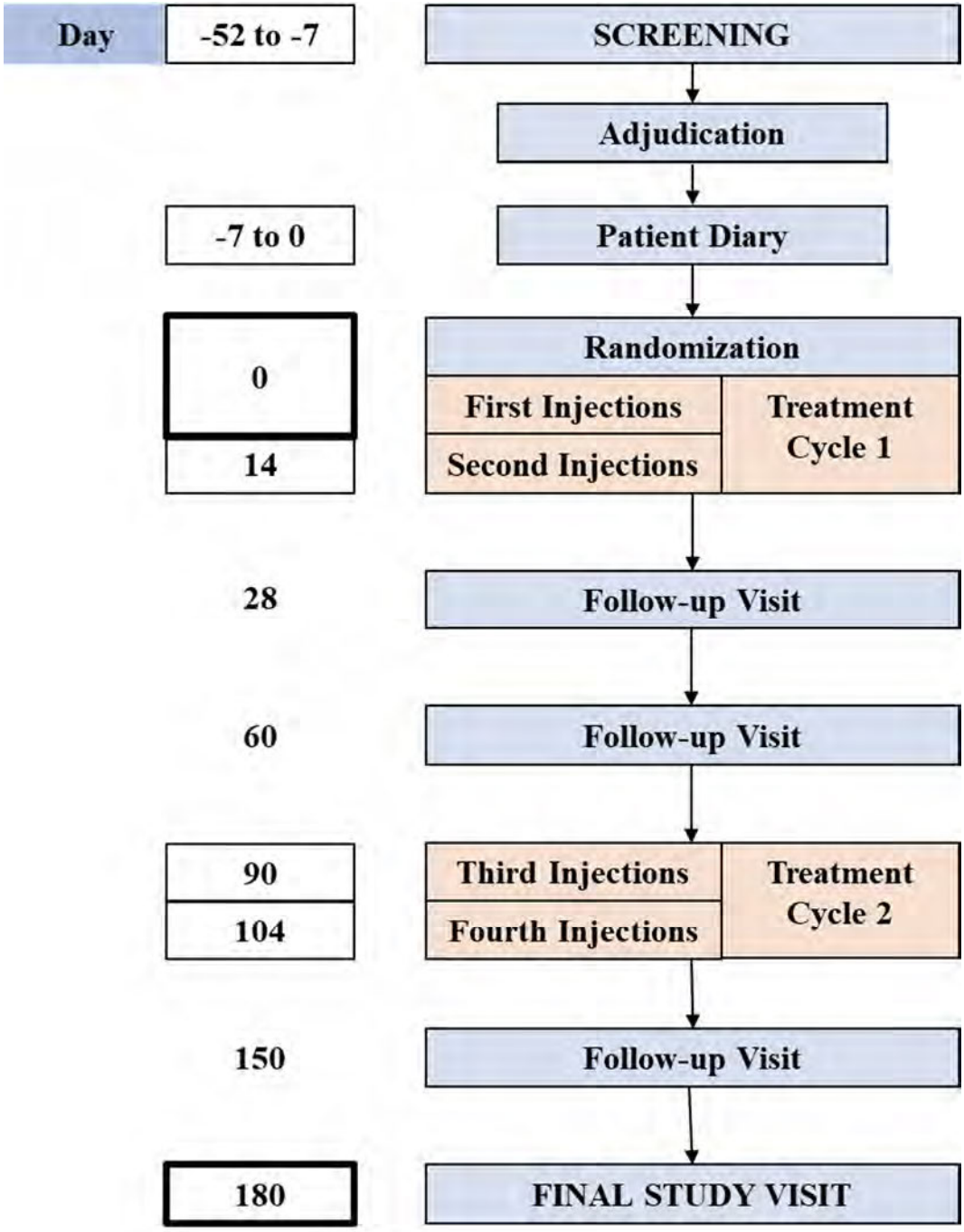
Number of Participants (N = 152 to approximately 250):

The target sample size is a minimum of 152 Participants and the maximum sample size is 250 Participants based on the proposed adaptive design analysis. The final sample size of Participants to be enrolled and evaluated will be determined by the independent Data Monitoring Committee (DMC). An interim analysis will be conducted after approximately 50% of Participants in the target sample (i.e., 76 Participants) have completed the primary efficacy endpoint at Day 180 or have withdrawn prematurely. The DMC will make a recommendation based on an unblinded (comparative) power analysis.

Data Safety Monitoring Board:

The independent DSMB will periodically review a limited set of unblinded (noncomparative) tables and/or listings, including all reported AEs, TEAEs, AESIs, SAEs, and TESAEs.

1.2. Study Schema



1.3. Schedule of Activities (SoA)

		Screening, Adjudication, and 7-day Diary			First Treatment Cycle: D0, D14						Second Treatment Cycle: D90, D104					
					1st Injections		2nd Injections				3rd Injections		4th Injections			
Study Day:		Days -52 to -7	Day -7	Days -7 to 0	Day 0		Day 14 [a]		Day 28	Day 60	Day 90		Day 104 [a]		Day 150	Day 180
Visit Window (days):							± 1		± 3	± 3	± 7		± 1		± 7	± 7
Procedure					Pre-dose	Post-dose	Pre-dose	Post-dose			Pre-dose	Post-dose	Pre-dose	Post-dose		
1	Informed Consent	X														
2	Demographics and Baseline Characteristics	X														
3	Medical History and Familial Cancer History	X														
4	Vital Signs, Weight	X			X	X	X	X	X	X	X	X	X	X	X	X
5	Height, Body Mass Index, Waist Size	X														
6	Complete Physical Examination	X			X		X		X	X	X		X		X	X
7	Cancer Screening	X														
8	Retinal Fundoscopy	X									X					X
9	12-Lead Electrocardiogram	X									X					X
10	Ultrasound right & left gastrocnemius muscles	X														
11	Serum Chemistry, Hematology, Lipid Profile	X			X						X					X
12	Estimated Glomerular Filtration Rate	X														
13	Urine Pregnancy Test	X			X						X					X
14	Urine Drug Analysis	X			X		X		X	X	X		X		X	X

		Screening, Adjudication, and 7-day Diary			First Treatment Cycle: D0, D14						Second Treatment Cycle: D90, D104					
					1st Injections		2nd Injections				3rd Injections		4th Injections			
Study Day:		Days -52 to -7	Day -7	Days -7 to 0	Day 0		Day 14 [a]		Day 28	Day 60	Day 90		Day 104 [a]		Day 150	Day 180
Visit Window (days):							± 1		± 3	± 3	± 7		± 1		± 7	± 7
Procedure					Pre-dose	Post-dose	Pre-dose	Post-dose			Pre-dose	Post-dose	Pre-dose	Post-dose		
15	HbA1c levels	X									X					X
16	Viral Screening	X														
17	Hospital Anxiety and Depression Scale (HADS)	X														
18	Concomitant Medications	X			X		X		X	X	X		X		X	X
19	Concomitant Procedures	X			X		X		X	X	X		X		X	X
20	Adjudication		X													
21	Randomization				X											
22	Study Injections: Engensis or Placebo				X		X				X		X			
23	Accurate Pain Reporting (APR) and Placebo Response Reduction (PRR)	X			X		X		X	X	X		X		X	X
24	Brief Pain Inventory-DPN (eDiary), Full BPI-DPN			X							X					X
25	Brief Pain Inventory-DPN (eDiary), Partial BPI-DPN					←				→		←			→	
26	Quality of Life (SF-36, EQ-5D)				X						X					X
27	Patient Global Impression of Change (PGIC)										X					X

		Screening, Adjudication, and 7-day Diary			First Treatment Cycle: D0, D14						Second Treatment Cycle: D90, D104					
					1st Injections		2nd Injections				3rd Injections		4th Injections			
Study Day:		**Days -52 to -7**	**Day -7**	**Days -7 to 0**	**Day 0**		**Day 14 [a]**		**Day 28**	**Day 60**	**Day 90**		**Day 104 [a]**		**Day 150**	**Day 180**
Visit Window (days):							± 1		± 3	± 3	± 7		± 1		± 7	± 7
Procedure					Pre-dose	Post-dose	Pre-dose	Post-dose			Pre-dose	Post-dose	Pre-dose	Post-dose		
28	Adverse Events (AEs) and Treatment-emergent Adverse Events (TEAEs)	X (AEs)			←					TEAEs		→				
29	Adverse Events of Special Interest (AESI)				←							→				
30	Cytokine Profile				X	X	X	X				X	X	X		
31	Anti-Hepatocyte Growth Factor Antibodies				X					X	X				X	X
32	Michigan Neuropathy Screening Instrument (MNSI)	X									X					X
33	Bedside Sensory Testing (BST)				X						X					X

FOOTNOTES FOR SCHEDULE OF ACTIVITIES

***Schedule of Activities** includes activities during Screening and all Study Visits. Additional data from daily eDiary entries will be transferred directly into a study database.

Abbreviations: D = Day; DPN = diabetic peripheral neuropathy; eDiary = electronic diary; ET = Early Termination; HbA1c = hemoglobin A1c; SF-36 = 36-Item Short Form Health Survey; EQ-5D = EuroQol Health Utilities Index

[a] The Day 14 Visit will be scheduled 13-15 days after the Day 0 Visit and the Day 104 Visit will be scheduled 13-15 days after the Day 90 Visit.

1. **Informed Consent** process is to be completed at Screening prior to conducting any study-specific procedures.
2. **Demographics and Baseline Characteristics** will include age, sex, race, and ethnicity collected at Screening.
3. **Medical History and Familial Cancer History:** A medical history and familial cancer history will be obtained at Screening, which will include a detailed assessment of past diabetes history, events, interventions, and procedures. Cancer history for 5 years will be collected at Screening.

4. **Vital Signs and Weight:** Vital signs will be measured at Screening, pre- and 2 hours (± 1 hour) post-dose at Study Injection Visits during Treatment Cycle 1 (Days 0 and 14) and Treatment Cycle 2 (Days 90 and 104), and at all other Study Visits (Days 28, 60, 150, and 180 or Early Termination). After the Participant has rested in the seated position for 5 minutes, vital signs will be collected, including temperature, sitting blood pressure, heart rate, respiratory rate, and oxygen saturation on room air. The method of temperature measurement should be according to the Site's policy and should be consistently applied. Weight will be collected pre-dose at Study Injection Visits (Days 0, 14, 90, and 104).
5. **Height, Body Mass Index (BMI), and Waist Size** will be collected only at Screening.
6. **Complete Physical Examinations** will be performed at Screening, and pre-dose on Day 0, 14, 90, and 104, and on Days 28, 60, 150, and 180; and at the last Visit if the Participant discontinues prior to Day 180. The examination will include the following: head, eyes, ears, nose, and throat (HEENT); heart; lungs; abdomen; extremities; lymph nodes; neurological; and skin/integumentary systems. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the CS abnormalities should be recorded as adverse events using appropriate medical terminology, except at Screening.
7. **Cancer Screening Tests** will include the following (note that past history refers to years before Screening):
   - **Mammogram** for breast cancer for female Participants aged 45 to 54 years, if not performed within the past 12 months; or if not performed within the past 24 months for female Participants aged ≥ 55 years. If the mammogram results are negative for cancer, the Participant will be allowed to enter the study.
   - **Primary human papillomavirus (HPV) test** for cervical cancer for female Participants aged 25 to 65 years, if not performed within the past 5 years; if primary HPV test is not available, an **HPV test in combination with cytology (PAP)** if not performed within the last 5 years, or **cytology (PAP) alone** if not performed within the past 3 years. If the test results are negative for cervical cancer, the Participant will be allowed to enter the study.
   - **Fecal immunochemical test (FIT) stool test** for colon cancer for Participants (male or female) aged ≥ 45 years and ≤ 75 years, if not performed within the past 12 months; or a **colonoscopy** (in lieu of an FIT stool test) if not performed within the past 5 years. If the test results are negative for colon cancer, the Participant will be allowed to enter the study. Participants aged ≥ 76 years will not be required to undergo colon cancer screening.
   - **Low-dose chest computed tomography (CT) scan** for lung cancer for current or previous smokers (male or female) who:
     - Are ≥ 50 years of age, are currently smoking, have a ≥ 30 pack-year history of smoking, and have not had a CT scan performed within the past 12 months
     - Are ≥ 50 years of age, quit smoking but have smoked within the past 15 years, and have a ≥ 30 pack-year history.

     If the test results are negative for lung cancer, the Participant will be allowed to enter the study.
   - **Prostate-specific antigen (PSA) test** for prostate cancer, if not performed within the past 12 months, for male Participants who are African-American aged ≥ 45 years or other races aged ≥ 50 years. If the test results are negative for prostate cancer, the Participant will be allowed to enter the study.
8. **Retinal Fundoscopy** will be performed by an ophthalmologist or optometrist at Screening, up to 45 days before the Day 90 Visit (pre-dose), and up to 30 days before the Day 180 Visit (and, if possible, upon Early Termination if the Participant discontinues after the Day 90 Visit). If the retinal fundoscopy results at Screening are deemed insufficient to determine eligibility, fluorescein angiography may need to be performed. Results of the fundoscopy examinations at Days 90 and 180 compared to results at Screening will be assessed by the Investigator.
9. **12-Lead Electrocardiogram (ECG)** will be performed at Screening, pre-dose on Day 90, and on Day 180. Any clinically significant findings at Screening will recorded as part of medical history. Clinically significant abnormalities are to be recorded as adverse events, except at Screening. The ECG recording and interpretation will be printed out and stored with the Participant's records.

10. **Ultrasound** of the right and left gastrocnemius muscles of the calf will be used to measure the depth to the muscles and width of the muscles at Screening in preparation for the IM injections of the study drug.
11. **Serum Chemistry, Hematology, and Lipid Profile:** These laboratory assessments will be evaluated at Screening to establish eligibility and baseline measurements for comparison with assessments on Days 0, 90, and 180.
    - **Chemistry** includes sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate, magnesium, glucose, amylase, lipase, creatine kinase, lactate dehydrogenase, and
        - Kidney function tests (blood urea nitrogen, creatinine)
        - Liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], total bilirubin, total protein, and albumin)
        - Cystatin C (at Screening to calculate eGFR)
    - **Hematology** includes platelet count, hemoglobin, hematocrit, white blood cell count, and neutrophil count
    - **Lipid Profile** includes total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides
12. **Estimated Glomerular Filtration Rate (eGFR)** will be calculated only at Screening using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula based on Cystatin C levels.
13. **Urine Pregnancy Test:** Women of childbearing potential must have negative urine pregnancy tests at Screening, on Day 0, Day 90, and Day 180/ET.
14. **Urine Drug Analysis** includes amphetamines (methamphetamine), barbiturates, benzodiazepines, buprenorphine, cannabinoid (THC), cocaine, oxycodone, methadone, opiates, phencyclidine (PCP), tricyclics (TCA), and ethyl alcohol. Cannabinoid detection is not an exclusion criterion but may be used in exploratory analyses. The urine drug analyses will be conducted at Screening, pre-dose on Days 0, 14, 90, and 104 and on Days 28, 60, 150, and Day 180. An ethyl alcohol saliva analysis will be used at Screening. Drug analyses will be performed by the central laboratory at all other time points.
15. **HbA1c** levels will be measured at Screening, on Day 90, and on Day 180.
16. **Viral Screening** is to be conducted at Screening and includes tests for human immunodeficiency virus (HIV), human T cell lymphotropic virus (HTLV) I/II antibody with reflex confirmatory assay, hepatitis B virus (HBV: IgM HBcAb, HBsAb, HBsAg, and a quantitative HBV if needed clinically), and anti-hepatitis C virus (HCV) antibodies and a positive qualitative PCR if needed clinically. Testing will be performed at a local laboratory. All tests for HIV, HTLV, HBV, and HCV must be completed and negative prior to randomization.
17. **Hospital Anxiety and Depression Scale (HADS**) will be completed at Screening.

18-19. **Concomitant Medications and Procedures:** Record all medications or vaccines, including over-the-counter or prescription medicines, vitamins, herbal supplements and procedures that the Participant was receiving during 30 days prior to completion of the informed consent process, pre-dose on Days 0, 14, 90, and 104, and on Days 28, 60, 150, and 180/ET. For each medication, treatment, or procedure the following information will be collected: medication trade or generic name or type of procedure, indication, start date, stop date or ongoing, dose, units, frequency, and route.

20. **Adjudication**: The Adjudication Committee, composed of the Sponsor Medical Director, Medical Monitor, and Clinical Operations personnel, reviews the relevant clinical information of each Participant on a timely basis to ensure strict adherence to the Inclusion/Exclusion Criteria. The Committee either confirms the eligibility for randomization of an individual Participant or confers with the Investigator regarding the status of a Participant as a screen failure
21. **Randomization:** Completion of Screening activities, randomization, and first Study Injections (Treatment Cycle 1, Day 0) will occur on the same day (Day 0).
22. **Study Injections** – IM injections of Engensis or Placebo to the right and left gastrocnemius muscles will administered during the First Treatment Cycle (1st and 2nd Study Injections on Days 0 and 14) and the Second Treatment Cycle (3rd and 4th Study Injections on Days 90 and 104). The Investigator or designee must follow up with a telephone call to the Participant within 2 to 3 days after Study Injections to ask the Participant about any reactions at any injection sites.

23. **Accurate Pain Reporting (APR):** The Accurate Pain Reporting training will be conducted at Screening, pre-dose on Day 0, Day 14, Day 90, and Day 104, and on Days 28, 60, 150, and 180/ET.
    Placebo Response Reduction (PRR): The Placebo Response Reduction training will be conducted at Screening, pre-dose on Day 0, Day 14, Day 90, and Day 104, and on Days 28, 60, 150, and 180/ET.
24. **Brief Pain Inventory (BPI-DPN) – Full Questionnaire:** will be administered through the eDiary daily starting 7 days prior to the Day 0 (note: this starts after adjudication), and for 7 days prior to the Day 90 and Day 180 Visits. If the eDiary contains fewer than 5 daily entries over the 7 days prior to Day 0 and Day 180, the Visit must be rescheduled (up to 3 days later) so that the Participant can record 5 daily entries over the 7 days.
25. **Brief Pain Inventory (BPI) – Partial Questionnaire** (questions 3, 5, and 9a from the full questionnaire) will be completed on the eDiary every day that the full BPI is *not* conducted, after randomization on Day 0 up to the Day 180 Visit.
26. **Quality of Life (SF-36, EQ-5D) Questionnaires** will be administered pre-dose on Days 0 and 90, and on Day 180/ET. The study coordinator will check the questionnaires for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic.
27. **Patient Global Impression of Change (PGIC)** will be administered pre-dose on Day 90 and on Day 180/ET.
28. **Adverse Events (AEs) and Treatment-Emergent Adverse Events (TEAEs):** AEs will be recorded after informed consent until the first injections on Day 0. After the start of the 1st Injections on Day 0 through Day 180, AEs will be recorded as treatment-emergent adverse events (TEAEs). Adverse events that are serious (SAEs) occurring after randomization and throughout the study will be recorded. SAEs occurring after the completion of the consent process and before the 1st Injections on Day 0 should be recorded and reported only if associated with a protocol-specified procedure. All SAEs occurring after the time of the 1st Injections through the last Study Visit on Day 180 should be recorded and reported to the Sponsor within 24 hours of awareness of the SAE by the Site.
29. **Adverse Events of Special Interest (AESIs):** All AESIs will be continuously monitored throughout the study. **Injection Site Reactions** must be initially assessed immediately after all injections at an Injection Visit, followed up by the Investigator or designee with a documented telephone call to the Participant within 2 to 3 days after Study Injections to ask the Participant about any reactions at any injection sites, and if any, the worst reaction will be recorded as a TEAE. Severe (Grade 3) and potentially life-threatening (Grade 4) Injection Site Reactions will be considered an AESI.
30. **Cytokine Levels** will be measured in blood samples collected pre- and post-dose (after 2 hours ± 1 hour post last injection) on Days 0 and 14, post-dose on Day 90, and pre- and post-dose on Day 104 for levels of tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interferon gamma (IFN-γ), and interleukins IL-6, IL-4, IL-10, and IL-12p70 analyzed at a central laboratory.
31. **Anti-Hepatocyte Growth Factor (HGF) Antibodies**: Blood samples will be collected pre-dose on Days 0 and 90, and on Days 60, 150, and 180/ET for detection of anti-HGF antibodies.
32. **Michigan Neuropathy Screening Instrument (MNSI)** will be administered at Screening to determine the baseline Physical Assessment score and assess eligibility, and pre-dose on Day 90 and on Day 180/ET for assessing disease progression during the study.
33. **Bedside Sensory Testing (BST)** will be administered on Day 0 at any time prior to dosing to provide information that may be of value in training the Participants on how to more accurately report their pain, and then pre-dose on Day 90, and on Day 180/ET to provide additional information that will allow exploratory analysis of BST sensory profiles.

2. INTRODUCTION

Engensis is a novel gene therapy treatment being developed for the durable management of

2.1. Study Rationale

Diabetic peripheral neuropathy is a bilateral neuropathy. Based on the excellent safety profile of Engensis observed in the Phase 1 and Phase 2 critical limb ischemia (CLI) studies, preliminary efficacy data from the Phase 1/2 studies, safety data from the Phase 1/2 studies and the Phase 3 studies of Engensis in Participants with DPN, we propose continued bilateral treatment in this Phase 3 study.

The purpose of this study is to evaluate the efficacy and safety of IM administration of Engensis on pain in Participants with painful DPN in the feet and lower legs, as compared to Placebo, as a second well-controlled study sufficient to support the efficacy and safety of Engensis.

Engensis will be tested against Placebo. The total dose per Treatment Cycle of Engensis plasmid DNA delivered per leg will remain within the dosing scheme of the Phase 2 study and the prior Phase 3 DPN study (16 mg per leg, for a total of 32 mg per Participant). As was done in the prior Phase 3 study (Protocol VMDN-003), Participants will receive Engensis or Placebo by IM injections in the gastrocnemius muscles in both legs during two Treatment Cycles: Treatment Cycle 1, Day 0 and Day 14 (13 to 15 days after the Day 0 Visit) and Treatment Cycle 2, Day 90 and Day 104 (13 to 15 days after the Day 90 Visit).

As in all prior/ongoing studies, Engensis will be delivered as a solution containing 0.5 mg/mL of VM202. Participants will be treated with an overall final dose of 32 mg Engensis or Placebo, dosages well within those supported by the body of pharmacology and toxicology safety studies of Engensis.

2.2. Background

2.2.1. Pathophysiology of Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) is a bilateral, particularly debilitating complication of diabetes characterized by pain that is burning, lancinating, tingling, or shooting (electric shock-like), occurring with paresthesia, and is typically worse at night. The pain can either be triggered by an external stimulus or be independent of external input. Unlike other painful sensations, which signal a warning in response to a harmful stimulus, neuropathic pain is maladaptive. Diabetic peripheral neuropathy accounts for significant morbidity by predisposing the foot to ulceration and lower extremity amputation.

Diabetic peripheral neuropathy manifests as three broad categories: sensory, motor, and autonomic, with the most prevalent form being somatic or sensorimotor neuropathy. Symptoms (e.g., burning, tingling, stabbing, or pins-and-needles) often exhibit a distal symmetric pattern, beginning at the base of the toes and ascending proximally up the lower leg as the disease progresses. Patients may also display muscle weakness, lack of coordination and ataxia, and loss of pain perception. Loss of protective sensation can lead to the formation of foot ulcerations, infections, and amputations.

The sequence of physiological events that result in DPN is poorly understood. The pathogenesis of diabetic neuropathy likely involves the interplay of hyperglycemia, ischemia, and oxidative stress. Figure 1 portrays the relationship of hyperglycemia to oxidative stress, metabolic alterations, vascular dysfunction, and neural damage.

Figure 1 The Neurodestructive Effects of Hyperglycemia

Increased polyol pathway flux. Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by aldose reductase and sorbitol dehydrogenase, respectively. Accumulation of sorbitol and fructose leads to reduced nerve myoinositol, decreased membrane Na^+/K^+-ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation.[1]

Non-enzymatic protein glycation. Advanced glycation end products occur because of nonenzymatic addition of glucose or other saccharides to proteins, lipids, and nucleotides. In diabetes, excess glucose accelerates advanced glycation end-product generation that leads to intracellular and extracellular protein cross-linking and protein aggregation. Activation of the advanced glycation end-product receptor alters intracellular signaling and gene expression, releases proinflammatory molecules, and results in an increased production of reactive oxygen species (ROS) that contribute to diabetic microvascular complications.

