Statistical Analysis Plan (SAP)

Protocol Title:	A 6-Month Extension Study Following Protocol VMDN-003-2 – 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
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1.0 Approvals

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2.0 Change History

Version/Date	Change Log
[redacted]	[redacted]

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Helixmith Protocol VMDN-003-2b

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This is a 6-month extension study (VMDN-003-2b) to evaluate the durability of efficacy and long-term safety of intramuscular (IM) administration of Engensis or Placebo that was administered in the double-blind, randomized, VMDN-003-2 Placebo-controlled Phase 3 Study. No treatments will be administered in this VMDN-003-2b extension study. The combined overall duration of the VMDN-003-2 and VMDN-003-2b studies will be 12 months.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol version 1.0 dated 11FEB2021 and CRF version 3.0 dated 06JUL2022. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Versions of the SAP up to initial sponsor approval will be known as a draft SAP. Changes following approval of the first version SAP, known as the “stable SAP”, will be tracked in the SAP Change Log. The finalized version of the SAP will be issued for sponsor approval prior to first planned IA.

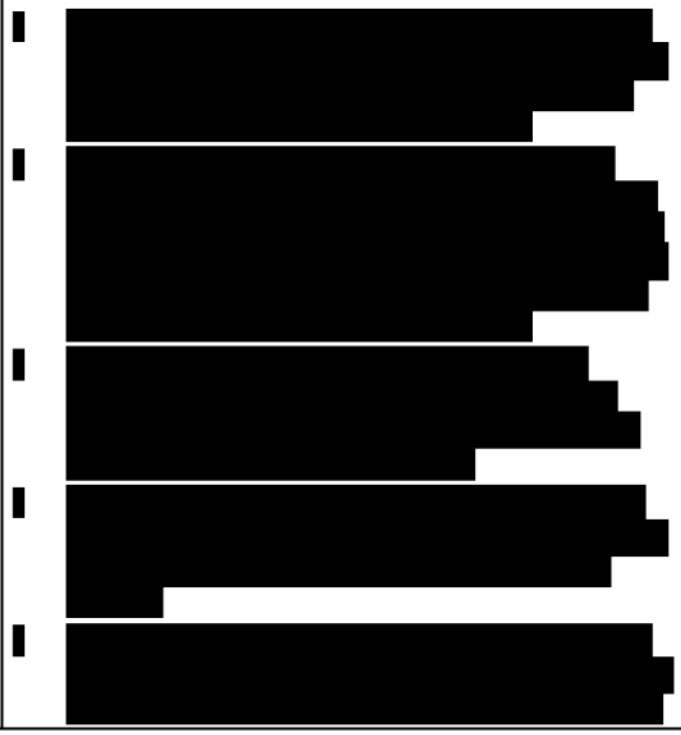
6.1 Changes from Protocol

Protocol states that a Participant is considered to have completed the study if the Participant completes the Day 365/ET Visit and has at least 5 days of the most recent 7 days with electronic diary (eDiary) entries prior to the Day 365/ET Visit. Protocol also defines the Per Protocol (PP) population as whether Participant received all injections in Study VMDN-003-2, based on the randomized treatments, and had a Day 365/ET Visit, including a 7-day ADPS. For purposes of analysis, Day 365/ET Visit here is not considered for early discontinuation for study completion status and will not be included in the definition of the Per Protocol population.

7.0 Study Objectives

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 (Study VMDN-003-2) to the 7 days prior to the Day 365 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 (Study VMDN-003-2) to the 7 days prior to the Day 270 Visit and Day 365 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 (Study VMDN-003-2) to the 7 days prior to the Day 270 Visit and Day 365 Visit for Engensis compared to Placebo

Objectives	Endpoints
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 clinically significant laboratory values for Engensis compared to Placebo
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
	

8.0 Study Design

VMDN-003-2b is a 6-month extension study following Study VMDN-003-2, which is an adaptive, Phase 3, double-blind, randomized, placebo-co, ntrolled, multicenter study designed to assess the efficacy and safety of Engensis (containing the active pharmaceutical ingredient VM202) in Participants with painful DPN.

The purpose of this study is to assess the durability of efficacy and long-term safety of Engensis compared to Placebo as measured by changes in Average Daily Pain Score (ADPS) of the full Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), Bedside Sensory Testing (BST), physical examinations, laboratory assessments, vital signs, treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and adverse events of special interest (AESIs).

Participants will be enrolled in the VMDN-003-2b study at completion of the Day 180 Visit of Study VMDN-003-2. Participants will continue to be identified by the same Participant number and the same treatment group (Engensis or Placebo) assigned by randomization in Study VMDN-003-2. No study drug or treatment will be administered in this VMDN-003-2b extension study. The double-blind treatment assignment from the prior study will be maintained for Investigators and Participants during this extension study.

8.1 Sample Size Considerations

The number of Participants to be enrolled in this 6-month extension study depends upon the number of subjects who complete the Day 180 Visit in Study VMDN-003-2 and provide written informed consent for this extension protocol (prior to or during their Day 180 Visit in the VMDN-003-2 study).

8.2 Randomization

There will be no randomization of Participants in this VMDN-003-2b extension study. All Participants who are entered into the VMDN-003-2b extension study will continue to be followed from the VMDN-003-02 study in a blinded fashion.

9.0 Population Sets

9.1 Intent-to-Treat (ITT) Population

This subset includes all enrolled Participants in this study who start this extension study at the Day 180 Visit (Study VMDN-003-2). Participants in the ITT population will be analyzed according to original treatment assignment in Study VMDN-003-2, regardless of actual treatment received. The primary analyses of the primary and secondary efficacy endpoints will