Oxidative Stress. Glucose can cause significant oxidative stress and damage when present in excess. Under physiological conditions, aerobic respiration is associated with the formation of a small number of free radicals or ROS. In a hyperglycemic state, however, particularly in endothelial cells, which do not have the ability to limit glucose entry into the cell, glucose accumulation exceeds the levels that glycolytic enzymes can handle.[2,3] The flood of excess glucose into endothelial cells is shunted into alternate metabolic pathways (e.g., polyol pathway, glycosylation, hexosamine pathway, the diacylglycerol activation of protein kinase C [PKC]). These pathways, particularly PKC, produce significantly larger amounts of ROS than aerobic respiration, overwhelming compensatory antioxidant mechanisms.[4,5,6,7,8,9,10,11] The resulting hyperglycemic oxidative stress contributes to endothelial dysfunction by inhibiting endothelial nitric oxide production and by initiating and promoting the deposition of modified lipids in the subendothelium. These factors accelerate atherosclerotic macrovascular disease and are associated with the development of apoptosis in neurons and supporting glial cells.[12]

Vascular Damage. Nerve tissue depends on adequate blood flow to deliver nutrients and remove metabolic waste. Normally, the capillary basement membrane allows the passage of nutrients into the cell and permits the removal of waste products. In patients with prolonged hyperglycemia, glucose is more likely to be deposited in the basement membrane, thus decreasing its permeability. Decreased permeability results in the buildup of toxic metabolites, resulting in poor cellular metabolism, further free radical formation, apoptosis, and a decline in vascularization of nervous tissues.

2.2.2. Current Treatment Options

Currently no approved drugs or interventional strategies are known to halt or reverse the progression of DPN. Treatments target pain reduction, physical function improvement, reduction of psychological distress, and quality of life improvements.

Long-term complications of both type 1 and type 2 diabetes can be reduced by tight glycemic control. To date, this is the only intervention specifically shown to arrest or postpone the onset and severity of peripheral neuropathy. The consequences of DPN can be ameliorated by the education of patients and their care providers as to foot care, proper footwear and of hyposensitive areas and pressure points, all to prevent the occurrence of ulcers and to lower the risk of infection of soft tissue and bone.[13]

The incidence of neuropathy is also associated with potentially modifiable cardiovascular risk factors, including an elevated triglyceride level, a high body mass index (BMI), smoking, and hypertension.

Four drugs have been approved by the Food and Drug Administration (FDA) specifically for the treatment of the symptoms of DPN: Nucynta ER (tapentadol), an opioid medication; Cymbalta (duloxetine), a serotonin and norepinephrine reuptake inhibitor; Lyrica (pregabalin), an anticonvulsant drug; and Qutenza (capsaicin), a transdermal patch. All are prescribed for the management of pain associated with DPN.

See the IB for presentation of guidelines issued by international organizations for the use of agents to treat DPN.

Another treatment option is α-lipoic acid, a naturally occurring antioxidant compound found in spinach and broccoli. α-Lipoic acid was recently studied in a multicenter, placebo-controlled

study of Participants with type 2 diabetes and symptomatic neuropathy. One hundred eighty-one (181) Participants were given daily oral doses of 600, 1200, or 1800 mg of α-lipoic acid or placebo. After 5 weeks, neuropathic symptoms improved in those Participants who received α-lipoic acid. The 600-mg dose appeared to provide the optimum risk-to-benefit ratio.[14]

There are also invasive treatment options. One option is surgical decompression of the lower-extremity peripheral nerves in patients with DPN but this is still considered an experimental intervention (see IB for details). Pancreatic transplantation in patients with diabetes can stabilize neuropathy and, in some instances, improve motor, sensory, and autonomic function.

Other treatments include off-label use of several drugs and devices. Drugs commonly prescribed to manage pain symptoms include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin–norepinephrine reuptake inhibitors (SNRIs). Other treatment strategies such as acupuncture, transcutaneous electrical nerve stimulation (TENS), capsaicin patches and creams, topical anesthetics, and isosorbide dinitrate (ISDN) spray may also be used. Each of these can alleviate some of the pain symptoms. None demonstrate any ability to improve the underlying neuropathy.

2.2.3. Unmet Clinical Need

Diabetic peripheral neuropathy is a serious complication of diabetes mellitus (DM), with painful DPN being a frequent manifestation of neuropathy. Tight glycemic control and treatment of cardiovascular risk factors are effective preventive measures, but DPN remains the most common complication of DM, affecting 60% to 70% of diabetics. Progressive DPN may result in loss of function in affected legs, infection, and amputation.

Current treatments provide symptomatic relief of the pain associated with DPN. A clear unmet medical need exists for treatments that address the underlying pathology of DPN and prevent the progressive destruction and loss of function associated with this disease.

2.2.4. Hepatocyte Growth Factor for the Treatment of Diabetic Neuropathy

Hepatocyte growth factor (HGF) is a multifunctional protein with highly potent angiogenic and neurotrophic properties produced by various cell types of mesenchymal origin such as fibroblasts, macrophages, and stromal cells.[15,16,17,18,19] Its biological function is mediated by its receptor c-Met, which is a member of the receptor tyrosine kinase family. In the peripheral nervous system and its associated tissues, c-Met is expressed in sensory neurons, Schwann cells, endothelial cells, and smooth muscle cells among others,[20,21] which all play important roles in the functions of the peripheral nerve and its regeneration after pathological insults. Indeed, HGF has been reported to act on sensory and motor neurons to enhance their survivability and neurite outgrowth, and also produces a neuroprotective effect in injured sensory neurons.[22,23,24,25,26] Local application of exogenous HGF has been shown to promote the growth of sympathetic neurons,[27,28,29,30,31,32] and to induce the formation of collateral vessels and increased blood flow both in rat diabetic and non-diabetic models.[33]

The challenge associated with delivering a targeted sustained dose of exogenous HGF is in overcoming the instability of HGF in blood circulation and its rapid clearance by the liver; HGF has an in vivo half life in rodent blood of less than 15 minutes.[34] One approach to maintaining a

durable supply of HGF in target tissues is to develop a gene transfer strategy that would allow for persistent expression of HGF protein in vivo. Consistent with this, liposome-mediated non-viral gene transfer of HGF effectively reversed various pathological changes including allodynia, hyperalgesia, and reduction of blood flow in rat diabetic and non-diabetic neuropathic models.[28,31] Unlike previous transfer models, Engensis does not contain any transfection agents. Although it is administered as a simple, naked plasmid DNA, IM injection of Engensis demonstrated both pain-relieving effects and nerve regeneration activities in animal models.

[redacted]

2.2.6. Nonclinical Data

Collectively, VM202 has been well tolerated in all nonclinical studies conducted to date, with the only evidence of toxicity consisting of mild, transient injection site irritation in rats at a dose level 11 times the clinical dose of 8 mg per leg (0.11 mg/kg for a 70-kg person). No evidence of systemic toxicity has been seen in any study, and human HGF has not been detected in the sera of rats or rabbits following IM injection. No evidence of genomic integration, potential germ cell transmission, or immunostimulatory effects was found following IM administration of VM202 to animals. Refer to the IB for additional details.

2.2.7. Clinical Data

Engensis has been or is being evaluated in 10 clinical studies in the USA and/or Korea. These include two studies (Phases 1 and 2) in critical limb ischemia (CLI), one study in peripheral artery disease (Phase 2), one study in coronary artery disease (Phase 1), four studies (one Phase 1/2, one Phase 2, and one Phase 3 and one Phase 3 extension) in Participants with painful DPN, a study (Phase 1/2) in amyotrophic lateral sclerosis (ALS), and one (Phase 3) study in diabetic Participants with chronic nonhealing foot ulcers (NHU). Engensis was well tolerated, the most frequent reaction being pain at injection sites in 1 to 4% of Participants, which was similar to that observed in the Placebo groups.

2.2.7.1. Phase 1 and 2 Studies with Engensis

Phase 1 and 2 clinical studies of Engensis have been completed in patients with CLI, DPN, and ALS. Efficacy has been demonstrated in each of the indications studied to date. In a Phase 1 study using Engensis as an adjunct therapy to coronary artery bypass grafting (CABG) in Participants with ischemic heart disease (IHD), Engensis showed an improvement in regional myocardial perfusion and wall thickness in the area injected with Engensis. In CLI Participants, significant improvements were seen in wound healing, skin perfusion, and pain reduction after administration of Engensis. Significant improvements in pain were detected in Participants with painful DPN treated with Engensis compared to placebo. In ALS Participants, significant improvement was seen using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). See the IB for more information.

2.2.7.2. Phase 3 Study and Extension in Participants with Painful DPN

Helixmith conducted a Phase 3, double-blind, randomized, placebo-controlled, multicenter study (VMDN-003) designed to assess the safety and efficacy of Engensis in Participants with painful DPN. The study enrolled Participants with DPN with significant pain at study entry (VAS score $\geq$ 4 cm). A total of 507 Participants were randomized (7 were removed due to ineligibility) in a 2:1 ratio to a final dose of 32 mg Engensis or to Placebo. DPN was verified symptomatically using the MNSI, and the Brief Peripheral Neuropathy Screening (BPNS) was used to confirm bilateral involvement. See the IB for more information.

Pain levels were confirmed by completion of a 7-Day Daily Pain and Sleep Interference Diary after prohibited medication washout Eligible Participants received IM injections in both calves on Day 0 and Day 14 and were re-treated on Day 90 and Day 104. Participants were followed for a total of 9 months.

The primary efficacy endpoint was the change in the average 24-hour pain score from Baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary. The co-primary efficacy endpoint was the outcome of at least a 50% reduction in the average 24-hour pain score from Baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary. Safety and tolerability assessments were performed throughout the 9-month follow-up.

An extension study was also conducted in a subset of Participants from the VMDN-003 study who were followed for an additional 3 months for a total of 12 months (VMDN-003b). The extension study enrolled 101 of the original 500 VMDN-003 Participants – 65 from the Engensis cohort and 36 from the Placebo cohort. Of the 101 Participants enrolled, 99 completed the full 3-month extension. See the IB for more information.

The primary endpoint of the extension study was safety; a key secondary endpoint was the change in the average 24-hour pain score from Baseline to the Day 365 follow-up from the Daily Pain and Sleep Interference Diary.

The VMDN-003 study did not meet either of its co-primary endpoints – the change in average 24-hour pain between Baseline and the 3-month follow-up and outcome of a pain score change of $\leq$ 50% at 3 months when compared to Placebo. The study also did not meet either key secondary endpoint – the change in the average 24-hour pain score from Baseline to the 6-month follow-up, and the outcome of reduction in average 24-hour pain score of at least 50% at 6 months. Engensis appeared to be safe and well tolerated in both the VMDN-003 and VMDN-003b trials.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The risks for the study medication and study procedures are summarized in the following table.

Table 1 Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks of Engensis		
Eye disorders	Eye disorders were observed in both Engensis and Placebo Participants, including diabetic retinopathy, which was observed at a higher incidence in the Placebo arm.	Presence of TEAEs will be assessed pre- and post-dose on Days 0, 14, 90, and 104, as well as Days 28, 60, 150, and 180 to detect new or worsening prior eye disorders. Retinal fundoscopic examinations will be performed at Screening and Days 90 and 180.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Angiogenesis and promotion of tumor growth (cancer)	Because HGF has the potential to create new blood vessels (angiogenesis), there may be a risk of promoting tumor growth (cancer).	During Screening, all Participants will undergo cancer screening to minimize randomizing patients at increased risk for cancer or who have subclinical (no overt signs or symptoms) cancer. In addition, Participants who have two or more first- degree relatives with breast, cervical, colon, endometrial, or prostate cancer will be excluded to minimize risk of cancer during the study.
	Hyperplasia of the vasa vasorum in the early stages of atherosclerosis is independent of angiogenesis, but the intimal neovascularization that follows the hyperplasia of the vasa vasorum is angiogenesis-dependent.	During Screening, Participants diagnosed to have had a cerebrovascular accident or myocardial infarction within 3 months before Screening will be excluded in addition to Participants with Class 3 or 4 heart failure.
Risks of Study Procedures		
Method of administration (IM injections of Engensis or Placebo)	The most common injection reactions are local pain and bruising.	Detailed instructions for IM administration of study drug will be provided to all Investigators to allow standardization of administration of Engensis to all Participants across all the sites. Study drug administered on Days 14 and 104 will be injected IM at offset sites on the gastrocnemius muscles from those at Days 0 and 90 to minimize IM injections being administered at the same location as was done two weeks earlier. Smaller-gauge needles (#27) will be used to minimize pain, trauma to the skin, and subcutaneous tissue. Longer needles will used to ensure intramuscular injections of study drug and to minimize extravasation of study drug into subcutaneous tissue.
Complications of venipuncture (for blood draws for laboratory tests)	Venipuncture complications include minor bruising, hypotension, and syncope.	Incidences of adverse events of bruising, hypotension, and syncope will be closely monitored throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risks from Cancer Screening	Possible risks for Participants are identified for Cancer Screening tests, which include: • Low-dose CT scan of the chest • Mammogram • FIT stool test or colonoscopy • Primary human Papillomavirus (HPV), HPV plus a Pap smear, or a Pap smear • a PSA test Possible risks include a small amount of radiation exposure from a low-dose chest CT scan (for Participants with a history of smoking) and mammogram (female Participants); adverse reaction to the sedative used during the exam, abdominal discomfort, bleeding from biopsy site if done, or a tear in the colon or rectum (for Participants meeting the criteria for colonoscopy); discomfort associated with mammography as well as discomfort or minor symptoms (e.g., bleeding) associated with Pap smears (female Participants); and discomfort or minor venipuncture complications (female and male Participants).	Because the risk of the cancer screening tests have been considered to provide more benefit than risk in patients at increased risk of developing or who have subclinical breast cancer, cervical cancer, colon/rectal cancer, endometrial cancer, lung cancer, or prostate cancer, a risk mitigation strategy does not seem to be warranted.

Adverse Events in Clinical Studies

Engensis has been well tolerated in all clinical studies conducted thus far. The preponderant adverse events have consisted of mild, transient injection site effects, including itching, erythema, pain, and muscle spasms. Other TEAEs that have been reported were generally mild to moderate. Refer to the IB for a table of AEs that occurred in ≥ 2% of trial Participants.

Five serious AEs (SAEs) have been reported to date as possibly related to study treatment

- colon cancer in the Phase 1 trial of CLI (assessed by the investigator to be possibly related to study treatment and, even though the sponsor noted that the Participant had a history of colon polyps, a relationship could not be ruled out)
- peroneal deep vein thrombosis (categorized as possibly related to the study injection) in the Phase 2 trial of CLI. The mechanism by which HGF or VM202 could be causative in the latter is not established

SAEs reported as possibly related in the VMDN-003 trial (Section 2.2.7.2) include

- vitreous hemorrhage of the eye (categorized as possibly related to the study drug but was probably related to underlying disease)
- myocardial infarction (categorized by Helixmith as possibly related to the study drug, although categorized by the investigator as not related to the study drug)

- adenocarcinoma (categorized as possibly related to the study drug by the investigator and not related to the study drug by Helixmith)

2.3.2. Benefit Assessment

Diabetic peripheral neuropathy is one of the most-commonly encountered neuropathic pain syndromes and affects nearly half of diabetic patients. Through its effects on somatic or sensorimotor neurons, disabling consequences on function and quality of life predominate that include sleep disturbances, dependence on narcotic analgesics for pain, and trauma and infection from sensory impairment.

Engensis induces relatively rapid and prolonged production of HGF, which, through its multiple mechanisms of actions on microvascular and neural repair, has the potential to improve outcomes in diabetic patients, as suggested by preceding studies.

2.3.3. Overall Benefit/Risk Conclusions

The overall profile of potential benefits and apparent safety for Engensis provide sufficient support to justify the conduct of the present study in its aim to meet the unmet needs of DPN patients.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of IM administration of Engensis on pain in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Change in the means of the Average Daily Pain Scores (ADPSs) from the Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo in the intent-to-treat (ITT) population
Secondary Efficacy	
• To evaluate the efficacy of IM administration of Engensis on the worst pain in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Change in the means of the Worst Pain scores from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
• To evaluate the efficacy of IM administration of Engensis on reducing pain in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Proportion of Responders (≥ 50% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
Secondary Safety	
• To evaluate the safety of IM administration of Engensis in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) for Engensis compared to Placebo • Incidence of injection site reactions for Engensis compared to Placebo • Incidence of clinically significant laboratory values for Engensis compared to Placebo
• To evaluate the possibility of cellular and/or humoral responses to Engensis compared to Placebo in Participants with painful DPN in the feet and lower legs	• Change from Baseline in the cytokine profile through post-dose to Day 104 for Engensis compared to Placebo

Objectives	Endpoints
	• Presence of anti-hepatocyte growth factor (HGF) antibodies following Engensis administration compared to Placebo
Exploratory Efficacy	
• To evaluate the efficacy of IM administration of Engensis on Quality of Life and Patient Reported Outcomes in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Patient Global Impression of Change (PGIC) on Day 90 and on Day 180 for Engensis compared to Placebo
• To evaluate the durability of the analgesic response to IM administration of Engensis in Participants with painful DPN in the feet and lower legs as compared to Placebo	• Proportion of Responders (≥ 50% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 180 Visit who were Responders on Day 104 (final injection visit) for Engensis compared to Placebo
• To determine whether IM administration of Engensis has a positive effect (reverses/reduces pain, improves neurological function and quality of life) on painful DPN as compared to Placebo	• Change in the Bedside Sensory Testing (BST) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Proportion of Responders (≥20, 30, 40, 60, and 70% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo • Change in the means of the ADPSs from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit for Engensis compared to Placebo • Changes in the severity scores (Average Daily Pain, Worst Pain, Least Pain, and Pain Right Now) from the full BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo

Objectives	Endpoints
	• Changes in Michigan Neuropathy Screening Instrument (MNSI) assessments from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the 36-Item Short Form Health Survey (SF-36) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the EuroQol Health Utilities Index (EQ-5D) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo • Changes in the means of the daily use of rescue medication from Day 0 to Day 90, from Day 0 to Day 180, and from Day 90 to Day 180 for Engensis compared to Placebo

4. STUDY DESIGN

4.1. Overall Design

VMDN-003-2 is an adaptive, Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to assess the efficacy and safety of Engensis (containing the active pharmaceutical ingredient VM202) in Participants with painful DPN as compared with Placebo.

Following completion of the ICF process, Screening activities (within -52 to -7 days prior to Day 0), followed by an adjudication process will determine Participants who meet all-but-one eligibility criteria. Completion of a 7-day diary prior to Day 0 completes the eligibility process for each Participant. Eligible Participants will be enrolled and randomly assigned in a double-blinded fashion and in a 1:1 ratio to either Engensis or Placebo.

Pain, quality of life, cytokine levels, and the presence of anti-HGF antibodies will be assessed during the study.

All Participants will receive sixteen (16) 0.5-mL injections (0.25 mg) of Engensis or Placebo in each calf gastrocnemius muscle at each of the two Visits (Days 0 and 14; Day 14 is 13 to 15 days after the Day 0 Visit) during the first Treatment Cycle. During the second Treatment Cycle, Participants will receive sixteen (16) 0.5-mL IM injections of Engensis or Placebo in each calf gastrocnemius muscle on Days 90 and 104 (Day 104 is 13 to 15 days after the Day 90 Visit).

4.1.1. First Treatment Cycle

Prior to the First Treatment Cycle, in addition to vital signs, physical exam, drug tests, and medical history, the full BPI-DPN, BST, SF-36, and EQ-5D will be administered, and blood will be collected to obtain baseline values of selected cytokines, anti-HGF antibodies, and for safety laboratory assessments (see SoA, Section 1.3). A urine pregnancy test will also be conducted on women of childbearing potential.

Participants will receive Engensis or Placebo by IM injections in the gastrocnemius muscle on both legs on Day 0 and Day 14 as shown in Table 2.

Table 2 Injection and Dosing Schedule - First Treatment Cycle: Days 0 and 14

First Treatment Cycle 1: Day 0		**First Treatment Cycle 1: Day 14**		**Total per Treatment Cycle**
Gastrocnemius				
Right	**Left**	**Right**	**Left**	
Number of Injections (Engensis[a] or Placebo) 1 injection = 0.5 mL				
16 injections	16 injections	16 injections	16 injections	64 injections
Engensis (0.5 mg/mL) Dose per Gastrocnemius Muscle				
4 mg	4 mg	4 mg	4 mg	
8 mg		8 mg		16 mg

[a] Engensis concentration is 0.5 mg/mL, therefore each injection of Engensis contains 0.25 mg (per 0.5 mL).

All Participants will receive sixteen (16) 0.5-mL injections of Engensis or Placebo in the gastrocnemius muscle of each leg at each of the two Visits during the First Treatment Cycle.

Each gastrocnemius muscle will receive a total of 8 mL each Treatment Cycle day. At 2 hours (± 1 hour) after injection on Day 0 and Day 14, vital signs and blood draws for cytokine levels will be performed and adverse events will be assessed according to the SoA in Section 1.3.

4.1.2. Second Treatment Cycle

Prior to the first injection of the second Treatment Cycle, in addition to vital signs, physical exam, drug tests, and medical history, the full BPI-DPN, SF-36, EQ-5D, MNSI, BST, and PGIC will be administered, and blood will be collected to obtain baseline values of selected cytokines, anti-HGF antibodies, and for safety laboratory assessments (see SoA in Section 1.3). A urine pregnancy test will also be conducted on women of childbearing potential.

Participants will receive Engensis or Placebo by IM injections in the gastrocnemius muscle of both legs on Day 90 and Day 104 (13 to 15 days after the Day 90 Visit) as shown in Table 3.

Table 3 Injection and Dosing Schedule – Second Treatment Cycle: Days 90 and 104

Second Treatment Cycle 2: Day 90		**Second Treatment Cycle 2: Day 104**		**Total per Treatment Cycle**
Gastrocnemius				
Right	**Left**	**Right**	**Left**	
Number of Injections (Engensis[a] or Placebo) 1 injection = 0.5 mL				
16 injections	16 injections	16 injections	16 injections	64 injections
Engensis (0.5 mg/mL) Dose per Gastrocnemius Muscle				
4 mg	4 mg	4 mg	4 mg	
8 mg		8 mg		16 mg

[a] Engensis concentration is 0.5 mg/mL, therefore each injection of Engensis contains 0.25 mg (per 0.5 mL)

All Participants will receive sixteen (16) 0.5-mL injections of Engensis or Placebo in the gastrocnemius muscle of each leg at each of the two Visits during the Second Treatment Cycle. Each gastrocnemius muscle will receive a total of 8 mL each Treatment Cycle day. At 2 hours (± 1 hour) after injection on Day 90 and Day 104, vital signs and blood draws for cytokine levels will be performed and adverse events will be assessed according to the SoA in Section 1.3.

4.2. Scientific Rationale for Study Design

VMDN-003-2 is designed as a well-controlled Phase 3 study, as it is a double-blind, randomized, placebo-controlled, and multicenter study that is sufficiently sized in numbers of Participants to evaluate the potential ability of Engensis to reduce neuropathic pain and disability in Participants with painful DPN.

Collection of efficacy data will be conducted via e-Diaries, which will be used to remind Participants to record their efficacy data daily and in real time.

4.3. Participant Input into Design

Participant input into the design of this study was not collected, as the same methods were used in previous studies with Engensis and did not lead to unacceptable numbers of Participants discontinuing the studies. In addition, the methods used to assess pain reduction (BPI-DPN) and patient clinical benefit of therapy (PGIC) have been validated and are the tools recommended by the regulatory authorities to assess efficacy (pain reduction) and response (clinical benefit) in patients with painful DPN.

4.4. Justification for Dose

As in all prior studies, Engensis will be delivered as a solution of 0.5 mg/mL VM202. Participants will be treated with Engensis to result in an overall final dose of 32 mg Engensis (or Placebo) during the study, delivered by IM injections to the gastrocnemius muscles of both legs; this dosage is well within those supported by the body of pharmacology and toxicology safety studies of Engensis. Safety studies in rabbit, rat, and mouse models demonstrate that doses more than 15 times the clinical dose (32 mg) to be used in this study resulted in no toxicities.

The Phase 2 DPN study (VMDN-002) in which a single Treatment Cycle was administered on Days 0 and 14 showed significant stable reductions in pain in many Participants in the clinical study, but the responder analysis showed that not all Participants achieved maximum possible levels of pain relief and justified adding a second set of treatment with Engensis. In the 3-month extension (VMDN-003b) of the Phase 3 DPN study in which Engensis had been administered in two Treatment Cycles (at Days 0 and 14, and again at Days 90 and 104), the efficacy endpoint of pain reduction at 1 year (or approximately 260 days after the final injections) was met, supporting the selection of the same dosing regimen for this study.

4.5. End of Study Definition

The end of the study is defined as the date on which the last Participant in the study completes the Day 180 Visit or is discontinued.

4.6. Study Completion

The study will be considered complete upon Sponsor approval of the clinical study report.

4.7. Completed Participants

A Participant is considered to have completed the study if the Participant completes the Day 180 Visit and at least 5 days of the most recent 7 days with electronic diary (eDiary) entries prior to the Day 180 Visit.

5. STUDY POPULATION

5.1. Inclusion Criteria

1. Male or female Participants age ≥ 18 years at time of completion of the informed consent process
2. Type 1 or 2 diabetes mellitus (DM) and on current Standards of Medical Care in Diabetes – 2020 optimal guideline-directed medical therapy in Participants (including vaccine recommendations if possible), AND without unstable diabetes or significant medical problems, such as progressive end-organ disease, within 3 months of or during Screening, in the judgment of the Investigator
3. Glycosylated hemoglobin A1c (HbA1c) of ≤ 10.0% using the first assessment collected during Screening
4. Documented diagnosis of bilateral painful DPN in both lower extremities at least 6 months prior to Screening
5. An ADPS ≥ 4 (standard deviation ≥ 0.3 and ≤ 1.5) that is completed during the 7 days prior to randomization (Day 0)
6. The physical examination component of the Michigan Neuropathy Screening Instrument (MNSI) score of ≥ 2.5
7. If on medication for painful DPN (other than gabapentin or pregabalin), must be on a stable dose defined as < 50% change in total dose over 3 months prior to completion of informed consent
8. Male Participants and their female partners must agree to use double-barrier contraception during the study or provide proof of postmenopausal state (minimum 1 year) or surgical sterility
9. Male Participants must not donate sperm during the study
10. Female Participants must be nonpregnant, nonlactating, and either postmenopausal for at least 1 year, or surgically sterile for at least 3 months, or agree to use double-barrier contraception from 28 days prior to randomization and/or their last confirmed menstrual period prior to study randomization (whichever is longer) until the end of the study
11. Capable and willing to comply with the requirements and restrictions of the protocol and informed consent form
12. Able to complete all screening activities within 52 days of signing the informed consent form

5.2. Exclusion Criteria

1. Other sources of pain that would prevent accurate assessment of DPN pain (e.g., thoracic and/or lumbar root proximal neuropathy, mononeuritis multiplex)

2. Peripheral neuropathy caused by a condition other than diabetes: e.g., anatomic (sciatic nerve compression), systemic (monoclonal gammopathy), metabolic (thyroid disease), and toxic (alcohol use) neuropathies
3. Has taken gabapentin or pregabalin during 30 days before completion of informed consent process or will take at any time during the study
4. Progressive or degenerative neurological disorder, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, vascular dementia, multiple sclerosis, or other neurological disorders determined by the Investigator to preclude participation
5. Symptomatic peripheral artery disease (PAD) or PAD requiring revascularization and/or that may interfere with the conduct of the study
6. Vasculitis, such as from Buerger's or other diseases
7. Systolic blood pressure >180 mm Hg on tolerable doses of standard antihypertensive medications at Screening determined by the Investigator to preclude participation
8. Hyperlipidemia or dyslipidemia not being treated with an optimal treatment regimen that follows the Standards of Care for hyperlipidemic/dyslipidemic patients with DM
9. Class 3 or 4 heart failure
10. Symptomatic bradycardia or untreated high degree atrioventricular block
11. Stroke or cerebrovascular accident or myocardial infarction within 3 months before Screening
12. eGFR < 30 mL/min/1.73 m^2 using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula based on Cystatin C levels
13. Progressive renal dysfunction, defined as a decrease in eGFR to chronic kidney disease (CKD) Stage 1, 2, or 3 in the past 6 months before Screening
14. Ophthalmologic conditions pertinent to signs or symptoms of proliferative diabetic retinopathy (PDR) or other ocular conditions that preclude standard ophthalmologic examination
15. Myopathy (e.g., Duchenne or Becker muscular dystrophy, polymyositis)
16. Any prior or planned lower extremity amputation (excluding toe amputations) due to diabetic complications or prior lower leg injury (e.g., scarring, muscle atrophy) in the calf area (gastrocnemius) that would significantly reduce the surface area of the skin or amount of intact skeletal muscle required for the 16 treatment injections of Engensis
17. Active infection requiring antimicrobial agent(s) (chronic infection or severe active infection that may compromise the Participant's well-being or participation in the study, in the Investigator's judgment)
18. Chronic inflammatory or autoimmune disease (e.g., Crohn's disease, rheumatoid arthritis)
19. Immunosuppression due to underlying disease (e.g., rheumatoid arthritis, systemic lupus erythematosus) or to currently receiving immunosuppressive drugs, (e.g., chemotherapy, corticosteroids) or to radiation therapy

20. Participants requiring chronic oral or injectable steroids and unwilling to refrain from taking these drugs for the duration of the study
21. Participants with a family medical history of 2 or more first-degree relatives (parent, sibling, child) diagnosed to have the same type of cancer – breast cancer, cervical cancer, colon cancer, endometrial cancer, lung cancer, or prostate cancer; or with a family medical history of Lynch Syndrome (hereditary non-polyposis colorectal cancer) in any first-degree relative; or who show positive results during cancer screening
22. Positive human immunodeficiency virus (HIV) or human T-cell lymphotropic virus (HTLV) I/II test at Screening
23. Participants with cancer who have not been cancer-free for ≥5 years with the following exceptions (not excluded): Participants with in-situ basal cell or squamous cell carcinoma
24. Participants with a prior history of stem cell transplant for cancer no matter how long they have been cancer-free
25. Active acute or chronic hepatitis B
26. Active hepatitis C
27. Clinically significant laboratory values or current medical conditions during Screening that, in the judgment of the Investigator, should be exclusionary
28. Hospital Anxiety and Depression Scale (HADS) score of ≥ 15 on either subscale
29. History of drug abuse (the habitual taking of addictive or illegal drugs) in the past 3 months and positive for Drugs of Abuse, with the exception of cannabis, during Screening
30. Participants unwilling to discontinue their use of the following during Screening at least 7 days before starting eDiary entries and not use any of the following during the study:
    - skeletal muscle relaxants
    - opioids
    - transcutaneous electrical nerve stimulation (TENS)
    - acupuncture
    - benzodiazepines (other than stable bedtime dose)
    - injectable or oral steroids
31. Participants not on a stable dose and not willing to remain on a stable dose during the study for the following drugs:
    - antidepressants
    - antiepileptics
    - duloxetine

32. Participants currently using the following medications and unwilling to discontinue topical use on the lower legs and feet and throughout the study:
    - capsaicin
    - anesthetic creams (except during Study Injections)
    - anesthetic patches
    - ISDN spray
33. Use of an investigational drug or treatment in past 30 days or previous participation in a clinical study with Engensis
34. Body mass index (BMI) ≥ 42 kg/m^2
35. Recent treatment for COVID-19 with ongoing sequelae

5.3. Number of Participants

The target sample size is a minimum of 152 Participants with a maximum sample size of 250 Participants. Participants will be randomized in a 1:1 ratio. Based upon the results of the adaptive design interim analysis, which will include at least 76 completed or discontinued Participants, the number of Participants randomized may be increased to a maximum of 250 Participants. The adaptive design provides for re-estimation of the sample size after 50% of Participants have completed their 6-month assessments or have discontinued. The total enrolled number of Participants may be increased to a maximum of 250 Participants if the results are promising (conditional power > 39.6%). The adaptive design process is described in the Statistical Analysis Plan (SAP).

5.4. Enrollment, Randomization, and Treatment Assignment

5.4.1. Enrollment Adjudication Process

All screening information (except the 7-day eDiary to be completed during Day -7 to Day 0) for each Participant prior to randomization will be sent to an Adjudication Committee (Figure 3). The Adjudication Committee is composed of the Sponsor Medical Director, Medical Monitor, and Clinical Operations personnel. The Adjudication Committee reviews the relevant clinical information of each Participant on a timely basis to ensure strict adherence to the Inclusion/Exclusion Criteria. The Committee either confirms the eligibility for randomization of an individual Participant or confers with the Investigator regarding the status of a Participant as a screen failure.

Once a Participant is deemed to meet all Inclusion/Exclusion Criteria, blinded randomization will be conducted via an Interactive Web Response System (IWRS) in a 1:1 ratio to receive either Engensis or Placebo. The unblinded Pharmacist or delegated staff will prepare the Engensis or Placebo injections for that Participant prior to First Injections by the Investigator or qualified designee on Day 0.

5.5. Participant Identification

To maintain confidentiality, the name of the Participant should not be recorded on any study document other than the informed consent form. All Participants who sign the informed consent form will be assigned a unique identifier in the following format: XX-YYY where XX is the 2-digit Site number and YYY is the 3-digit sequential ID number starting with 001 for the first Participant consented at that Site. For example, the first Participant consented at Site 11 will be assigned 11-001. ID numbers for screen failures will not be reused. If a screen failure is later reconsented for rescreening, a new ID number will be assigned.

5.6. Screen Failures

A consented Participant who does not meet all eligibility criteria will immediately cease further study-related testing; the cessation will be communicated to the Sponsor or designee within 24 hours.

A minimal amount of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes eligibility criteria, demographic data, screen failure details, and other pertinent materials.

5.7. Rescreening

Participants who provided informed consent but failed to meet all eligibility criteria may be rescreened with Sponsor written permission via the adjudication process.

The following Screening assessments, if completed during the first Screening and found to meet eligibility criteria, may not need to be repeated when the Participant returns for rescreening:

- Viral screening if performed within 3 months of signing the new informed consent
- Retinal fundoscopy if performed within 30 days of signing the new informed consent

All other Screening assessments will need to be repeated.

5.8. Lifestyle Considerations

5.8.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions for this study.

5.8.2. Caffeine, Alcohol, and Tobacco

There are no caffeine, tobacco, or alcohol restrictions for this study. Tobacco use for current smokers [pack-year history = (packs smoked per day) x (years as a smoker)] will be recorded at Screening.

5.8.3. Supplements

There are no restrictions on herbal medicines or dietary supplements or changes in their use during the study. The use of any supplements during the study will be recorded on the Participant's medical record and the electronic case report form (eCRF) as concomitant medications.

5.8.4. Activity

There are no restrictions on activity. Participants should be advised to continue their normal activity level during the study.

6. STUDY INTERVENTION

6.1. Study Intervention(s) Administered

Refer to the Injection Guideline for administration of Engensis or Placebo.

6.1.1. Engensis

Engensis contains the active pharmaceutical ingredient VM202, a plasmid DNA containing a novel genomic cDNA hybrid human HGF coding sequence, HGF-X7, that expresses two isoforms of HGF, HGF_{728} and HGF_{723}. The plasmid has 7,377 base pairs with a human cytomegalovirus (HCMV) enhancer / promoter, a growth hormone polyadenylation terminator sequence, ColEl originator, and the kanamycin resistance gene on a pCK backbone.

The components of Engensis are provided in Table 4.

Table 4 Components of Engensis

Component	Function	Composition
VM202	Active pharmaceutical ingredient	2.5 mg
Sucrose	Suspension medium	55 mg (1.1%)[a]
Sodium Chloride	Suspension medium	45 mg (0.9%)[a]
Sterile Water for Injection	Suspension medium	5 mL

[a] Concentration after reconstitution in 5 mL water for injection.

6.1.2. Placebo

Placebo will be sterile Engensis vehicle. The components of Engensis vehicle are provided in Table 5. Engensis excipients are supplied in a sterile glass vial in liquid form. Each vial is only to be used for one Participant. Visually, Placebo is indistinguishable from reconstituted Engensis. The Participant, Investigator, and study nurse will not be able to distinguish Placebo from Engensis.

Table 5 Components of the Placebo

Component	Function	Composition
Sucrose	Suspension medium	55 mg (1.1%)
Sodium Chloride	Suspension medium	45 mg (0.9%)
Sterile Water for Injection	Suspension medium	5 mL

6.1.3. Summary of Study Intervention Characteristics

Study Arm	Engensis	Placebo
Study Drug	Engensis	Placebo
Type	Biologic	N/A
Formulation	Lyophilized product to be reconstituted	Injectable liquid
Amount of Active Drug	2.5 mg Engensis per vial	N/A
Dosage Level per Treatment Cycle	Total of 16 mg per Treatment Cycle, with each cycle composed of 2 days of 16 injections each to the right and left gastrocnemius muscles, spaced 2 weeks apart	Each Treatment Cycle composed of 2 days of 16 injections each to the right and left gastrocnemius muscles, spaced 2 weeks apart
Route of Administration	IM injection	IM injection
Use	Experimental	Placebo
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Engensis will be provided in a vial. Each vial will be labeled per country requirement.	Placebo will be provided in a vial. Each vial will be labeled per country requirement.
Former Names	VM202	N/A

Abbreviations: IM = intramuscular; N/A = not applicable

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Engensis Preparation

Engensis is supplied in a sterile glass vial containing lyophilized drug product with 2.5 mg of Engensis. Engensis will be reconstituted by the unblinded Pharmacist or delegated staff with 5 mL of sterile non-bacteriostatic water for injection (WFI) for a final Engensis concentration of 0.5 mg/mL (see Injection Guidelines). Each reconstituted vial is to be used for only one Participant.

6.2.2. Storage of Engensis and Placebo

The unblinded Pharmacy staff is responsible for receiving and storing study drug according to the pharmacy manual.

Engensis and Placebo must be stored in a refrigerator at temperatures between 2°C and 8°C.

Reconstituted Engensis must be used within 12 hours. Engensis should never be frozen. Further information regarding study drug administration can be found in the Injection Guidelines.

A temperature log for the investigational drug product and Placebo storage refrigerator unit must be maintained, and the refrigerator unit temperature must be recorded on a daily basis from receipt until final reconciliation and return of the investigational drug product by the monitor or designee. Temperature monitoring will be the responsibility of the Investigator or the assigned designee(s).

In the case of temperature excursions, products should be placed in quarantine and not dispensed, and the Investigator or the assigned designee(s) should contact the unblinded clinical research associate (CRA) as soon as possible to receive further instructions.

6.2.3. Product Accountability

In accordance with federal regulations (21 CFR 312.62), Investigators are required to keep accurate records showing final disposition of all investigational drugs.

Engensis is to be used only in accordance with this protocol and under supervision of the Pharmacist or delegated staff. A tear-off label will be provided with Engensis and Placebo, which should be applied to the Participant's drug accountability form by the unblinded Pharmacist or delegated staff when study medication is dispensed. The Pharmacist will maintain an accurate record of the receipt of Engensis and Placebo, including the date received. Specifically, the Pharmacist or assigned designee will confirm that all study drug supplies are received intact and in the correct amounts per the shipping form. In addition, an accurate study drug disposition record will be kept, specifying the date, time, and amount dispensed, to whom it was dispensed (Participant-by-Participant accounting), and the accounts of any drug accidentally or intentionally destroyed. This inventory record must be available for inspection by the unblinded clinical research associate (CRA) at any time. Copies of this record will be provided to the Sponsor by the Pharmacist or delegated staff at the conclusion of the study.

After the study is completed, the Pharmacist or delegated staff must account for all study drug used, unused, partially used, returned, and destroyed. All investigational product, Engensis and Placebo, including used, partially used, unused, and damaged product, will be returned to the Sponsor by the site after reconciliation by the unblinded CRA. Study medication from the Site will be returned to the Sponsor as directed in writing by the Sponsor for reconciliation.

6.3. Measures to Minimize Bias

6.3.1. Randomization

Participants are to be randomized on Day 0. Randomization will be conducted via an IWRS in a 1:1 ratio for Participants to receive either Engensis or Placebo.

6.3.2. Stratification

Participants will be stratified between the Engensis and Placebo groups according to their baseline ADPSs of < 7 and ≥ 7. The ADPS for the baseline determination will be considered missing if fewer than 5 of 7 days of the ADPS entries are provided. Participants will not be

randomized if the baseline ADPS has fewer than 5 days of the ADPS entries.

6.3.3. Blinding

Participants, Investigators, Site staff, CRO staff, and Sponsor staff will be blinded to treatment assignments except for the designated unblinded Clinical Research Associate (CRA), Sponsor Clinical Supplies Manager, the unblinded Medical Monitor, and the Site's unblinded Pharmacist or delegated staff.

The unblinded pharmacy staff are responsible for receiving, storing, preparing, and dispensing study drug per the Pharmacy Manual. An Investigator and the designated unblinded Medical Monitor(s) may be unblinded to the treatment assignment for a Participant with an SAE when the treatment decision requires knowledge of the treatment assignment.

To avoid potential bias, Investigators and study staff are expected to refrain from sharing safety and treatment outcomes with other participating Sites.

The DSMB, independent of the Sponsor, may review individual unblinded Participant narratives in the case of an SAE or multiple SAEs for which the DSMB Chair requests unblinding, but will not have access to unblinded tables and listings unless requested by the DSMB Chair when assessing a potential safety signal. While the study is ongoing and prior to database lock, the datasets will remain blinded with no preliminary summary of the study by the individual treatment arms except when requested by the DSMB Chair.

6.3.4. Maintenance of the Blind

Once the Participant has been adjudicated and deemed eligible for potential randomization, the drug depot will prepare and ship both Engensis and Placebo vials to the Site pharmacy. The pharmacy will keep both Engensis and Placebo vials and the dose preparation worksheet in a secure location with access limited to unblinded pharmacy personnel responsible for preparing the syringes with assigned study treatment. The Investigator or designee will randomize the Participant using the IWRS system on Day 0 after confirming eligibility criteria.

The unblinded Pharmacist or delegated staff will receive a notification from the IWRS system indicating into which arm the participant has been randomized. The Pharmacist or delegated staff will prepare Engensis or Placebo per the Pharmacy Manual.

Blinding will be achieved by having study drug syringes prepared by the pharmacy staff and ensuring that the study drug vials are never left in a location where they could be seen by blinded study staff (e.g., study coordinator, study nurse, Investigator). The Engensis and Placebo vials are readily distinguishable from each other, even from a distance. However, because reconstituted Engensis is indistinguishable from Placebo, syringes containing Engensis are indistinguishable from syringes containing Placebo.

The pharmacy staff and select individuals such as the unblinded CRA will be unblinded to the treatment assignments. The Participant and study personnel, including study coordinators, study nurses, laboratory technicians, Investigators, and blinded CRAs, will remain blinded until all data has been entered into the database and the database is locked.

IN CASE OF EMERGENCY (i.e., SERIOUS ADVERSE EVENT [SAE]) AND ONLY WHEN THIS INFORMATION INFLUENCES THE PARTICIPANT'S MEDICAL MANAGEMENT, the Investigator may contact the designated unblinded Medical Monitor to request unblinding of the treatment assignment. The date and reason for unblinding will be documented in the electronic data capture (EDC) system.

6.4. Study Intervention Compliance

All Site personnel involved with the receipt, storage, preparation, administration, and destruction of study drug are required to document their understanding of the Study Drug Injection Guidelines. Refer to the Injection Guidelines.

All study drug will be administered under the supervision of the Investigator.

Compliance with study drug administration instructions will be assessed through the review of accountability and preparation logs as well as the reconciliation of used and unused vials, vials destroyed, and vials returned to the Sponsor.

6.5. Concomitant Therapy

All concomitant therapies should be captured in the Concomitant Therapy section of the eCRF.

6.5.1. Rescue Medicine

The only allowed rescue medication is acetaminophen. On Day 0, the Site will dispense extra-strength acetaminophen (500 mg) provided by the Sponsor. The Participant will be instructed to take up to 2 caplets every 6 hours as needed for DPN pain for a maximum of 6 caplets (3 grams) / day. The study-issued acetaminophen is only to be used for DPN pain, and the Participant is not to use any other source of acetaminophen for DPN pain. The Participant may use up to 1 gram per day of a source of acetaminophen other than the study-issued acetaminophen for conditions other than DPN pain. The Participant will be provided with an eDiary to record their pain level (NRS = 0-10 scale) before use, the date and time of use, and the amount of acetaminophen used. The Participant will be asked to return the eDiary and the unused rescue medication at each Visit. At each Visit, the Site will reconcile how many caplets were used, as documented in the eDiary, with how many caplets remain in the bottle(s). New bottle(s) of acetaminophen will then be dispensed by the Site to the Participant.

6.6. Dose Interruption

No intentional modifications of the number or concentration of doses will be permitted. An unintentional interruption of the number of injections (32 per Study Injection Visit) is only allowed if the participant experiences an AE related to study drug administration or other health-related events (e.g., illness) during the study, or if the full set of injections cannot be prepared. If the full set of study injections cannot be administered during the normal Study Injection Visit, the Participant should be scheduled to receive the remaining injections within 48 hours. If this is not possible, then the remainder of the injections for that visit will not be administered.

6.7. Prohibited and Restricted Medications and Procedures

Prohibited medications and procedures are listed in Section 10.4, Appendix 4.

6.7.1. Medications That May Interfere with Engensis Bioactivity

Certain steroids (except inhaled, ocular, or intra-articular steroids) may interfere with the bioactivity of Engensis and are therefore prohibited from use during the study. Participants must agree to not take any of these drugs for the duration of the study. A list of the prohibited medications in this category can be found in Section 10.4, Appendix 4.

6.7.2. Medications and Procedures That May Interfere with Assessment of Pain

Participants may participate in the study if they are willing to discontinue use of the following therapies 7 days prior to starting the 7-Day BPI-DPN eDiary. Participants must refrain from use of these therapies for the duration of the study:

- skeletal muscle relaxants
- opioids
- benzodiazepines (except for stable bedtime dose)
- injectable steroids
- capsaicin applied to the lower legs or feet
- local anesthetic creams and patches applied to the lower legs or feet (except local/topical anesthetic cream applied immediately prior to study drug injections
- ISDN spray applied to the lower legs or feet
- transcutaneous electrical nerve stimulation (TENS), acupuncture

A list of prohibited medications and procedures in this category can be found in Section 10.4.

If not using a stable dose of duloxetine (Cymbalta), any antidepressants (e.g., amitriptyline and venlafaxine), or any other antiepileptics (e.g., valproic acid, carbamazepine, and vigabatrin) during Screening, Participants must agree to not start these drugs during the study. Potential Participants on these medications on the day of informed consent must maintain a stable dose during the study. Participants may not use pregabalin (Lyrica) or gabapentin (Neurontin) at any time during the study.

6.8. Prior and Concomitant Medications, Treatments, and Procedures

Medications and treatments taken within 30 days prior to Day 0 will be recorded on the Medication and History eCRF at the Day 0 Visit. Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, herbal supplements, and topical anesthetics for post-injection pain and procedures that the Participant is receiving at the time of enrollment or receives during the study must be recorded on the Concomitant Medications or Concomitant Procedures eCRF.

For each medication or treatment, the following information will be collected:

- Medication trade or generic name, or procedure
- Indication for which the medication/procedure was given
- Dose/strength, route, and frequency of administration
- Date started and date stopped (or continuation at study exit)
- Reason for use

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy. Acetaminophen is the only rescue medication allowed in this study. Up to 3 grams per day will be allowed. Use of rescue medication will be recorded each day in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary to discontinue study drug for a Participant. If study drug is discontinued, the Participant will remain in the study to be evaluated for safety if the Participant agrees to continue participating in the study. See Section 1.3 (SoA) for any further assessments that need to be completed.

7.2. Participant Discontinuation/Withdrawal/Early Termination from the Study

Any Participant may voluntarily discontinue the study at any time without prejudice. The Investigator may discontinue a Participant from the study at any time if, in the Investigator's judgment, the Participant's health or safety would be compromised by remaining in the study.

Specific reasons for study discontinuation include the following:

- Participant's decision
- Investigator's decision
- Adverse event
- Insufficient compliance with study requirements
- Lost to follow-up
- Other

The specific reasons for Participant discontinuation will be recorded.

The following assessments will be performed, if possible, for Participants who discontinue prior to the Day 180 Visit, at the Early Termination Visit (ET; see Section 1.3, SoA).

- APR and PRR
- Full BPI-DPN
- MNSI
- BST
- PGIC
- SF-36 and EQ-5D
- Complete physical examination
- Vital signs, weight
- Retinal fundoscopy
- Serum chemistry, lipid profile, and hematology
- ECG
- Urine pregnancy test
- Urine drug analysis
- HbA1c

- Concomitant medications / procedures
- Adverse events
- Anti-HGF antibodies

7.3. Lost to Follow-up

A Participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled Visits and is unable to be contacted by the Site by Day 180 (+7 days).

The following actions must be taken if a Participant fails to return to the clinic for a required Study Visit:

- The Site must attempt to contact the Participant and reschedule the missed Visit as soon as possible. The Site must counsel the Participant on the importance of maintaining the assigned Visit schedule and ascertain whether the Participant wishes to and/or should continue in the study.
- If no response is obtained from the Participant, the Investigator is encouraged to contact one of the Participant's relatives or his/her general practitioner.
- Before a Participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the Participant, including at least three telephone calls and, finally, a certified letter to the Participant's last known mailing address. These contact attempts should be documented in the source records.
- Should the Participant continue to be unreachable, the Participant will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in Section 1.3 (SoA).

Protocol waivers or exemptions are not allowed. Adherence to the protocol requirements, including those specified in the SoA, is essential.

8.1. Screening Activities

8.1.1. Screening Days -52 to -7

Prior to Screening, Participants will give informed consent and then be initially screened using the symptoms portion of the MNSI. Only Participants with a MNSI physical assessment score of ≥ 2.5 will be allowed to proceed with the full screening procedures.

If the MNSI criteria are met, the rest of Screening will proceed. Prior to randomization, Participant eligibility will be assessed as follows:

- Evaluation of eligibility criteria
- Medical history
- Concomitant medications and procedures
- Vital signs
- Complete physical exam, including height, weight, waist circumference, and BMI
- ECG
- Cancer history and cancer screening tests where applicable
- Smoking status (current or never smoker; for smokers, the pack-year history or number of packs/day and number of years smoking will be recorded)
- Retinal fundoscopy
- Ultrasound of right and left gastrocnemius muscles
- Serum chemistry, hematology, and lipid profile
- HbA1c
- eGFR
- Urine pregnancy test (for women of childbearing potential only)
- Urine drug analysis
- Viral screening – HIV, Anti-Human T-Cell Lymphotropic Virus (HTLV) I/II antibody with reflex confirmatory assay, Hepatitis B core antibody (IgM HBcAb), antibody to Hepatitis B antigen (HBsAb), Hepatitis B surface antigen (HBsAg) in addition to a quantitative HBV viral load if needed clinically, and Hepatitis C antibodies (Anti-HCV) and a positive qualitative PCR to assess HCV viral load
- Hospital Anxiety and Depression Scale (HADS)
- Accurate Pain Reporting (APR)

- Placebo Response Reduction (PRR)

8.1.1.1. Cancer Screening Tests

All Participants in this study must undergo screening for multiple types of cancer according to current guidelines. Some diagnostic tests and procedures performed prior to completion of informed consent and that are documented in the Participant's medical history may be acceptable where noted.

Note that Participants with a first-degree relative (mother/father, sister/brother, daughter/son) with a diagnosis of Lynch Syndrome (hereditary non-polyposis colorectal cancer [HNPCC]) or Participants who have **2 or more first-degree relatives** (parent, sibling, child) diagnosed with the same type of cancer – breast cancer, cervical cancer, colorectal cancer, endometrial cancer, lung cancer, or prostate cancer – are not to undergo cancer screening, as these Participants will be excluded from the study.

Cancer screening tests for those **without a first-degree relative or with one first-degree relative** with a family history of the indicated cancer include the following (note that past history refers to years before Screening):

- **Mammogram** for breast cancer for female Participants aged 45 to 54 years, if not performed within the past 12 months; or if not performed within the past 24 months for female Participants aged ≥ 55 years. If the mammogram results are negative for cancer, the Participant will be allowed to enter the study.
- Primary **HPV test** for cervical cancer for female Participants aged 25 to 65 years, if not performed within the past 5 years; if primary HPV test is not available, an **HPV test in combination with cytology (PAP) if not** performed within the past 5 years; or **cytology alone** if not performed within the past 3 years.[35] If the test results are negative for cervical cancer, the Participant will be allowed to enter the study.
- **FIT stool test** for colon cancer for Participants (male or female) aged ≥ 45 years and ≤ 75 years, if not performed within the past 12 months; or a **colonoscopy** (in lieu of an FIT stool test) if not performed within the past 5 years.[36,37,38,39] If the test results are negative for colon cancer, the Participant will be allowed to enter the study. Participants aged ≥ 76 years will not be required to undergo colon cancer screening.
- **Low-dose chest CT scan** for lung cancer[40,41,42,43] for current or previous smokers (male or female) who:
    - Are ≥ 50 years of age, are currently smoking, have a ≥ 30 pack-year history of smoking, and have not had a CT scan performed within the past 12 months
    - Are ≥ 50 years of age, quit smoking but have smoked within the past 15 years, and have a ≥ 30 pack-year history

    If the low-dose chest CT scan test results are negative for lung cancer, the Participant will be allowed to enter the study.

- PSA test for prostate cancer, if not performed within the past 12 months, for male Participants who are African-American aged ≥ 45 years or other races aged ≥ 50 years.[44] If the test results are negative for prostate cancer, the Participant will be allowed to enter the study.

See Section 8.4.2 (Medical History) for information and references for familial risk for cancer and Section 8.5.4 (Adverse Events of Special Interest) for information and references for increased risk of cancer with obesity and in type 2 diabetes patients.

8.1.1.2. Hospital Anxiety and Depression Scale

The HADS questionnaire will be completed by Participants at Screening through use of an eDiary. There are two separate scales for depression or anxiety and the exclusionary cutoff of ≥ 15 applies to either subscale. The Investigator should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins at the Screening Visit. The HADS questionnaire is presented in Section 10.6, Appendix 6.

8.1.2. Screening Days (-7 to 0)

Following adjudication based on screening activities completed by Day -7, Participants will complete a 7-day diary that includes the Brief Pain Inventory for Diabetic Painful Neuropathy (BPI-DPN) prior to Day 0 as a final eligibility assessment prior to randomization on Day 0 (see Section 8.3.1).

8.2. Participant Training

8.2.1. Accurate Pain Reporting

The Accurate Pain Reporting (APR) training instructs Participants how to report pain scores accurately and reliably, and on the proper use of pain scales, with the aim of increasing the reporting accuracy of Participant pain. Participants will receive training at Screening, pre-dose on Days 0, 14, 90, and 104, and on Days 28, 60, 150, and 180/ET.

8.2.2. Placebo Response Reduction

The Placebo Response Reduction (PRR) training teaches the Participant about the appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide Participants with truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical studies. Participants will receive training at Screening, pre-dose on Days 0, 14, 90, and 104, and on Days 28, 60, 150, and 180/ET.

8.3. Efficacy Assessment and Procedures

8.3.1. Brief Pain Inventory for Diabetic Painful Neuropathy

The Brief Pain Inventory for Diabetic Painful Neuropathy (BPI-DPN) assessment tool (Section 10.7, Appendix 7) will be administered through use of an eDiary. The Investigator

should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins. The BPI-DPN will be conducted using the full BPI-DPN questionnaire and/or the partial BPI-DPN questionnaire.

Scores obtained from the full BPI-DPN for 7 days prior to the Day 0, Day 90, and Day 180/ET Visits will be used to determine ADPSs. The ADPS is the mean of at least 5 daily pain scores recorded in the eDiary. If the eDiary contains fewer than 5 daily entries over the 7 days prior to the Day 0 and Day 180 Visits, the Visit must be rescheduled so that the Participant can record 5 daily entries over the 7 days prior to the rescheduled Visit. The scores from the 7 days prior to Day 0 and the 7 days prior to Day 180 will be used in the primary endpoint.

Participants will use the eDiary to rate their Average Daily Pain and Worst Daily Pain on a daily basis from Days 0 to 180 to allow an assessment of onset, peak, and duration of pain relief in the active treatment group versus Placebo.

8.3.2. Quality of Life/Participant Reported Outcome Measures

8.3.2.1. Patient Global Impression of Change

The Participant's impression of change after treatment will be measured with the Patient Global Impression of Change (PGIC) questionnaire through use of an eDiary. The Investigator should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins (Section 10.8, Appendix 8). This questionnaire measures the Participant's perception of how treatment has affected their level of activity, symptoms, emotions, and overall quality of life. Each descriptor is ranked on an intensity scale of 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse. The test will be self-administered during the Day 90 and Day 180/ET Visits.

Upon completion of the questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic.

8.3.2.2. Short Form Health Survey

The 36-item Short Form Health Survey (SF-36; Section 10.9, Appendix 9) will be administered through use of an eDiary. The Investigator should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins to measure the Participant's perception of their overall health status pre-dose on Days 0 and 90 and on Day 180/ET. This 36-question survey measures the Participant's perception of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

Upon completion of the questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic.

8.3.2.3. EuroQol Health Utilities Index

The EuroQol Health Utilities Index (EQ-5D) instrument (Section 10.10, Appendix 10) will also be administered through use of an eDiary. The Investigator should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins to measure the Participant's perception of their overall health status pre-dose on Days 0 and 90 and on Day 180/ET. The instrument has two parts – the descriptive system that measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; and the visual analog scale that records the Participant's self-rated health.

Upon completion of the questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic.

8.3.3. Bedside Sensory Testing

Sensory tests will be performed at 3 predefined locations: dorsum of the foot, mid-shin, and mid-thigh, except low threshold mechanoreceptive function, which will be conducted at the bottom of the foot at any time prior to dosing on Day 0 and Day 90. The BST should also be done on day 180. The Investigator should ensure that the Participant is seated comfortably before data collection begins.

The Bedside Sensory Testing is presented in Section 10.11, Appendix 11.

8.3.4. Michigan Neuropathy Screening Instrument

The Michigan Neuropathy Screening Instrument (MNSI) (Section 10.12, Appendix 12) will be administered through use of an eDiary (for the Participant) or an electronic tablet (for the Site) during Screening in order to confirm the diagnosis of DPN, based on the cutoff ≥ 2.5,[45,46] and on Day 90 and the Day 180/ET Visit to track disease progression. The Investigator should ensure that the Participant is provided with instructions and is trained to use the eDiary and to complete the assessment tool properly before data collection begins. The MNSI comprises a Participant questionnaire (15 questions) and a physical evaluation that includes a foot inspection, vibration sensation testing, muscle stretch reflexes, and monofilament testing.

Upon completion of the MNSI questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the Participant prior to leaving the clinic. The Participant will be required to electronically sign and date the questionnaire.

8.4. Safety Assessments

8.4.1. Physical Examinations

Complete physical examinations (PEs) will be performed at Screening, pre-dose on Days 0, 14, 90, and 104, and on Days 28, 60, 150, and 180/ET; and at the last Visit if the Participant discontinues prior to Day 180. The complete PE will include the following: an examination of the skin/integumentary systems, general appearance, head, neck (including thyroid), eyes, ears, nose, throat, lymph nodes, chest (lungs), heart, abdomen, musculoskeletal system, neurological system, and any additional assessments needed to establish baseline status or evaluate symptoms or AEs. Height, BMI, and waist circumference will be recorded only during Screening. Any physical examination abnormalities considered to be clinically significant (CS) should be added to AEs using medically appropriate terminology.

8.4.2. Medical History and Familial History of Cancer

A detailed description of the Participant's current disease status, past medical conditions (including cancer), and medication and treatment history will be recorded at the Screening Visit.

The medical history (including treatment history) will include a detailed assessment of past diabetes history including DPN, events, interventions, and procedures. Other potential causes of peripheral neuropathy will be documented (e.g., alcohol consumption, hypothyroidism, collagen vascular diseases, vasculitis, or B-12 or folate deficiency).

All medication history within 30 days before randomization will also be collected at Screening.

Any untoward medical events that occur from the time of signing of informed consent and during Screening (prior to study drug administration) will be captured as new medical problems and added to the medical history. A change in medical status or medical history from time of signing of informed consent up to immediately prior to taking the first dose of study drug is also to be added to the medical history.

The Investigator or qualified medical personnel who routinely perform these evaluations in patients with DPN will conduct the examination, determine findings, and assess any abnormalities as to clinical significance.

Cancer history will be collected for the 5 years prior to Screening. In addition, familial history of cancer will also be recorded at Screening. Familial risks for cancer have been identified for breast,[47] colon,[48,49,50] endometrial,[51] lung,[52] and prostate[53,54] cancer. In addition, if the Participant has Lynch Syndrome, a hereditary non-polyposis colorectal cancer, this information will be recorded at Screening.[55]

Elevated risks of cancer for type 2 diabetes or obesity are detailed in Section 8.5.4, Adverse Events of Special Interest.

8.4.3. 12-Lead Electrocardiograms

12-Lead electrocardiograms (ECGs) will be performed during Screening, pre-dose on Day 90, and on Day 180. Any clinically significant abnormalities are to be recorded. The ECG recording will be printed, and the Investigator or delegated staff will initial and date the printout to indicate

their review of the findings. The trace and the interpretation will then be stored with the Participant's records.

8.4.4. Ultrasound of Right and Left Lower Legs

A posterior-to-anterior (P-A) ultrasound of the right and left lower extremities will be performed at Screening to assess the surface area and depth of skin, subcutaneous tissue, and fat covering the gastrocnemius muscles of each leg and the location of other anatomical components that might interfere with the Engensis Injections.

- The surface area of the gastrocnemius muscle available for placement of the 16 injections of Engensis (which must be injected into skeletal muscle to be effective) will be calculated by multiplying the length (medial and lateral condyles of the femur to the top of the Achilles tendon/gastrocnemius aponeurosis) and the width (widest section that includes the medial and lateral heads of the gastrocnemius muscle) identified by ultrasound.
- The depth of the skin and subcutaneous tissue to the surface of the gastrocnemius muscle as well as the thickness of the gastrocnemius measured by ultrasound will be used to determine the length of needle that will need to be used for accurate injection of Engensis into the skeletal muscle tissue (to a depth of at least 1 cm into the muscle).
- The location(s) of the Achilles tendon/gastrocnemius aponeurosis and other sites of fibrous tissue or connective tissue within the medial and lateral heads of the gastrocnemius muscle of each leg will be identified by ultrasound. Engensis must not be injected into connective tissue, fibrous tissue, or tendons as HGF cannot be expressed from the plasmid in these tissues.

8.4.5. Vital Signs

Vital signs will be measured at Screening, pre- and post-dose at Study Injection Visits during Treatment Cycle 1 (Days 0 and 14) and Treatment Cycle 2 (Days 90 and 104), and at all other Study Visits. Weight will be collected pre-dose at Study Injection Visits. After resting in the seated position for 5 minutes, vital signs measured will include temperature, sitting blood pressure, heart rate, respiratory rate, and oxygen saturation on room air. The method of temperature measurement should be according to the Site's policy and should be consistently applied.

8.4.6. Clinical Laboratory Assessments

See Section 1.3 (SoA) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition.

All protocol-required laboratory assessments must be performed in accordance with the

laboratory manual and the SoA.

8.4.6.1. Local and Central Laboratory Assessments

The following laboratory assessments for safety and establishing eligibility will be performed at local laboratories during Screening as noted in the SoA. Everything from Day 0 to 180 will be performed by the central laboratory.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study. The laboratory reports must be filed with the source documents and uploaded into the EDC. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition.

All protocol-required laboratory assessments must be performed in accordance with the laboratory manual and the SoA.

8.4.6.1.1. Hematology

- White blood cell count
- Neutrophil (including calculated absolute neutrophil count)
- Hemoglobin
- Hematocrit
- Platelet count

8.4.6.1.2. Kidney Function Tests

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated glomerular filtration rate (eGFR, calculated using the chronic kidney disease epidemiology collaboration [CKD-EPI] formula based on Cystatin C levels)

8.4.6.1.3. Liver Function Tests

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)
- Total bilirubin
- Total protein
- Albumin

8.4.6.1.4. Clinical Chemistry

- Electrolytes (sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate, magnesium)

- Glucose (random collection, i.e., not necessarily fasting)
- Amylase
- Lipase
- Lactate dehydrogenase
- Creatine kinase
- HbA1c
- Cystatin C (for calculation of eGFR)

8.4.6.1.5. Lipid Profile

- Total cholesterol
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)
- Triglycerides

8.4.6.1.6. Additional Tests

- Urine pregnancy test
- Urine drug analysis

8.4.6.1.7. Viral Screening

- HIV
- HTLV I/II antibody with reflex confirmatory assay
- HBcAb (IgM)
- HBsAb
- HBsAg
- HBV viral load (if needed clinically)
- Anti-HCV antibodies and a positive qualitative PCR to assess HCV viral load

8.4.6.2. Central Laboratory Analytical Testing

- Anti-HGF antibodies
- Cytokines

8.4.7. Retinal Fundoscopy

Proliferative diabetic retinopathy, defined as the presence of new proliferating blood vessels (neovascularization) arising from the retina or optic disc and growing on the retinal surface or into the vitreous cavity, will be assessed by retinal fundoscopy during Screening for eligibility and repeated at Day 90 and Day 180/Early Termination. Retinal fundoscopy must be performed

by an ophthalmologist or optometrist within 52 days prior to Day 0 and within 45 days of Day 90, and within 30 days of Day 180. The same ophthalmology practice should be used for all measurements of individual participation. In cases where fundoscopy alone is deemed insufficient to determine eligibility, fluorescein angiography may be performed during Screening.

8.5. Adverse Events and Serious Adverse Events

The definitions of AEs, TEAEs, and SAEs can be found in Section 10.2, Appendix 2.

8.5.1. Time Period and Frequency for Collecting AE, TEAE, SAE, and TESAE Information

Medical occurrences that begin before the start of study intervention and not related to required study procedures, but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) and not as AEs.

All medical occurrences will be considered AEs/SAEs if identified during the screening period and are related to study-required procedures or interventions and will be collected starting after completion of the informed consent process to Day 0 prior to randomization.

All TEAEs and treatment-emergent SAEs (TESAEs) will be collected after study drug administration on Day 0 through Day 180 (see definition of TEAE, Section 10.2).

All SAEs, including TESAEs, will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2.5, Appendix 2. The Investigator will submit any updated SAE/TESAE data to the Sponsor within 24 hours of its availability.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a Participant has been discharged from the study, and he/she considers the event to be possibly, probably, or definitely related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.5.2. Method of Reporting AEs, TEAEs, SAEs, TESAEs, and AESIs

The method of recording, evaluating, and assessing causality of AEs, SAEs, TEAEs, TESAEs, and AESIs and the procedures for completing and transmitting SAE reports are provided in Section 10.2, Appendix 2.

Care will be taken not to introduce bias when identifying AEs/TEAEs and/or SAEs/TESAEs. Open-ended and non-leading verbal questioning of the Participant is the preferred method to inquire about AE occurrences.

8.5.3. SAE Reporting to the Sponsor or Designee

All SAEs/TESAEs should be reported to the Sponsor or designee within 24 hours of knowledge of the SAE/TESAE occurring.

8.5.4. Adverse Events of Special Interest

Categories of AESIs

There are four main categories of AESIs: 1) those considered to be related to the angiogenesis potential of Engensis, 2) other medical problems in this patient population, 3) severe (Grade 3) and potentially life-threatening (Grade 4) Injection Site Reactions, and 4) COVID-19 infections occurring after randomization of the participants. The Sponsor is responsible for deciding which events are deemed as AESIs

8.5.4.1. AESIs Related to Angiogenesis

Atherosclerosis

Hyperplasia of the vasa vasorum in the early stages of atherosclerosis is independent of angiogenesis, but the intimal neovascularization that follows the hyperplasia of the vasa vasorum is angiogenesis-dependent.[56] Angiogenesis increases oxygen and nutrients to the artery wall and supports initial plaque growth. Once the atherosclerotic plaque develops, intimal angiogenesis is thought to contribute to characteristics of an unstable plaque, plaque hemorrhage, and plaque rupture. Therefore, diagnoses suggestive of recent coronary artery disease since Baseline will be evaluated as AESIs.

Proliferative diabetic retinopathy

Neovascularization is an advanced stage of diabetic retinopathy that is due to relentless abnormal fibrovascular proliferation.[57] Because the angiogenic potential of Engensis may promote the development of or stimulate abnormal fibrovascular proliferation in the retina, new fundoscopic changes or symptoms of proliferative diabetic retinopathy that occur after Baseline are considered AESIs.

Cancer

Angiogenesis plays an important role in the proliferation and metastatic spread of cancer as these processes are dependent on an adequate supply of oxygen and nutrients and removal of waste products.[58] All types of cancer reported after randomization will be deemed to be AESIs.

Diabetes mellitus and obesity (BMI ≥30) each increases the risk of several types of cancer.[59,60] In type 2 DM, there is a 2- to 3-fold increased risk for pancreatic cancer, a 2-fold increased risk for hepatobiliary and endometrial cancers, a 50% increased incidence of colorectal cancer, and a 20% increased risk for breast cancer.[61] Obese postmenopausal women have an increased risk of breast cancer,[62] and obesity is associated with a modestly increased risk of colorectal cancer,[63,64] pancreatic cancer,[65] and prostate cancer.[66]

Because the medical problems of type 2 DM and obesity (BMI ≥30) increase the risks of several types of cancers, cancer screening tests have been implemented to exclude obese diabetic patients with even higher than expected risks of developing cancer based on medical history or cancer screening tests, or who have various types of subclinical cancer.

8.5.4.2. AESIs Related to Other Medical Problems

Several medical problems are frequently observed in patients with diabetic peripheral neuropathy

that should be considered AESIs. These medical problems are listed below by type of medical problem.

Infections and infestations; Skin and Subcutaneous disorders

Because patients with diabetic peripheral neuropathy are at an increased risk to develop skin lesions (e.g., blisters, ulcers) and various lower limb infectious complications (e.g., cellulitis, osteomyelitis) that may be associated with systemic infections (e.g., bacteremia, sepsis, or septic shock), all of these types of medical problems that occur after Randomization (Day 0) will be considered AESIs. In addition, any amputations involving the lower extremity, development of Charcot foot, or other similar complications will also be considered AESIs.

Peripheral Arterial Disease

An overlap of DPN and peripheral arterial disease (PAD) apparently exists in type 2 diabetic patients.[67] Because Participants with DPN may develop signs or symptoms of PAD after randomization in the VMDN-003-2 trial, detailed evaluations of Participants considered to have PAD will be considered AESIs.

Diabetic Neuropathies

Because Participants in this study may develop other types of peripheral diabetic neuropathies while in the study, the following events will be considered to be AESIs in Participants with DPN: diabetic mononeuropathy, diabetic mononeuropathy multiplex, and diabetic polyradiculopathy. The occurrence of these other types of peripheral neuropathies in a Participant with DPN may indicate a more severe form of diabetic peripheral neuropathy.

Because Participants in this study may develop various manifestations of autonomic neuropathy (typically involves the gastrointestinal, genitourinary tract, cardiovascular systems) after randomization, the clinical manifestations of diabetic autonomic neuropathy will be considered to be AESIs.

Glycemic Control

Hypoglycemia, hyperglycemia, hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia are to be listed as AESIs based on the Common Terminology Criteria for Adverse Events (CTCAE) grading if they are Grades 3 or 4.

Metabolic complications of DM (such as diabetic ketoacidosis [DKA], hyperglycemic hyperosmolar non-ketotic coma, lactic acidosis, metabolic acidosis [overlaps with DKA]) are to be listed as AESIs.

8.5.4.3. Injection Site Reactions

Immediately following completion of injections of Engensis or Placebo at each Study Injection Visit (on Days 0, 14, 90, and 104), the Investigator or designee must evaluate all injection sites for any reactions and record the findings on the Injection Site Reaction (ISR) CRF. Within 2 to 3 days after each Study Injection Visit, a documented telephone call will be placed from the clinical site to the Participant to ask if there are any Injection Site Reactions (across all injection sites on both calves), and if any ISRs occurred, the worst reaction across all injection sites is to be reported as a TEAE and will be considered an AESI if severe (Grade 3) or potentially life-threatening (Grade 4). Grading of severity of ISRs is presented in Section 10.3, Appendix 3.

For an ISR to qualify as an AESI, the severity of the ISR should be Grade 3 or 4 according to the grading presented in Table 6. Injection Site Reactions that are observed by the PI or reported by the participant within 2 to 3 days after Study Injections on Days 0, 14, 90, and 104. The PI should conduct an unscheduled visit, if warranted, to assess the ISR. The ISRs that remain unresolved after 2 to 3 days will continue to be assessed at subsequent Visits as ongoing AEs until resolved.

8.5.4.4. COVID-19 Infections

A diagnosis of a COVID-19 infection occurring in participants after randomization will be recorded as an AESI and their disposition during the trial following the diagnosis of the COVID-19 infection will be tracked.

8.5.5. Follow-up of AEs/TEAEs, SAEs/TESAEs, and AESIs

After the initial AE/TEAE/SAE/TESAE report, the Investigator is required to proactively follow each Participant at subsequent Visits/contacts. All SAEs and AESIs (see Section 8.5.4) will be followed until resolution, stabilization, the event is otherwise explained, or the Participant is lost to follow-up (as defined in Section 7.3).

8.5.6. Regulatory Reporting Requirements for SAEs/TESAEs

Prompt notification by the Investigator to the Sponsor of an SAE/TESAE is essential to ensure that legal obligations and ethical responsibilities towards the safety of Participants and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs), and Investigators.

For all studies, Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then notify the IRB if appropriate according to local requirements.

8.5.6.1. Sponsor's Responsibility

All AEs and SAEs will be reported on an annual basis to FDA in accordance with the IND regulation (21 CFR 312). Per the 2010 FDA Guidance Document for Industry and Investigators "Safety Reporting Requirements for INDs and BA/BE Studies," events categorized as "possibly" or "probably" related will be treated as "suspected adverse reactions." Events categorized as "definitely" related will be treated as an "adverse reaction."

All serious and unexpected study-drug-related or suspected adverse reactions will be reported to FDA and to all participating Investigators as an IND Safety Report within 15 calendar days of

the event after the Sponsor determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32). Any unexpected fatal or life-threatening, study-drug-related, or suspected adverse reaction will be reported to the Agency within 7 calendar days after the Sponsor's initial receipt of the information.

The Sponsor will notify all participating Investigators of any new safety information that alters the current risk-benefit assessment of the study medication or that would be sufficient to consider changes in Engensis administration or in the overall conduct of the study.

8.5.7. Pregnancy and Contraception

8.5.7.1. Pregnancy Test (Women of Childbearing Potential Only) and Contraception

Female Participants must be nonpregnant, nonlactating, and either postmenopausal for at least 1 year, or surgically sterile for at least 3 months, or agree to use double-barrier contraception from 28 days prior to randomization and/or their last confirmed menstrual period prior to study randomization (whichever is longer) until 2 months after study completion. Male Participants must also agree to use double-barrier contraception from randomization until 2 months after study completion.

Double-barrier female contraception may include, but is not limited to, intrauterine device with spermicide, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide.

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed during Screening and before randomization (Day 0); results of the test must be negative. The β-HCG test will also be performed at Day 180 or the last Study Visit to evaluate whether the Participant is pregnant.

The rhythm method and contraception by a partner are not considered acceptable methods of contraception.

8.5.7.2. Pregnancy

The Investigator will collect pregnancy information on any female Participant who becomes pregnant while participating in this study. The initial information will be submitted to the Sponsor within 24 hours of learning of a Participant's pregnancy.

Further dosing will be discontinued for any female Participant who becomes pregnant during the study.

The Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the Participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or stillbirth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Other abnormal pregnancy outcomes (e.g., fetal death, congenital anomalies, ectopic pregnancy)

are also considered SAEs and will be reported.

Any post-study pregnancy-related SAE considered possibly, probably, or definitely related to the study drug by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study Participants, he or she may learn of an SAE through voluntary reporting.

The Investigator will record a narrative description of the course of each pregnancy and its outcome.

8.5.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Except for signs and symptoms of diabetic peripheral neuropathy (i.e., numbness, pain, tingling or burning sensation, cramps, and increased sensitivity to touch), all disease-related events or disease-related outcomes qualify as AEs or SAEs.

8.6. Immunogenicity Assessments

Pre-dose and post-dose (after 2 hours ± 1 hour post last injection) blood samples will be collected on Days 0 and 14, post-dose on Day 90, and pre-dose and post-dose samples will be collected on Day 104 for measurement of levels of TNF-α, IL-1β, IFN- γ, IL-6, IL-4, IL-10, and IL-12p70.

A blood sample will be collected pre-dose on Days 0 and 90, and on Days 60, 150, and 180 for detection of anti-HGF antibodies.

9. STATISTICAL CONSIDERATIONS

Detailed statistical methods are described in the Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

The sample size for the primary efficacy endpoint is calculated based on the hypothesis for the primary efficacy endpoints.

The primary efficacy endpoint is the change in the mean ADPS recorded at the Day 0 and Day 180 Visits obtained from 5 to 7 daily entries in the BPI-DPN eDiary prior to those Visits.

The statistical hypothesis for the primary efficacy endpoint (Hypothesis I) is:

$$H_0: \mu_t = \mu_p \text{ versus } Ha: \mu_t \neq \mu_p, \text{ (I)}$$

where μ_t and μ_p are the mean pain change from Baseline to 6-month follow-up for the Engensis and Placebo groups, respectively. A negative mean value means a reduction in the pain score, and a positive mean value means an increase in the pain score. The statistical power is 80%.

Details on the assumptions for sample size determination are described in the Statistical Analysis Plan.

9.2. Populations for Analyses

9.2.1. Intent-To-Treat Population

This subset includes all Participants who are randomized (Participants). All Baseline characteristics will be summarized based on intent-to-treat (ITT). Participants in the ITT will be analyzed according to original treatment assignment, regardless of actual treatment received. The primary analyses of the primary and secondary efficacy endpoints will be based on this ITT population.

9.2.2. Safety Population

The safety analysis population will contain all Participants who receive at least one Study Injection.

9.2.3. Modified Intent-to-Treat Population

The modified ITT (mITT) population includes all Participants who meet the following:

- Underwent (any) injections
- Correctly completed at least 5 out of 7 days of the BPI-DPN eDiary at Baseline and the 6-month follow-up

Participants will be grouped based on the randomly assigned treatments, not the actual treatment received. The mITT population will be used in the sensitivity analyses for the primary and secondary efficacy endpoints.

9.2.4. Per Protocol (PP) Population

The Per Protocol population is a subset of mITT. It includes all mITT Participants who meet all the following criteria:

- The Participant met major protocol eligibility criteria determined by Clinical Data Review Committee (CDRC) prior to database lock and breaking the randomization codes.
- The Participant received all injections based on the randomized treatments and had a Day 180 Visit, including a 7-day ADPS.

Additional criteria, if any, will be established before unblinding the randomization code by the independent CDRC that is masked to the treatment information of each Participant.

The PP population will be used in the sensitivity analyses for the primary and secondary efficacy endpoints.

9.3. Statistical Analyses

The Statistical Analysis Plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned endpoints and the statistical analyses.

9.3.1. Primary Endpoint(s)

As described in Section 3, the primary efficacy endpoint is:

Change in the means of the ADPSs from the BPI-DPN from the7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo in the ITT population

9.3.2. Secondary Endpoints

The secondary efficacy endpoints include the following:

- Change in the means of the Worst Pain Scores from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
- Proportion of Responders (≥ 50% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 180 Visit for Engensis compared to Placebo

Safety endpoints include:

- Incidence of TEAEs and TESAEs for Engensis compared to Placebo
- Incidence of injection site reactions for Engensis compared to Placebo
- Incidence of clinically significant laboratory values for Engensis compared to Placebo
- Change from Baseline in the cytokine profile through post-dose on Day 104 for Engensis compared to Placebo
- Presence of anti-HGF antibodies following Engensis administration compared to Placebo

9.3.3. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Patient Global Impression of Change (PGIC) on Day 90 and on Day 180 for Engensis compared to Placebo
- Proportion of Responders (based on ≥ 50% reduction in the means of ADPS from the BPI-DPN) from the 7 days prior to Day 180 who were Responders on Day 104 (final injection visit) for Engensis compared to Placebo
- Changes in the Bedside Sensory Testing (BST) from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo
- Proportion of Responders (≥ 20, 30, 40, 60 and 70% reduction in the means of ADPSs from the BPI-DPN) from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
- Changes in the means of the Average Daily Pain Scores (ADPSs) from the BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit for Engensis compared to Placebo
- Changes in the severity scores (Worst Pain, Least Pain, Average Pain, and Pain Right Now) from the full BPI-DPN from the 7 days prior to the Day 0 Visit to the 7 days prior to the Day 90 Visit and the 7 days prior to the Day 180 Visit for Engensis compared to Placebo
- Changes in Michigan Neuropathy Screening Instrument (MNSI) assessments from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo
- Changes in Quality of Life in the SF-36 from Baseline to Day 90 and Day 180 for Engensis compared to Placebo
- Changes in Quality of Life in the EQ-5D from Baseline to Day 90 and to Day 180 for Engensis compared to Placebo
- Changes in the means of the daily use of rescue medication from Day 0 to Day 90, from Day 0 to Day 180, and from Day 90 to Day 180 for Engensis compared to Placebo

9.3.4. Safety Analyses

Safety analyses in this study will evaluate the safety profile of Engensis as compared to Placebo. No formal statistical testing will be conducted for the safety analyses. All Participants in the safety subset will be included in these analyses. Participants will be grouped by treatment received. All summaries will be derived based on available data. No imputation will be performed for missing values. All safety analyses will be made on the Safety Population.

9.3.5. Interim Analysis

An interim analysis will be conducted after approximately 50% of Participants in the target sample size (i.e., 76 Participants) have completed the primary efficacy endpoint at Day 180 or have withdrawn prematurely. The conditional power will be calculated and used to support a

decision regarding the following three options:

- Continue enrolling participants to the prespecified target sample size
- Continue enrolling participants to a sample size of ___
- Stop enrolling participants based on futility (CP<39.6%)

The Statistical Analysis Plan will describe the planned interim analysis in greater detail.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

10.1.1.1. Institutional Review Board

Prior to the initiation of the study, the protocol, the informed consent form, and Investigator's Brochure will be submitted to the IRB for approval. By signing the "Statement of Investigator" form (Form FDA 1572), the Investigator is ensuring that an IRB compliant with the requirements set forth in 21 CFR 56 will be responsible for the initial and continuing review of the proposed clinical study. A copy of the IRB approval letter for the protocol, the informed consent, and the protocol signature page must be submitted to the Sponsor prior to release of investigational supplies to the Study Site. The approval letter must refer to the specific protocol and the informed consent form. The Study Site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol. A list of the IRB members, their titles or occupations, and their institutional affiliation, or an IRB assurance number must be provided to the Sponsor prior to release of study supplies.

Health authority regulations require that all advertisements for Participant recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to the Sponsor for approval prior to IRB submission.

The Investigator is responsible for notifying the IRB of any SAEs as required by the IRB. A copy of the notification must be forwarded to the Sponsor or its designee.

Status reports must be submitted to the IRB at least once a year (or more frequently as required by the IRB), and the IRB must be notified of completion or termination of the study.

10.1.1.2. Informed Consent Process

The Investigator has the responsibility to inform each Participant, prior to the Screening evaluation, of the purpose of this clinical study, including possible risks and benefits, and document the informed consent process in the Participant's chart. An informed consent form (ICF) containing the required elements of informed consent must be generated by the Investigator. After approval by the Sponsor, the ICF must be submitted to and approved by an IRB. Prior to entry into the study or initiation of any study-related procedures, the Participant must read, sign, and date the ICF. The person executing the consent must also sign and date the IRB-approved ICF. One original ICF is to be retained by the Study Site, and a copy is to be given to the Participant. The informed consent process must be documented in the Participant's source/medical record.

The ICF must be written in a language in which the Participant is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language ICFs be submitted to the IRB for approval. The Investigator must forward a copy of the ICF, the certified foreign language translation, and an IRB approval letter to the Sponsor.

The Investigator will explain the study purpose, procedures, and Participant's responsibilities to the Participant. The Participant's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained. The Participant will sign and date the ICF. The Investigator or a qualified designee will also sign and date the ICF. The original ICF will be retained with the Participant's records; a copy will be provided to the Participant.

If the ICF is amended during the study, the Investigator or a qualified designee must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB. For each new version of the ICF, the IRB will be consulted to determine if Participants who have not completed the study must be re-consented to the new ICF.

10.1.1.3. Obligations of the Sponsor and the Investigator

The Sponsor will select Investigators on the basis of multiple criteria that include their expertise in the area of DPN, their Site personnel's experience in conducting investigational clinical studies, their prospects for recruiting Participants to the study, and the proficiency with which he/she responds to the requirements of the Sponsor.

The Sponsor and Investigator must comply with all applicable regulations. In addition, the Investigator must follow local and institutional requirements pertaining, but not limited, to investigational product, clinical research, informed consent including the use and disclosure of the Participants' protected health information (PHI), and IRB regulations. The Sponsor will notify the Investigator of protocol and amendment approvals by regulatory authorities when applicable.

The Investigator and clinical research coordinator will be available to respond to reasonable requests and audit queries made by the authorized regulatory agency representatives. The Investigator and clinical research coordinator will provide the Sponsor with advance written notification if they plan to relocate to another institution.

Except where the Investigator's signature is specifically required, the term "Investigator" as used in this protocol and protocol-related documents is understood to refer to the Principal Investigator (PI) or appropriate Study Site personnel whom the PI designates to perform a certain duty. This delegation of authority needs to be documented appropriately and signed by the PI. The PI is ultimately responsible for the conduct of all aspects of the clinical study.

Sub-investigators or other appropriate Study Site personnel (e.g., listed on the Form FDA 1572) are eligible to sign for the PI on laboratory reports and may be designated to verify and electronically sign eCRFs.

10.1.2. Financial Disclosure

10.1.2.1. Conflict of Interest Policy

The independence of the study from any actual or perceived influence is critical. Therefore, any actual conflict of interest or financial interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study should be disclosed. Furthermore, persons who have a perceived conflict of interest or financial interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this

study.

10.1.2.2. Financial Disclosure

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

10.1.3. Participant Selection and Informed Consent Process

The Investigator will screen Participants who meet the eligibility criteria. The Investigator will not exercise selectivity, so that bias is prevented. All Participants must sign an ICF that has been approved both by the Sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with the current revision of the Declaration of Helsinki as well as current ICH and Good Clinical Practice (GCP) guidelines.

Prior to randomization, Participants will receive a comprehensive explanation of the proposed treatment including the nature and risks of the study, alternate therapies, any known AEs, the investigational status of the product, and the other elements that are part of obtaining proper informed consent. Potential Participants will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically any saved blood samples. Potential Participants will be allowed sufficient time to consider participation in the study after having the nature and risks of the study explained to them. The ICF must not include any exculpatory statements. The ICF and any separate Health Insurance Portability and Accountability Act (HIPAA) authorization form, if applicable, should be reviewed and approved by the Sponsor prior to IRB/IEC submission.

The Sponsor will provide to the Investigator, in writing, any new information that significantly bears on the Participants' risk in receiving the study drug. This new information will be communicated by the Investigator to Participants in accordance with IRB/IEC requirements. The ICF will be updated, and Participants will be re-consented, if necessary.

Site staff may conduct standard-of-care procedures and employ recruitment efforts prior to Participant consent; however, before any protocol-specified procedures are performed to determine protocol eligibility, an ICF must be signed. Participants will be given a copy of all consent forms that they sign.

By signing the ICF, the Participant agrees to complete all evaluations required by the study unless the Participant withdraws voluntarily or is terminated from the study for any reason.

10.1.4. Data Protection and Confidentiality

The data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. At the end of the study, a clinical study report will be written by the Sponsor.

10.1.4.1. Confidentiality

Participant confidentiality and privacy are strictly held in trust by the Investigators, their staff, and the Sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to Participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical companies supplying study product may inspect all documents and records required to be maintained by the Investigator including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for Participants. The Clinical Study Site will permit access to such records.

The Participant's contact information will be securely stored at each Clinical Site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, applicable regulatory agencies, institutional policies, and/or Sponsor requirements.

Participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor or their designee. This will not include the Participant's contact or identifying information. Rather, individual Participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by Clinical Sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4.2. Data Protection

In accordance with GCP and with the national data protection laws, all information concerning the Participants in the study must be treated as strictly confidential by all persons involved in the study.

The Investigator acknowledges that any and all information acquired from the Sponsor or developed or acquired in connection with the study is strictly confidential. The Investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of the Sponsor in writing. Such consent will be deemed to have been given for disclosure to any person for whom the Investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

Potential Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the Participant who will be required to give consent for their data to be used as described in the ICF.

Potential Participants must be informed that their medical records may be examined by Clinical

Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Committee Structure

10.1.5.1. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been chartered for this study to review all safety data during the study and safeguard the interests of the Participants. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to the Sponsor regarding the safety of Engensis. The DSMB will meet periodically and review a limited set of unblinded tables and/or listings, including all reported AEs/TEAEs, SAEs/TESAEs, and AESIs. The data analyses for the DSMB meetings will be directly provided to the DSMB members; no data will be released to the Sponsor and blinded designees. No adjustment will be made for multiple testing due to the DSMB data review.

The DSMB will consist of two physicians with expertise in clinical studies and one statistician. Members of the DSMB will be independent of study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflicts of interest. An independent biostatistician will be available for consultation.

The DSMB will operate under the rules of the charter, which have been reviewed at organizational meetings of the DSMB. Each data element that the DSMB requires to assess the safety of Engensis will be agreed upon prior to study start. Routine DSMB meetings will be regularly scheduled per the DSMB Chair to review safety and 12-week pooled all-cause mortality data, including unblinded Participant narratives. The DSMB Chair may request additional unblinded information at any time to further understand a safety trend. Ad hoc DSMB meetings can be convened at any time at the discretion of the DSMB Chair or the Sponsor. However, the DSMB Chair may not share any unblinded information with the Sponsor unless it is deemed necessary for the Sponsor to address a potential safety concern. The DSMB will provide recommendations to the Sponsor in accordance with the DSMB Charter.

10.1.5.2. Institutional Biosafety Committee

The Sites at which this study is being conducted will ensure that an Institutional Biosafety Committee (IBC) is in place. The IBC will ensure that the Site conforms to the requirements set forth in the Section IV-B-2 of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (April 2019), promulgated by the NIH Office of Science Policy (OSP).

The Investigator will be responsible for petitioning the IBC and obtaining approval prior to enrolling any Participant in the study. The Investigator will also be required to obtain and follow all biohazard safety guidelines promulgated by the IBC, and to report all findings as required to the IBC and the OSP.

10.1.6. Data Quality Assurance

10.1.6.1. Clinical Monitoring

The Sponsor or designee will visit (in person or remotely, according to FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, March 2020, updated 27 Jan 2021) the Clinical Site for monitoring. The Sponsor's clinical monitor shall ensure that the Investigator understands the investigational status of the product, all protocol requirements, and his/her regulatory responsibilities as an Investigator. The clinical monitors will visit (in person or remotely) Clinical Sites at appropriate intervals to ensure compliance with the protocol and to verify the accuracy, completeness, and correctness of data reported and accountability of Engensis supplies.

The clinical monitor shall be available for consultation by the Investigator and serves as a liaison between the Clinical Site and the Sponsor. The clinical monitor or other authorized representatives of the Sponsor may inspect all data, documents, and records required to be maintained by the Investigator including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for Participants. The Clinical Site will permit access to such records. The Investigator will obtain, as part of the informed consent process, HIPAA-compliant authorization from Participants to use and disclose the requisite and relevant PHI and permission for authorized representatives of the Sponsor, or regulatory authorities including the FDA, to review, in confidence, any records identifying Participants in the clinical study.

10.1.6.2. Access to Study Documents and Study Monitoring

The Sponsor or its designee will monitor the progress of this study. The clinical monitor, as a representative of the Sponsor, has the obligation to follow this study closely.

The Sponsor or its designee may meet with Investigators prior to the initiation of the study in order to review the adequacy of the Participant population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol.

The Sponsor or its designee may meet with the Investigator(s) at the time that study Participants begin to be enrolled to ensure that Participants are being properly selected and that study data are being correctly recorded.

During the study, the clinical monitor will visit (in person or remotely) the study facilities regularly and use telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the Clinical Site (in person or remotely), the monitor will review the source documents used for data entry in the EDC system to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. Source documents must contain all data entered in the EDC system. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its representatives, and the FDA and other regulatory agencies.

Upon completion of the study, the clinical monitor will conduct a final visit (closeout) to the Site. The objectives of this visit are to confirm that all regulatory records and reports are complete, verify that study drug and other supplies have been accounted for, and ensure that the Investigator is aware of his/her responsibilities post-study.

10.1.6.3. Quality Assurance and Quality Control

Each Clinical Site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical study is conducted, data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The Clinical Site will provide direct access to all study-related source data documents and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

The Pharmacist must ensure that Engensis and Placebo are stored as specified in the protocol and Pharmacy Manual. The Pharmacist must maintain accurate records of the receipt of all Engensis and Placebo supplies and details of the dispensing and administration as specified in the Pharmacy Manual. The Engensis and Placebo must be administered only at the institution specified on the Form FDA 1572 for the Site.

The study will be conducted in accordance with the principles of GCPs: 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312, Subpart D; the 2016 ICH Guideline on Good Clinical Practice (ICH E6(R2)); and HIPAA.

The Investigator at the Clinical Site must sign the Investigator Statement of Agreement.

10.1.6.4. Data Quality Assurance

The Sponsor's employees and/or their contracted representatives use SOPs designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and GCP guidance.

A quality assurance audit may be conducted by the Sponsor or its designee at any time during or after completion of a study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all ICFs, source documents, medical records, and regulatory documentation; an assessment of study conduct and protocol compliance; and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review.

All Participant data relating to the study will be recorded on an electronic CRF (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized Site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of Participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.6.5. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff under the supervision of the Investigator. During the study, the Investigator will maintain complete and accurate documentation for the study.

All eCRF data will be entered into a validated database compliant with 21 CFR Part 11. Laboratory data will be either manually entered or imported to the clinical database electronically. All data entry, verification, and validation will be performed in accordance with the current SOPs of the Sponsor or its designee. The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures are completed.

The Clinical Site will be provided with eCRFs and ePRO/eCOA devices in which to record all the protocol-specified data for each Participant. Entries made in the eCRF must be verifiable against source documents, or in certain circumstances as directed by the Sponsor, entries will have been directly entered into the eCRF; in such cases, the entry in the eCRF will be considered as the source data. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each Participant's eCRF, verifying that the information is true and correct. Queries generated by Data Management will be sent to the Clinical Site for resolution. The Investigator is responsible for the review and approval of all responses to eCRF queries.

10.1.6.6. Protocol Deviations

The Investigator will not deviate from this protocol for any reason without prior written approval by the Medical Monitor on behalf of the Sponsor except in the case of a medical emergency when the change is necessary to eliminate an apparent and immediate hazard to the Participant. In the event of such an emergency, the Investigator will notify the Medical Monitor immediately by phone, notify the IRB, and confirm with the Medical Monitor in writing within 5 working days of the change being implemented.

Protocol deviations will be tracked through the EDC.

10.1.6.7. Source Documents

As defined in the ICH Guidelines for Good Clinical Practice E6(R2), Section 1.52, source documents may include: original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, Participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x rays, Participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).

Source documents provide evidence for the existence of the Participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's Site.

The Investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.

10.1.7. Data Management

All Participant data will be entered into a password-protected validated EDC system by authorized Site personnel according to the CRO's SOPs.

Data discrepancies identified via programmed edit checks, manual data review or discovered during data monitoring will be addressed and resolved. An audit trail in the EDC system will list all changes made to the data, with a date/time stamp and user initials. Upon database lock, occurring after data are declared clean and eCRFs have been approved by the Investigator, the CRO will provide SAS datasets to the Sponsor and designated Statistician for data analysis via secure data transfer specified in the Study Data Management Plan.

10.1.8. Recordkeeping and Retention

Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the Clinical Site, the Sponsor and its representatives, and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to Participants will identify Participants only by Participant identification number. Complete Participant identification will be kept by the Investigator. This information will be treated with strict adherence to professional standards of confidentiality.

The Investigator must in reasonable time, upon request from any properly authorized officer or employee of the FDA/relevant health authority/regulatory agency, permit such officer or employee to have access to requested records and reports, and copy and verify any records or reports made by the Investigator. Upon notification of a visit by the FDA/relevant health authority/regulatory agency, the Investigator will contact the Sponsor immediately. The Investigator will also grant the Sponsor's representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

The Investigator must provide the Sponsor or its designee with the following documents prior to study initiation and retain a copy in the study file:

- A completed and signed Form FDA 1572. If, during the study, any changes occur that are not reflected on the current 1572, a new 1572 must be completed and returned to the Sponsor or its designee for submission to the FDA
- Current signed curricula vitae (within 2 years prior to study initiation) and current medical licenses for the Investigator and all co-Investigators listed on the 1572
- A copy of the original approval by the IRB for conducting the study. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB-approved ICF
- The IRB member list and/or DHHS General Assurance Number (if the IRB has an Assurance number)
- A copy of the original approval by the IBC for conducting the study, if applicable. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IBC policy.
- Signed Financial Disclosure Forms for all personnel listed on the 1572 with a statement of non-voting by study staff
- The signature page of this protocol signed and dated by the Investigator
- The signature page of the IB signed and dated by the Investigator

In addition to the documents listed above, the Clinical Site will also retain the following items:

- Certifications and laboratory reference ranges for all local laboratories used for this study
- A copy of delegation of authority log
- All original ICFs with required signatures
- All IRB correspondence (e.g., informed consent [including any approved revisions], protocol, AE, advertisements, newsletters)
- All IBC correspondence
- A copy of the Study Monitoring Log
- Clinical and nonclinical supply shipment forms
- Copies of all pertinent correspondence pertaining to the study (except budget issues) between the Sponsor and the Site
- Copies of all SAE reports submitted to the Sponsor
- Copies of all Investigator Safety Reports submitted to the Site by the Sponsor
- Copies of approved package labelling, if applicable

10.1.9. Study and Site Start and Closure

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the Sponsor to Investigators and regulatory authorities. If the study is prematurely terminated or suspended, the Investigator will promptly inform Participants and the IRB and will provide the reasons for the termination or suspension. Participants will be contacted, as applicable, and be informed of changes to Study Visit schedules.

The Sponsor reserves the right to discontinue the study for any safety, ethical, or administrative reason at any time.

The Sponsor or designee reserves the right to close a Clinical Site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion.

The Investigator may initiate Clinical Site closure at any time, provided reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a Clinical Site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of Participants by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the Participants and should ensure appropriate Participant therapy and/or follow-up.

10.1.10. Publication Policy

The study will be conducted in accordance with the publication and data sharing policies and regulations as defined in the agreement between the Sponsor and the institution. In addition, this study will be registered at www.ClinicalTrials.gov and in any other protocol registries required by the regions in which the study is conducted, and the results from this study will become publicly available.

None of the data resulting from this study will be allowed to be presented or published in any form, by the Investigator or any other person, without the prior written approval of the Sponsor.

10.1.11. Insurance

Matters relating to insurance for this study are to be defined in the agreement between the Sponsor and the institution.

10.2. Appendix 2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE/TEAE is any untoward medical occurrence associated with the use of an investigational product or study procedure in a clinical study Participant whether or not considered related to the study intervention. • NOTE: An AE/TEAE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention or procedure.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, or clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the Participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the Participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of TEAE

Treatment-Emergent Adverse Event is defined as:

- An event that emerges during treatment, having been absent at pretreatment, or worsens relative to the pretreatment state, as defined in the E9 Guidance.
- The TEAE is not related to causality / drug relatedness. It may or may not be related to the drug but is considered a TEAE due to its appearance at or after the treatment has been administered.

10.2.3. Definition of SAE/TESAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the Participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the Participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the Participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

10.2.4. Recording and Follow-Up of AE/TEAE and/or SAE/TESAE

AE and SAE Recording

- When an AE/TEAE or SAE/TESAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/TEAE and SAE/TESAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the Participant's medical records to the Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- Instances may arise when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all Participant identifiers, with the exception of the Participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the Participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • Situations may arise in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, the Investigator must always assess causality for every event before the initial transmission of the SAE data to the Sponsor or designee. Death or hospitalization are not to be specified as an SAE; these are criteria to determine seriousness. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.2.5. Reporting of SAEs/TESAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection tool. • The Site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given Site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a Site receives a report of a new SAE from a study Participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the Site can report this information or to the Medical Monitor or SAE coordinator by telephone.

10.3. Appendix 3. Grading of Injection Site Reactions

A global assessment across all injection sites on each leg is to be performed following each treatment. The injection site reaction with the most severe pain/tenderness, erythema/itching/urticaria, and bruising/swelling/bleeding on each leg is to be used for reporting injection site reaction grades (mild, moderate, severe, or life-threatening) following each treatment. Severe (Grade 3) and potentially life-threatening (Grade 4) Injection Site Reactions will be AESIs. Two sources were used for compiling the following grading guidelines for Injection Site Reactions (Table 6):

1. FDA Guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007.
2. National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) v5.0, Nov. 27, 2017.

Table 6 Injection Site Reaction Grading

Reaction at Injection Site[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Pain, tenderness	Mild discomfort to touch, with or without warmth, erythema, itching Does not interfere with daily activity No or local treatment	Symptoms with or without swelling and/or phlebitis Interferes with daily activity Use of non-narcotic pain reliever	Symptoms with or without swelling or phlebitis or mild infection Precludes daily activity Use of narcotic pain reliever and/or oral antibiotics	Symptoms with severe infection or tissue injury or ulceration Requires advanced medical and/or surgical care, including IV medications
Erythema, itching, urticaria	Mild, localized itching, erythema or urticaria. Does not interfere with activity Use of topical treatment	Symptoms with skin changes beyond local injection site(s) Interferes with movement and daily activity Use of NSAIDs and/or antihistamines	Symptoms with widespread skin changes Interferes with daily activity Use of oral steroids or immunosuppressives	Bronchospasm, anaphylactoid, or anaphylactic reaction Requires advanced medical care, including IV medication
Bruising, swelling, bleeding	Mild, localized swelling, ecchymosis or hematoma Does not interfere with activity No treatment	Moderate ecchymosis or hematoma Interferes with daily activity Requires leg elevation, conservative treatment	Extensive ecchymoses, large hematoma Precludes activity Requires minimally invasive drainage	Hypotension, life-threatening consequences Requires transfusion, urgent intervention

[a] Injection Site Reactions are a category of AEs and should be recorded as AEs using these grading guidelines.

10.4. Appendix 4. Prohibited Medications and Procedures

Table 7 Prohibited Medications – Steroids

Drug	Example of Common Name(s)	Maximum Dose Allowed During Study
Steroids		
Injected or oral corticosteroids[a]	prednisone, betamethasone, dexamethasone, cortisone, hydrocortisone, triamcinolone	None
Topical corticosteroids on the lower legs or feet	prednisone, betamethasone, dexamethasone, cortisone, hydrocortisone, triamcinolone	None on the lower legs or feet[b]

[a] Inhaled, ocular, and intra-articular steroids are allowed.
[b] Topical corticosteroid use is allowed on body surfaces other than the lower legs and feet.

Table 8 Prohibited Medications and Procedures – Opioids and Other Therapies

Drug or Procedure	Maximum Dose Allowed During Study
Acupuncture	None
Anesthetic creams (for use only during injections) and patches, including capsaicin, on lower legs and feet	None
Benzodiazepines	None, except for stable bedtime dose
Gabapentin, pregabalin	None
Isosorbide dinitrate spray on lower legs and feet	None
Opioids (e.g., morphine, oxycodone, tramadol, methadone, fentanyl)	None, except after trauma or surgery
Skeletal muscle relaxants (e.g., cyclobenzaprine, metaxalone, chlorzoxazone)	None
Transcutaneous electrical nerve stimulation	None

10.5. Appendix 5. Abbreviations and Definitions

10.5.1. Abbreviations

Abbreviation	Definition
ADPS	Average Daily Pain Score
AE	adverse event
AESI	adverse event of special interest
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase (SGPT)
Anti-HCV Ab	hepatitis C antibodies
APR	Accurate Pain Reporting
AST	aspartate transaminase (SGOT)
β-HCG	Beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
BPNS	Brief Peripheral Neuropathy Screening
BUN	blood urea nitrogen
BST	Bedside Sensory Testing
CABG	coronary artery bypass grafting
cDNA	complementary DNA
CDRC	Clinical Data Review Committee
CFR	Code of Federal Regulations
CKD-EPI	chronic kidney disease epidemiology collaboration
CLI	critical limb ischemia
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	clinical research organization
CS	clinically significant
CT	Computed Tomography
DIP	distal interphalangeal
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DMC	Data Monitoring Committee

Abbreviation	Definition
DNA	deoxyribonucleic acid
DPN	diabetic peripheral neuropathy
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol Health Utilities Index
FIT	Fecal Immunochemical Test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody (IgG and IgM)
HBsAb	antibody to hepatitis B surface antigen
HBsAg	hepatitis B surface antigen
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HEENT	head, eyes, ears, nose, and throat
Hgb	Hemoglobin
HGF	hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPV	primary human papillomavirus
HTLV	human T cell lymphotropic virus
IB	Investigator’s Brochure
IBC	Institutional Biosafety Committee
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ	interferon gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
IHD	ischemic heart disease
IL-1β	interleukin-1beta
IM	Intramuscular
IND	Investigational New Drug application
IRB	Institutional Review Board
ISDN	isosorbide dinitrate
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IWRS	Interactive Web Response System
LDL-C	low-density lipoprotein cholesterol
mITT	modified intent-to-treat
MNSI	Michigan Neuropathy Screening Instrument
NCS	not clinically significant
NDA	New Drug Application
NHU	nonhealing foot ulcer
NIH	National Institutes of Health
NRS	Numerical Rating Scale
OSP	Office of Science Policy
P-A	posterior to anterior
Pap	Papanicolaou
PAD	peripheral arterial disease
PCR	polymerase chain reaction
PCP	Phencyclidine
PDR	proliferative diabetic retinopathy
PE	physical examination
PGIC	Patient Global Impression of Change
PHI	protected health information
PI	Principal Investigator

Abbreviation	Definition
PKC	Protein kinase C
PP	per protocol
PRO	Pro re nata (“as the situation demands”)
PRR	Placebo Response Reduction
PSA	Prostate Specific Antigen
QC	quality control
QoL	Quality of Life
ROS	reactive oxygen species
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-Item Short Form Health Survey
SoA	Schedule of Activities
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TCA	tricyclic antidepressants
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TENS	transcutaneous electrical nerve stimulation
THC	Cannabinoid
TNF-α	tumor necrosis factor alpha
VAS	Visual Analog Scale
VEGF	vascular endothelial growth factor
WFI	water for injection

10.5.2. Definitions

Active Infection	Chronic infection or severe active infection that may compromise the Participant's well-being or participation in the study, in the Investigator's judgment
Allowed Opioid Use	When Participants require opioids for non-DPN post-trauma pain or pain after surgery that was unanticipated during Screening, short-acting formulations are to be used, enabling a more rapid washout and reduced effect on DPN-related pain
Average Daily Pain Score (ADPS)	The mean of at least 5 daily pain scores recorded for Question 5 of the BPI-DPN (Section 10.7) in eDiary during the 7 days prior to the Visits on Day 0, Day 90, and Day 180
Worst Daily Pain Score	The mean of at least 5 worst daily pain scores recorded for Question 3 of the BPI-DPN (Section 10.7) in eDiary during the 7 days prior to the Visits on Day 0, Day 90, and Day 180
Day 14, etc.	Day 14 (for example) refers specifically to the actual day of the Visit designated as the Day 14 Visit, and not to the 14th day of the study for a Participant.
Drug Abuse	The habitual taking of addictive or illegal drugs
Drugs of Abuse	Amphetamines, barbiturates, benzodiazepines, buprenorphine, cocaine, fentanyl, meperidine, methadone, opiates, oxycodone, oxymorphone, phencyclidine, tramadol
EMLA Cream	A mixture of lidocaine 2.5% and prilocaine 2.5%
First-degree relative	Parent, sibling, or child
Highly Effective Contraception Method	See Section 8.5.7
Injection Site Reaction	An AE located in close proximity to the injection sites on the calves and first observed within 48 hours following Study Injections
Investigator	The PI or appropriate Study Site personnel whom the PI designates to perform a certain duty
Lower Leg	The part of the leg between the knee joint and the ankle joint. Does not include the foot.
Medical Monitor	The Responsible Medical Officer or designee
Participant	An individual who has signed informed consent to be entered into the study
Placebo	Placebo comprises 45 mg sodium chloride and 55 mg sucrose in 5 mL of water for injection. Engensis vials contain the same excipients.
Primary HPV Test	A Primary HPV test is an HPV test that is done by itself for screening. The US Food and Drug Administration has approved certain tests to be primary HPV tests. This is the recommended test by the ACS; however, it is not always available.

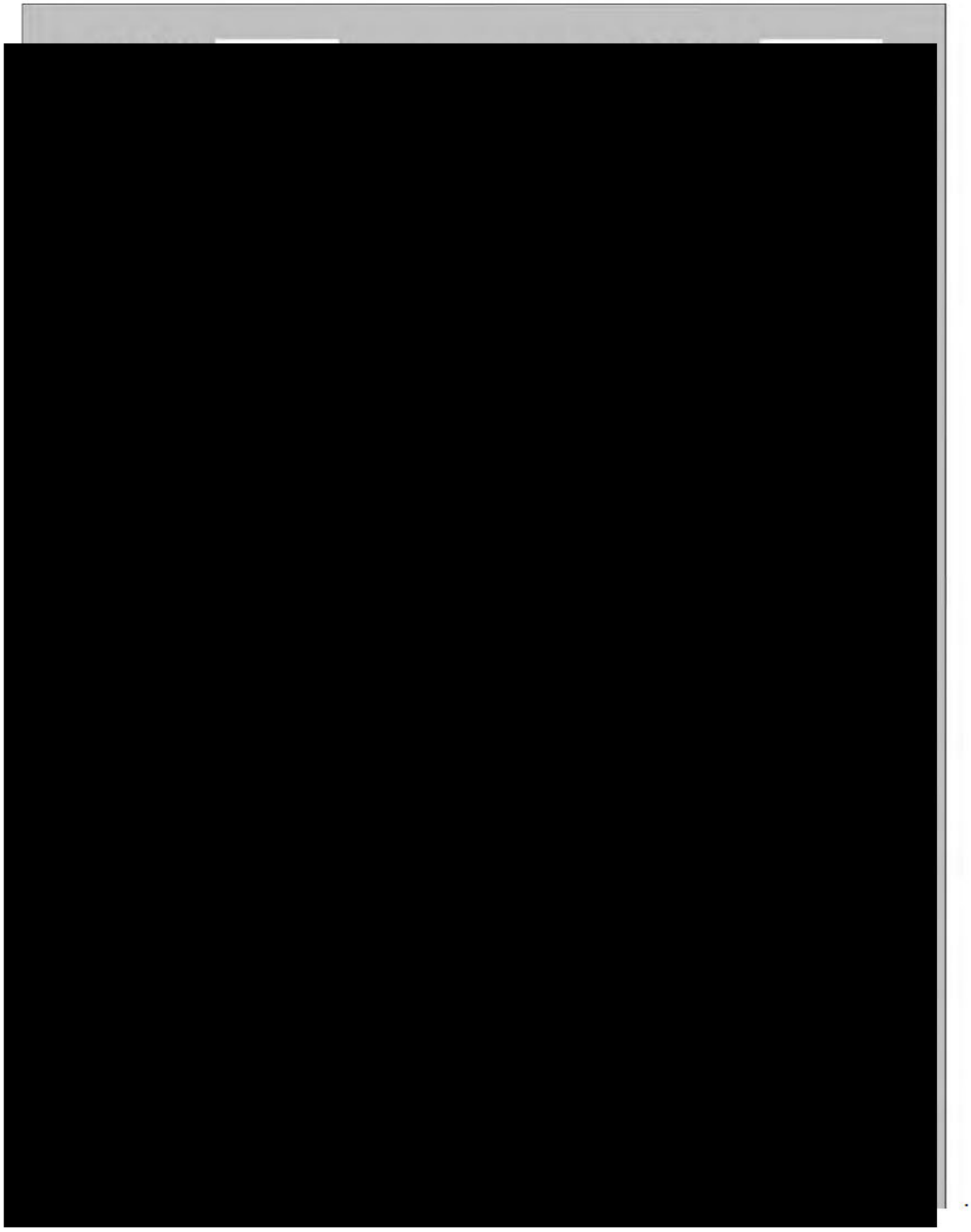
Safety Analysis Population	All Participants who receive a Study Injection
Site	A clinical research facility participating in the VMDN-003-2 study
Sponsor	Helixmith Co., Ltd. and its representatives contracted to provide services for study conduct
Stable Dosing Regimen	≤ 50% change in total daily dose relative to dosing at baseline of any medication
Stage 4 or 5 Kidney Disease	eGFR < 30 mL/min/1.73 m^2
Study Drug	Engensis or Placebo
Study Injection	Injection of Engensis or Placebo
Treatment Cycle	Two sets of Study Injections 14 days apart comprising a single dose
Unstable Diabetes	Elevations and/or depressions in blood sugar causing episodes of diabetic ketoacidosis (DKA) and/or hypoglycemia

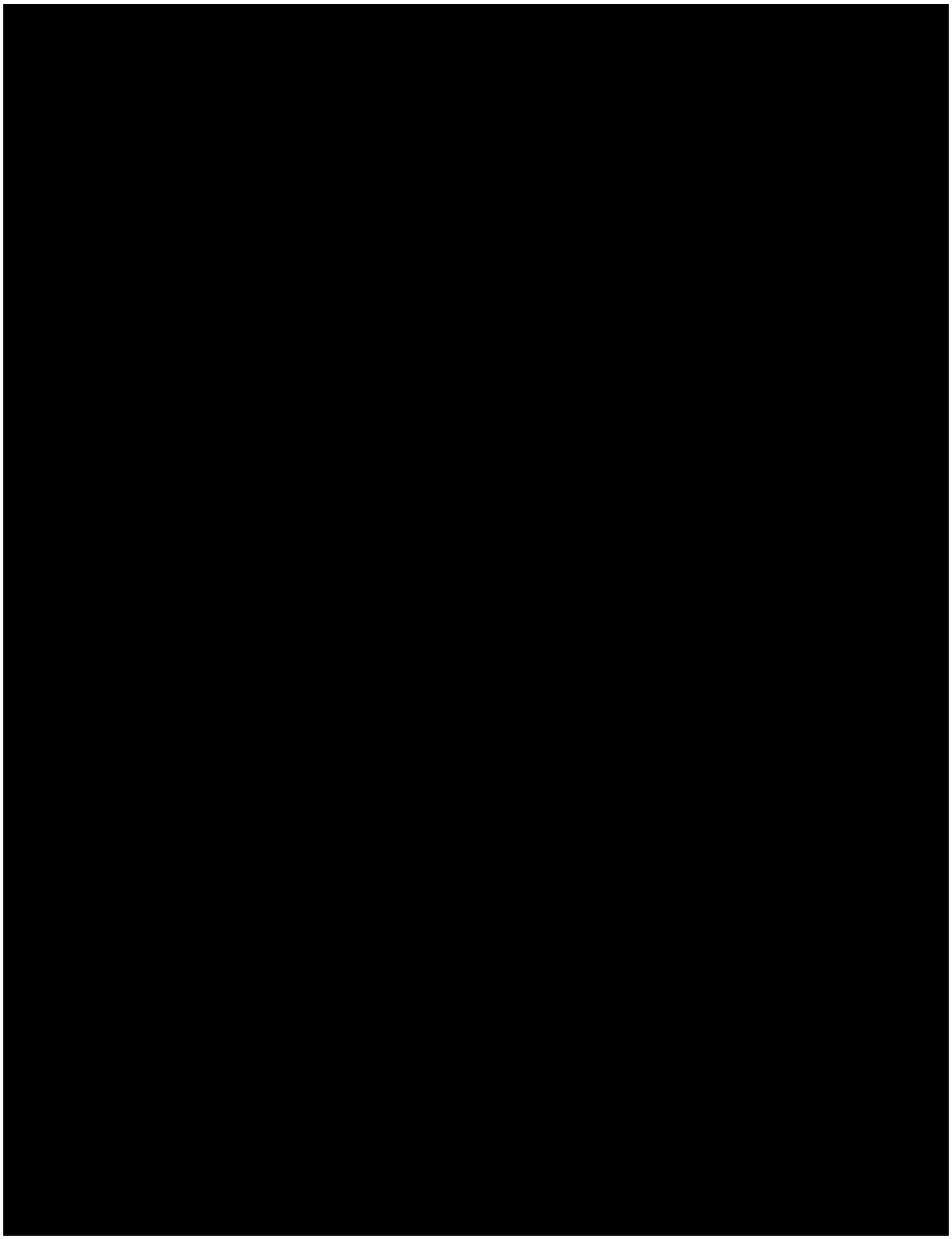
10.6

[redacted]

10.7. Appendix 7. Brief Pain Inventory for Participants with Diabetic Peripheral Neuropathy (BPI-DPN)

The paper version of the BPI-DPN Short Form is shown below. Participants will be using an [redacted]

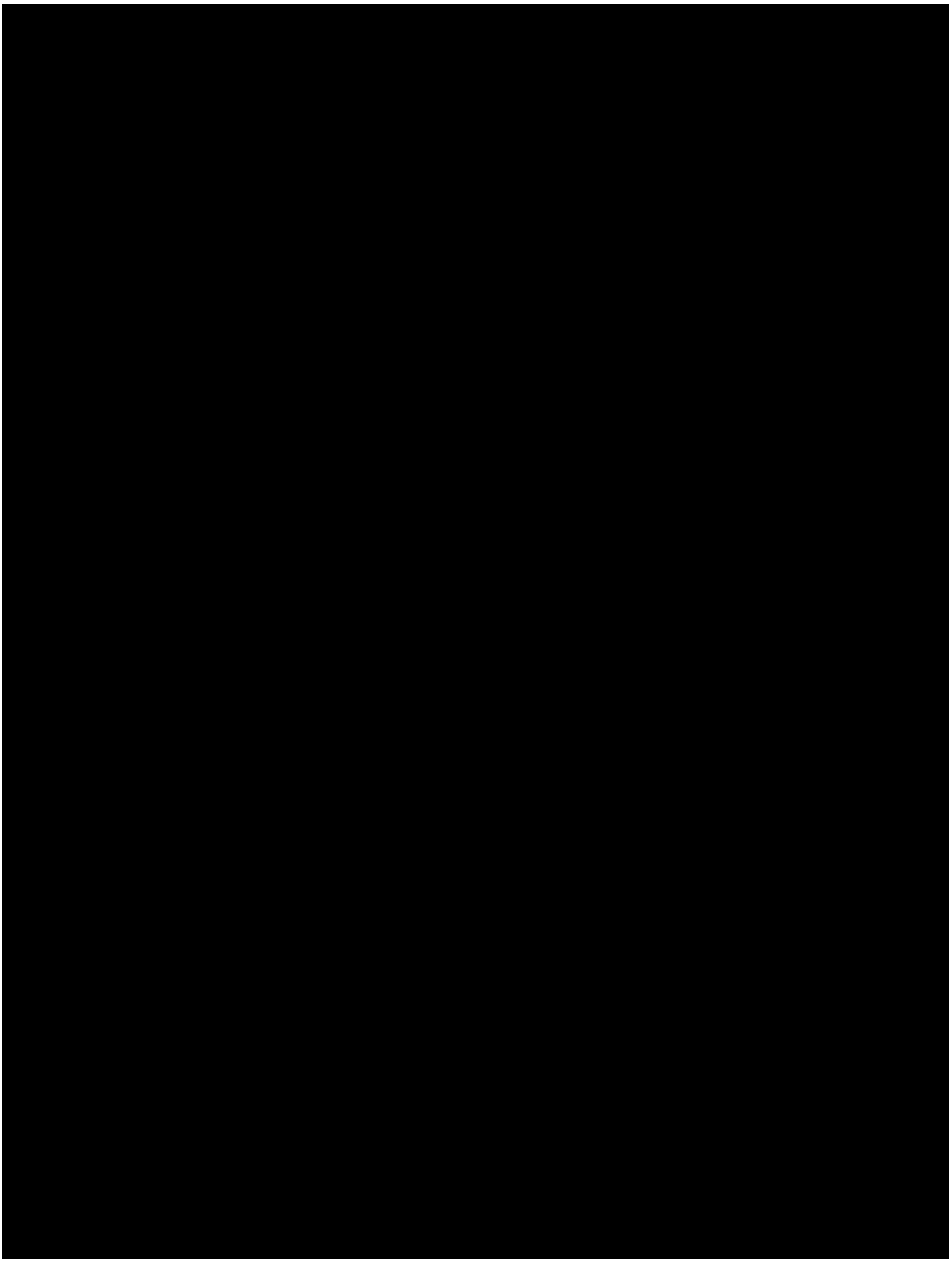


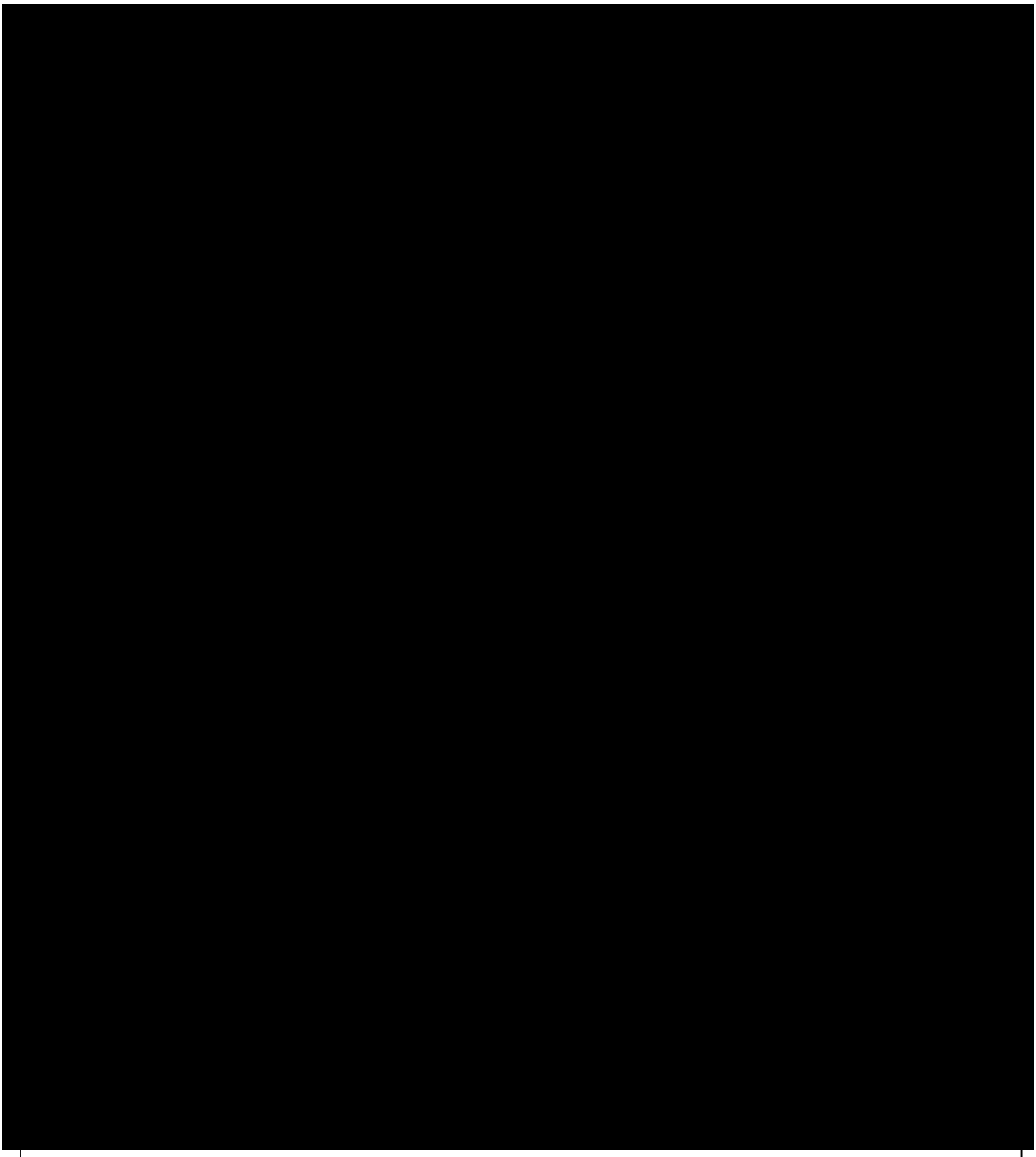


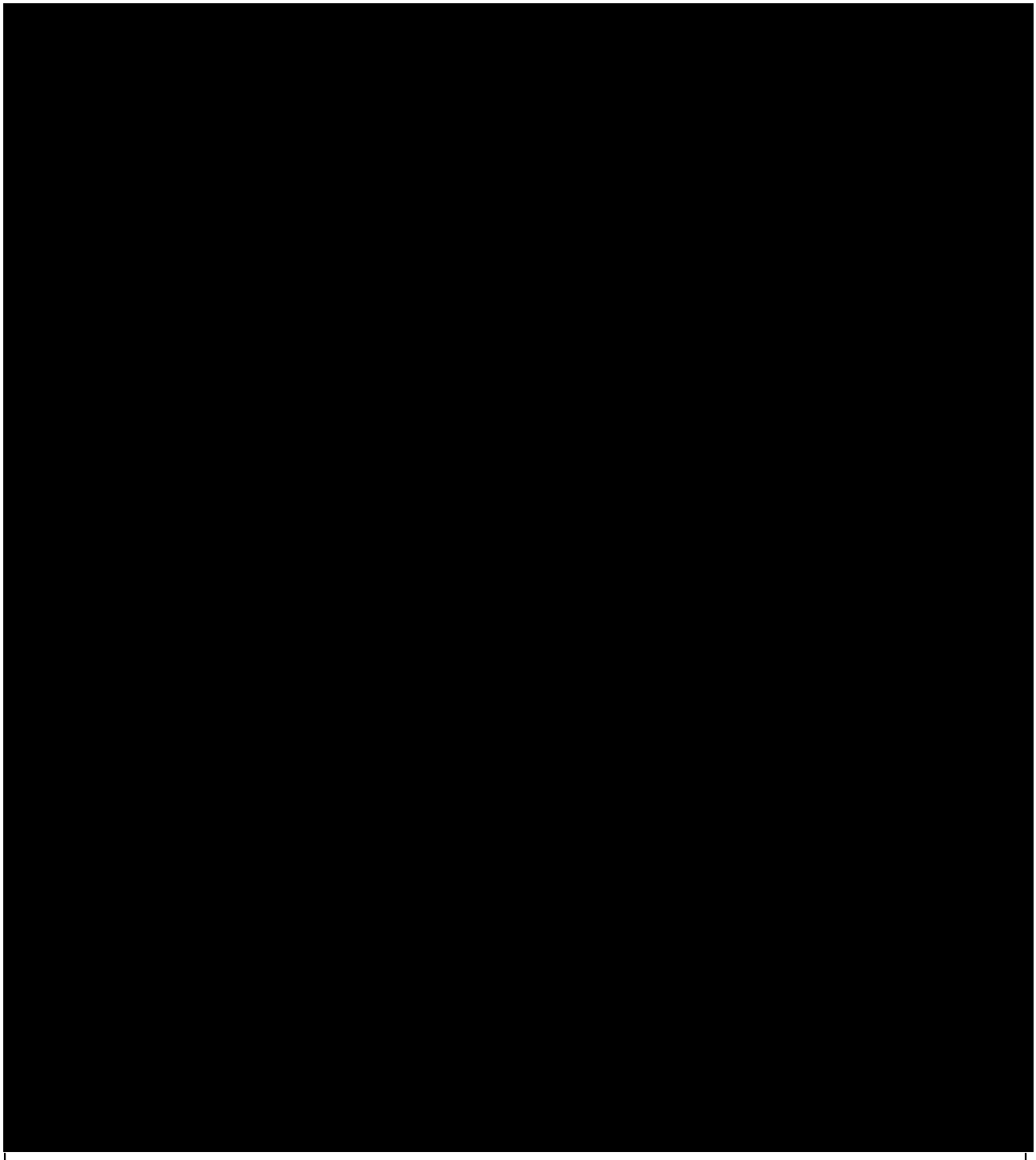
Participant's Initials: _____ Date: _____

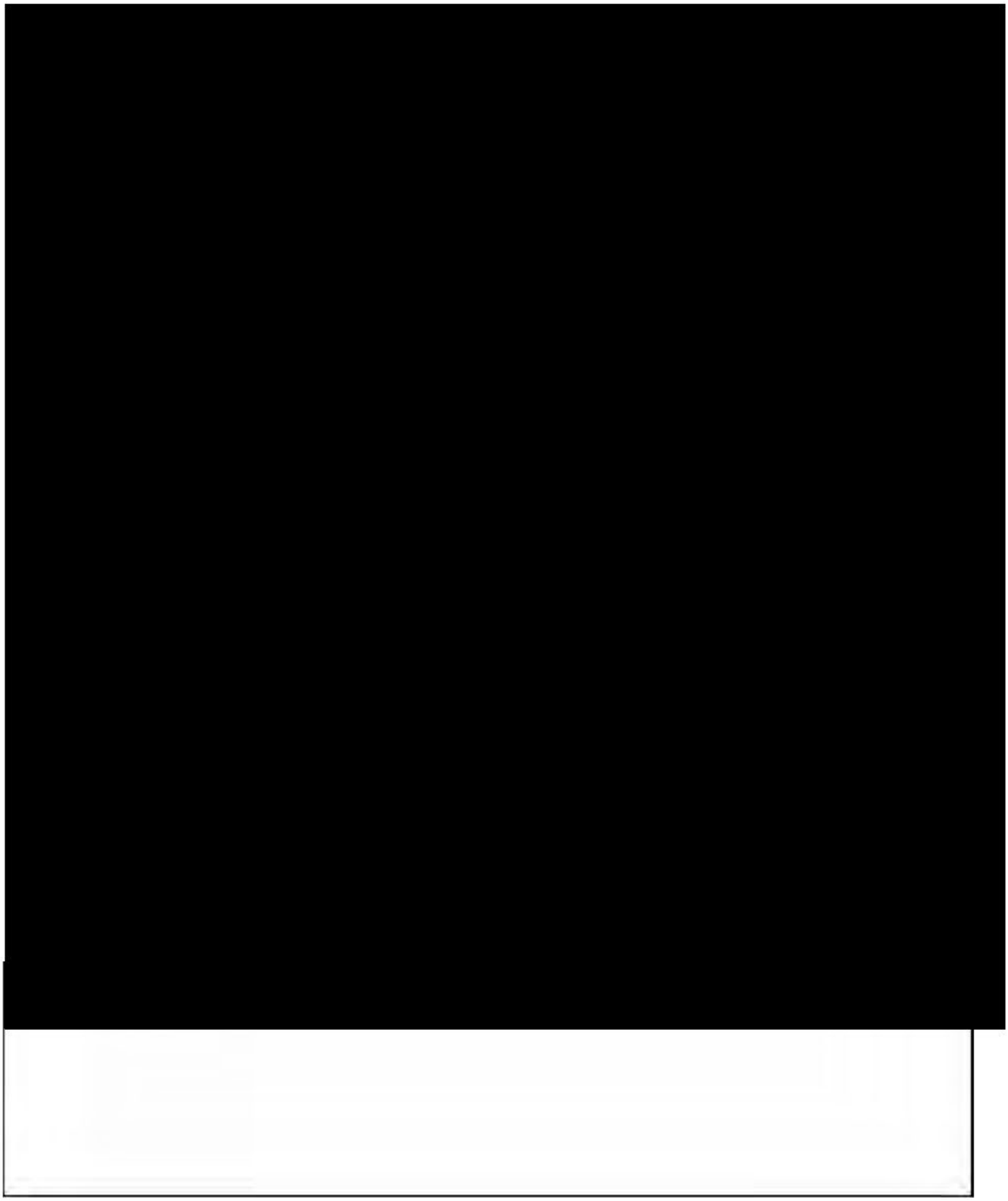
10.9. Appendix 9. Short Form Health Survey (SF-36) Example

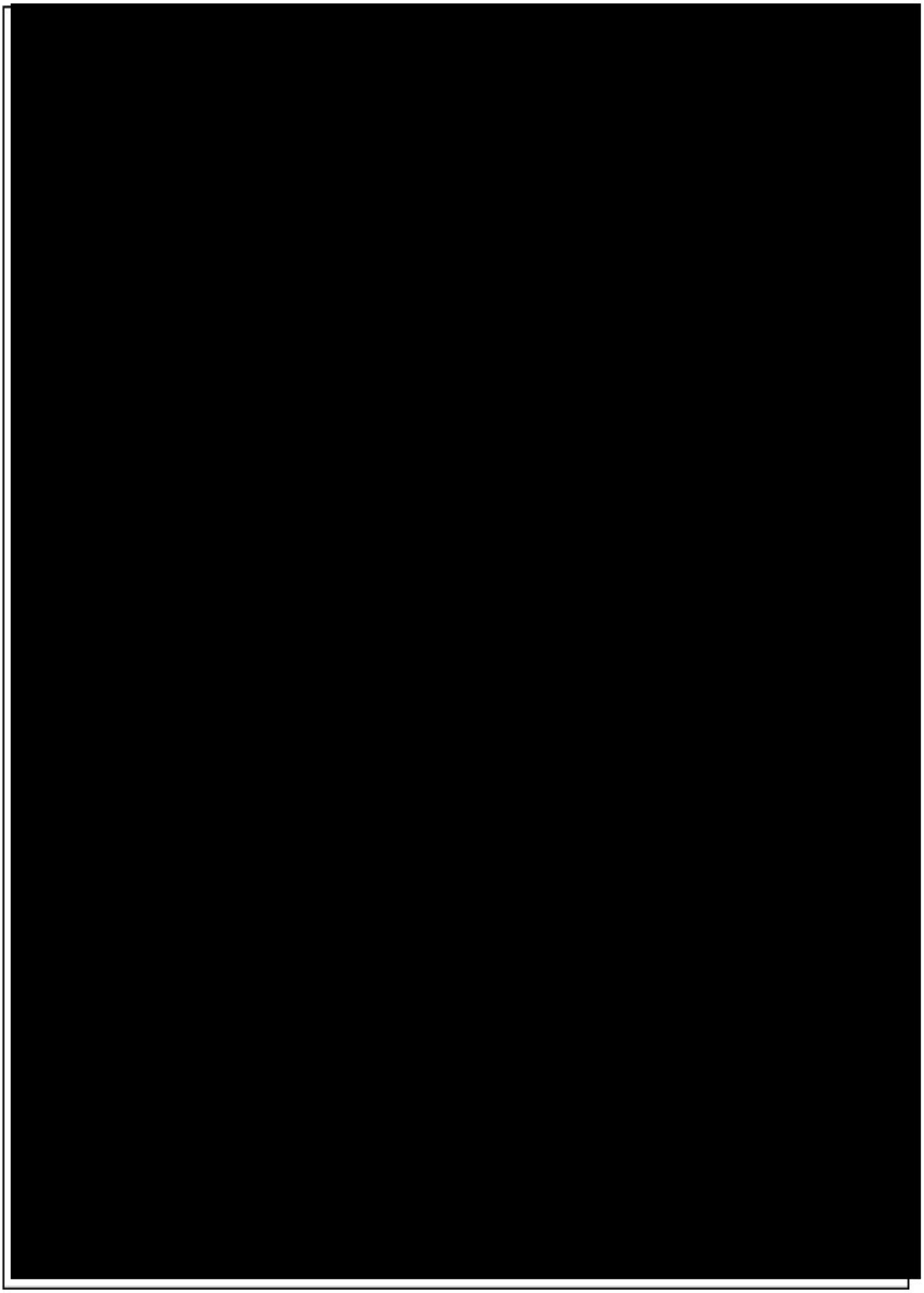
Short Form 36 (SF-36) Quality of Life Scale

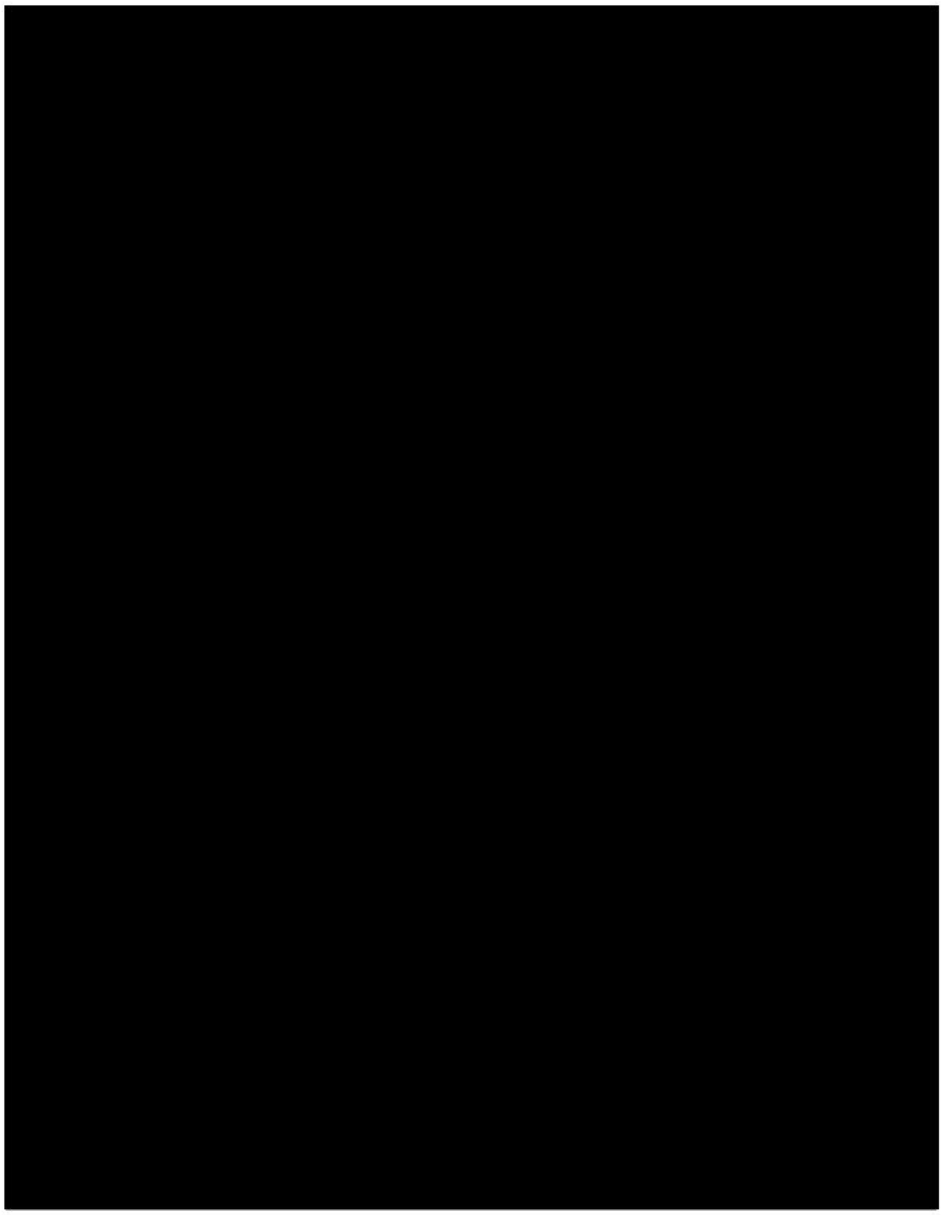












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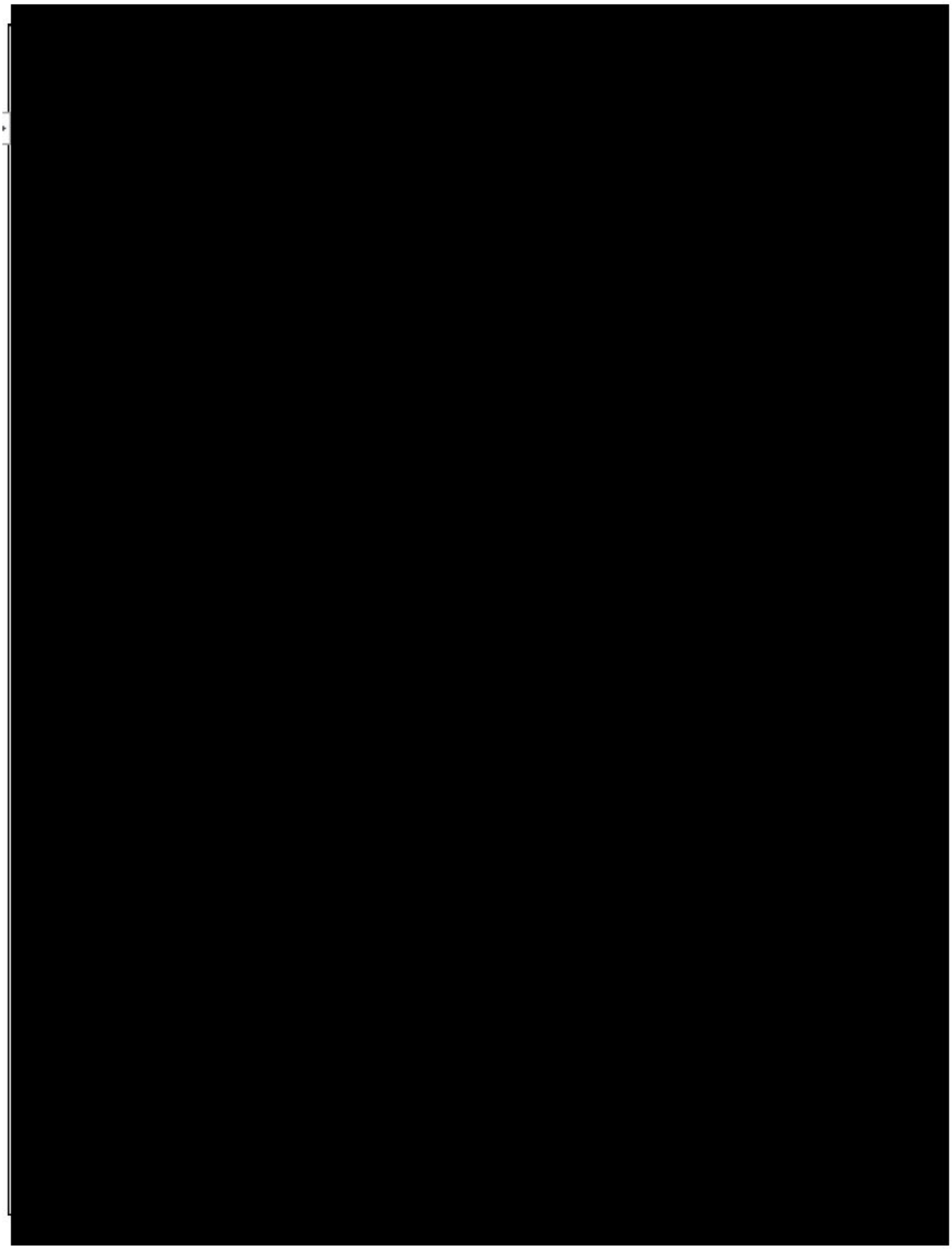
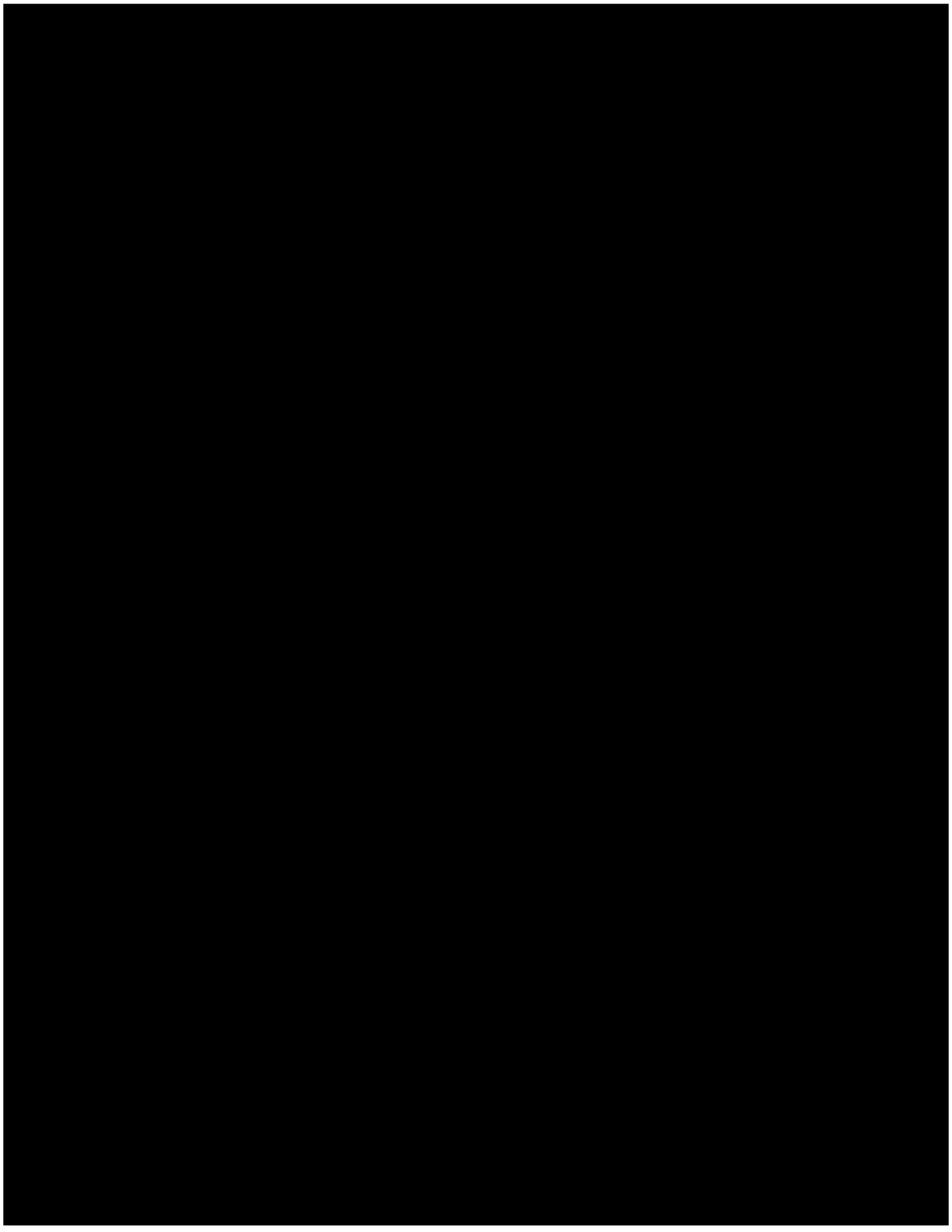
10.11. Appendix 11. Bedside Sensory Testing (BST)





Administering Bedside Sensory Testing (BST)

Administration. An Investigator should administer BST at Baseline (Day 0) and Days 90 and 180 Visits. All sensory tests are being performed at 3 predefined locations: dorsum of the foot, mid-shin, and mid-thigh, except low threshold mechanoreceptive function, which will be conducted at the bottom of the foot only.

The Participant should be seated comfortably during all five procedures of the BST.

Procedure 1: Neuropen Test. The Neuropen test allows assessment of the extent of damage of the low threshold mechanoreceptive small fibers.

Method of Administration. Application of the von Frey filament (10 g) to ten random locations on the bottom of the foot

Summary Score. Frequency count of von Frey stimuli detected (range 0-10; 0 = none detected; 10 = all detected) for bottom of the foot; then reverse score frequency count to align with interpretation of other sensory tests.

Procedure 2: Foam Brush Test. Allodynia, a phenomenon in which exposure to a non-painful stimulus is perceived as painful, is associated with small fiber neuropathy. The foam brush test allows for assessment of Dynamic Mechanical Allodynia.

Method of Administration. Stroke each anatomical location with brush making plus shape.

Summary Score. Single 0-10 NRS pain intensity rating for each anatomical location

Procedure 3: Safety Pin Test. Hyperalgesia, a phenomenon in which exposure to a painful stimulus is perceived as more painful than it should be, is associated with small fiber neuropathy. The safety pin test allows for the assessment of punctate hyperalgesia.

Method of administration. Tap safety pin five times within each anatomical location

Summary Score. Average of five 0-10 NRS pain intensity ratings in each anatomical location

Procedure 4: Von Frey Filament Test. Temporal Summation is a phenomenon in which exposure to the application of consecutive repeated stimuli is perceived as more painful than exposure to a single stimulus. The Von Frey filament test allows for quantification of Temporal Summation.

Method of Administration. Apply von Frey filament five times in rapid succession within each anatomical location

Summary Score. Delta between first and last 0-10 NRS pain intensity rating in each anatomical location

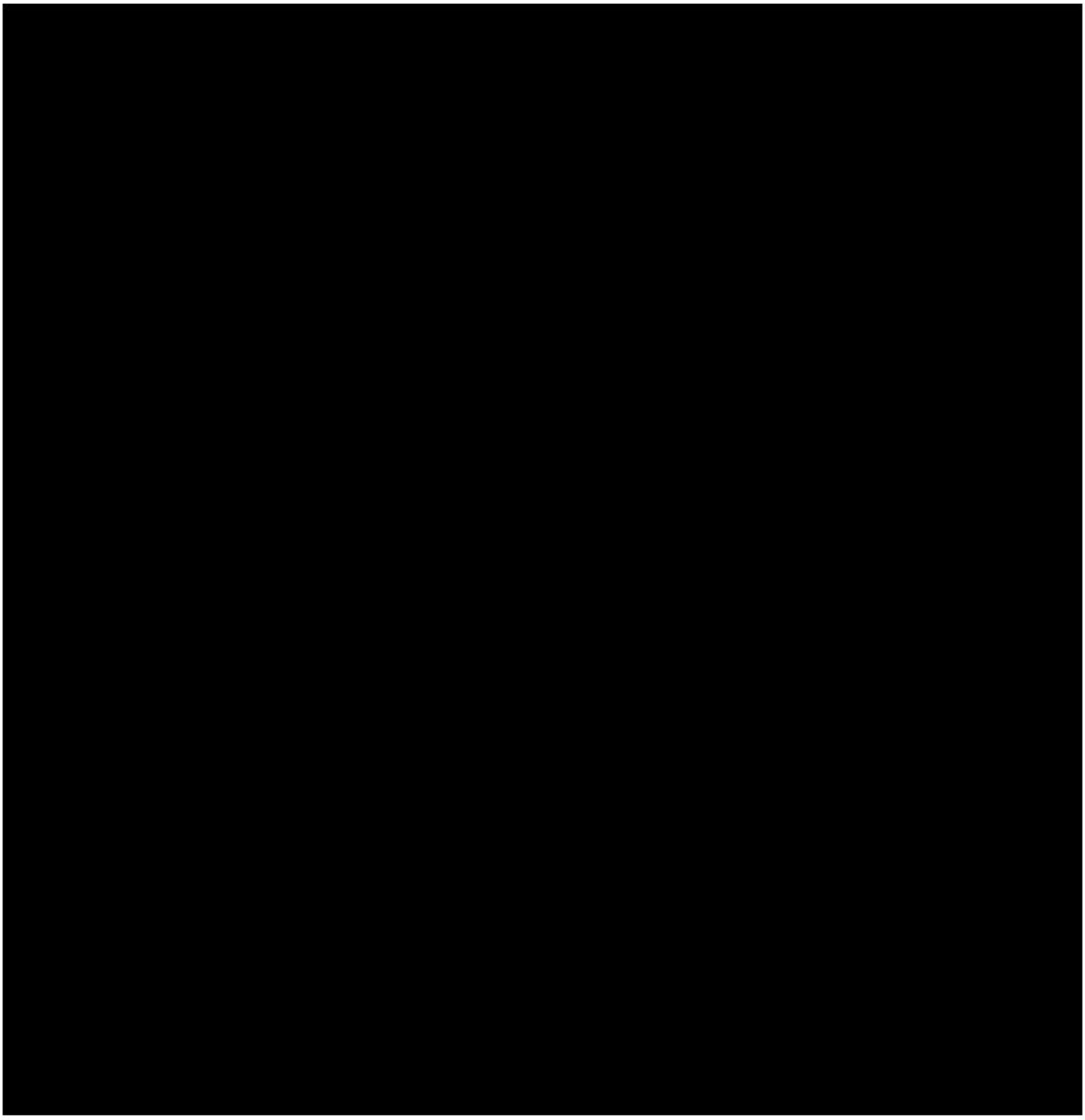
Procedure 5: Tuning Fork Test. Allodynia, a phenomenon in which exposure to a non-painful stimulus is perceived as painful, is associated with small fiber neuropathy. The tuning fork test allows for assessment of Cold Allodynia.

Method of Administration. Apply tuning fork for 10 seconds at each anatomical location.

Summary Score. Single 0-10 NRS pain intensity rating for each anatomical location

10.12. Appendix 12. Michigan Neuropathy Screening Instrument

MICHIGAN NEUROPATHY SCREENING INSTRUMENT



How to Use the Michigan Neuropathy Screening Instrument

History. The history questionnaire is self-administered by the Participant. Responses are added to obtain the total score. Responses of "yes" to items 1-3, 5-6, 8-9, 11-12, 14-15 are each counted as one point. A "no" response on items 7 and 13 counts as 1 point. Item #4 is a measure of impaired circulation and item #10 is a measure of general aesthenia and are not included in scoring. To decrease the potential for bias, all scoring information has been eliminated from the Participant version.

Upon completion of the questionnaire, the study coordinator will check the questionnaire for completeness. Note, the Participant will be asked to initial and date the questionnaire.

Physical Assessment. For all assessments, the foot should be warm (> 30°C).

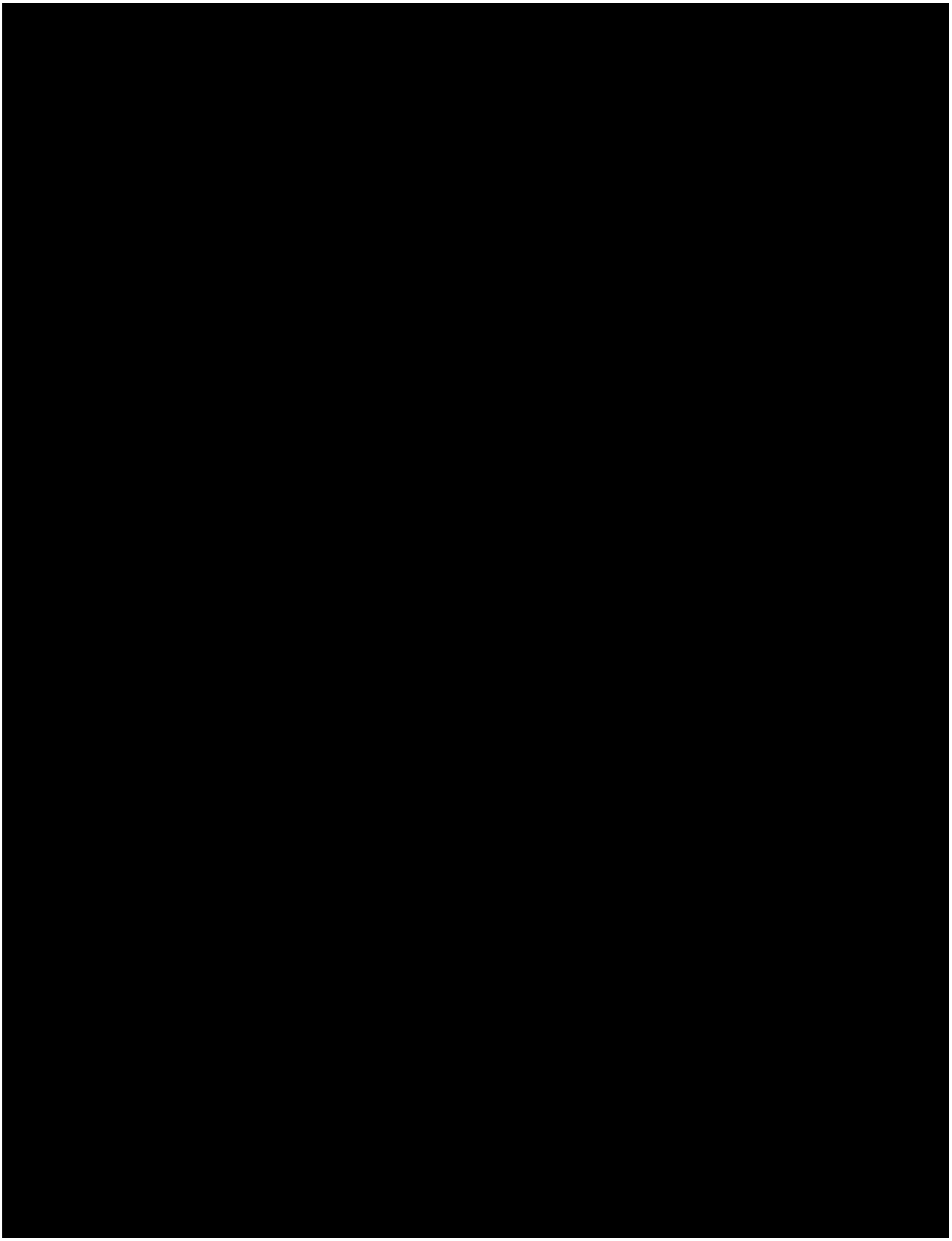
Foot Inspection: The feet are inspected for evidence of excessively dry skin, callous formation, fissures, frank ulceration or deformities. Deformities include flat feet, hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot) and amputation.

Vibration Sensation: Vibration sensation should be performed with the great toe unsupported. Vibration sensation will be tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the boney prominence of the distal interphalangeal (DIP) joint. Participants, whose eyes are closed, will be asked to indicate when they can no longer sense the vibration from the vibrating tuning fork. In general, the examiner should be able to feel vibration from the hand-held tuning fork for 5 seconds longer on his distal forefinger than a normal Participant can at the great toe (e.g., examiner's DIP joint of the first finger versus Participant's toe). If the examiner feels vibration for 10 or more seconds on his or her finger, then vibration is considered decreased. A study should be given when the tuning fork is not vibrating to be certain that the Participant is responding to vibration and not pressure or some other clue. Vibration is scored as 1) present if the examiner senses the vibration on his or her finger for < 10 seconds, 2) reduced if sensed for ≥ 10 or 3) absent (no vibration detection.)

Muscle Stretch Reflexes: The ankle reflexes will be examined using an appropriate reflex hammer (e.g., Trommer or Queen square). The ankle reflexes should be elicited in the sitting position with the foot dependent and the Participant relaxed. For the reflex, the foot should be passively positioned, and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon should be percussed directly. If the reflex is obtained, it is graded as present. If the reflex is absent, the Participant is asked to perform the Jendrassic maneuver (i.e., hooking the fingers together and pulling). Reflexes elicited with the Jendrassic maneuver alone are designated "present with reinforcement." If the reflex is absent, even in the face of the Jendrassic maneuver, the reflex is considered absent.

Monofilament Testing: For this examination, it is important that the Participant's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The 10-gram filament should initially be pre-stressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly, (< 1 second) with an even pressure. When the filament bends, the force of 10 grams has been applied. The Participant, whose eyes are closed, is asked to respond yes if he/she feels the filament. Eight correct responses out of 10 applications is considered normal, one to seven

correct responses indicate reduced sensation, and no correct answers translates into absent sensation.



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Section # and Name	Description of Change(s)	Brief Rationale
	Removed direct bilirubin, indirect bilirubin, and globulin (also in Section 8.4.6.1.3 Liver Function Tests)	Total bilirubin results sufficient; globulin testing no longer available in most sites
	Added text “to calculate eGFR” to Cystatin C testing (also in Section 8.4.6.1.4 Clinical Chemistry)	Define use for Cystatin C results
	Trace and interpretation will be signed by Investigator or delegated staff following review of findings and stored in Participant’s records (also in Section 8.4.3.12 Lead Electrocardiogram)	Clarification of need for signatures to indicate review; interpretation of ECG results to be collected
	Methaqualone and propoxyphene removed from urine drug analysis testing	Drugs are no longer available in the US
	Specified saliva analysis for ethyl alcohol testing at site during Screening. Noted that drug analysis will be performed by central laboratory at other time points.	Kit provided to sites for drug testing uses saliva analysis for ethyl alcohol. Clarify that central laboratory will conduct all other drug testing.
	HTLV I/II antibody with reflex confirmatory assay, quantitative HBV viral load assay, and positive qualitative PCR for HCV added (also in Section 8.1, Screening and Section 8.4.6.1.7 Viral Screening).	Add further specifics for viral screening as clarification for sites
	Add language for follow-up telephone call after injections to study injection footnote	Reiterate that injection site reactions must be checked 2 to 3 days after injection
	Administration of BST on Day 0 to follow randomization (also in Section 8.3.3 Bedside Sensory Testing)	Clarification of test timing on Day 0
2.2.7 Clinical Data	Removed statement about no systemic effects	Correction

Section # and Name	Description of Change(s)	Brief Rationale
2.3.1 Risk Assessment	Under Angiogenesis and promotion of tumor growth (cancer), added hyperplasia of vasa vasorum and exclusion of Participants with cerebrovascular accident or myocardial infarction	Provide additional risk information
4.1.1 First Treatment Cycle	Vital signs, physical exam, drug tests, medical history, BST, pregnancy test added to list	Provide complete list of assessments during First Treatment Cycle
4.1.2 Second Treatment Cycle	Vital signs, physical exam, drug tests, medical history, BST, MNSI, pregnancy test added	Provide complete list of assessments during Second Treatment Cycle
5.1 Inclusion Criteria	Inclusion Criterion #2 – Added "such as" before progressive end-organ disease	Clarify that progressive end-organ disease is an example of significant medical problems
	Inclusion Criterion #12 – Added to ensure potential Participant can complete all screening activities within 45 days	Potential Participant needs to be rescreened if screening activities cannot be completed within 45-day window
5.2 Exclusion Criteria	Exclusion Criterion #3 – Modified language around timing of gabapentin and pregabalin use	Clarification
	Exclusion Criterion #7 – Hypertension definition modified to systolic blood pressure > 180 mmHg on tolerable doses of standard antihypertensive medications	Review of literature supports definition of hypertension of systolic blood pressure > 180 mmHg on antihypertensive medication
	Exclusion Criterion #16 – Added language to remove toe amputations as exclusion	Allow potential Participants with toe amputations on study
	Exclusion Criterion #23 – Restored exclusion for Participants who have not been cancer-free for ≥5 years; restored in-situ basal cell, squamous cell cancers as excluded	Ensure that potential Participants with higher likelihood of cancer are excluded
	Exclusion Criterion #25 generalized	Exclude any active acute or chronic hepatitis B
	Exclusion Criterion #26 generalized	Exclude any active hepatitis C

Section # and Name	Description of Change(s)	Brief Rationale
	Exclusion Criterion #27 – added "or current medical conditions" to reasons that Investigator can exclude potential Participants	Allow Investigator to exclude potential Participant based on current medical conditions
	Exclusion Criterion #29 – Cannabis use removed as exclusion	Cannabis use not exclusionary
	Exclusion Criterion #31 – Modified language regarding stable dose requirement	Simplify explanation of stable dose
	Exclusion Criterion #33 – Changed use of investigational drug or treatment exclusion from 6 months to 30 days	Effects from most drugs gone after 30 days
	Exclusion Criterion #35 – Added exclusion of potential Participants who were recently treated for COVID-19 and have ongoing sequelae	Exclude potential Participants who might have complications from recent COVID-19 infection
6.2.2 Storage of Engensis and Placebo	Added that products should be placed in quarantine in cases of temperature excursion	Ensure quarantining of product not maintained at correct temperature
6.2.3 Product Accountability	Added that all investigational product is to be returned to the Sponsor after reconciliation	Ensure that sites know to return all drug to sponsor
6.3.3 Blinding	Exceptions to remaining blinded were added for unblinded Medical Monitor, Site's unblinded Pharmacist or delegated staff	Clarification of unblinded personnel
6.5 Concomitant Therapy, 10.3 Care of Patients with Diabetes Mellitus and Conditions Associated with DPN Management	Removed Appendix 3; added that all concomitant therapies to be captured on eCRF	Description of Standard of Care for DPN not needed in protocol (information available from medical organizations); add method for recording concomitant therapies
6.5.1 Rescue Medication	Reorganized description of acetaminophen use as rescue medication	Clarification

Section # and Name	Description of Change(s)	Brief Rationale
6.6 Dose Interruption	Added language in case full set of injections cannot be prepared	Add circumstance for which unintentional interruptions of Engensis injections would be allowed
6.7.2 Medications and Procedures That May Interfere with Assessment of Pain	"If not using a stable dose" added to duloxetine	Clarification and consistency
8.1 Screening (Days -52 to -7)	Added weight, waist circumference to physical exam	Make consistent with Schedule of Activities
	Added "where applicable" to Cancer Screening Tests	Clarification to add screening tests for cancer only as applicable to potential Participant
	Urine drug analysis added	Make consistent with Schedule of Activities
8.4.2 Medical History and Familial History of Cancer	"Including DPN" added to past diabetes history	Ensure that DPN history captured by site
8.4.6.1 Local and Central Laboratory Assessments	Rearranged text regarding local lab testing	Ensure that local labs used for Screening tests only
8.4.7 Retinal Fundoscopy	Added allowance for fundoscopy within 30 days prior to Day 180	Allow flexibility of retinal fundoscopy timing for Day 180
8.5.1 Time Period and Frequency for Collecting AE, SAE, TEAE, and TESAE Information	Added that medical events before study start are to be recorded as medical history; TESAEs added; timing for collection of adverse event reporting reorganized	Provide clearer definition of terminology based on timing of events
8.5.2 Method of Reporting AEs, SAEs, TEAEs, and TESAEs	Corrected section title, text; added AESIs, TESAEs	Correction, consistency with other parts of protocol
8.5.4 Adverse Events of Special Interest; 8.5.4.4 COVID-19 Infections	Added COVID-19 infections that occur after randomization to list of AESIs	Capture COVID-19 infections as an AESI in the safety database
8.5.4.3 Injection Site Reactions	Timing of first observation and grading, together with close proximity to injection site of ISR added for consideration of ISR as AE; timing for follow-up for unresolved ISRs added	Additional information for ISRs to qualify as AEs; length of follow-up required for unresolved ISRs

Section # and Name	Description of Change(s)	Brief Rationale
8.5.7.1 Pregnancy Test	Need for male Participants to use double-barrier contraception during study added	Ensure that male Participants practice double-barrier contraception as well
9.1 Sample Size Determination; 9.3.1 Primary Endpoint(s)	"Mean" added to ADPS for statistical analysis for primary efficacy endpoint	Clarification that mean ADPS will be used
9.3.2 Secondary Endpoints, 9.3.3 Exploratory Efficacy Endpoints	Rearranged and updated	Match endpoint list with Section 3 Objectives and Endpoints
10.1.5.1 Data Safety Monitoring Board	Added TEAEs, SAEs, TESAEs, and AESIs to list of items being reviewed by DSMB	DSMB to review all safety data
	Changed from 6- to 12-week pooled data	Longer period for pooled data is appropriate for timing of enrollment and Participant visits during study
	Narratives rather than Participant profiles will be provided to DSMB (also in Section 6.3.3 Blinding)	Clarification
10.1.6.2 Access to Study Documents and Study Monitoring	Removed designation of CRO for study monitoring	Study monitoring being conducted by Sponsor
10.2.1 Definition of AE	Reworded AE definition	Clarification
10.4 Prohibited Medications and Procedures	Table 9 – Added gabapentin, pregabalin	Both medications not allowed on trial
10.5.2 Definitions	Injection Site Reaction – Changed from 24 to 48 hours	Correction; consistency with earlier text
	Primary HPV test definition added	Clarification of what constitutes primary HPV test
	Propoxyphene removed from list of Drugs of Abuse	Propoxyphene no longer available in the US
	Uncontrolled hypertension deleted	Definition no longer needed
10.9 Appendix 9. Short Form Health Survey (SF-36)	Added "Example" to the title	Appendix content may not be an exact replica of the actual survey used

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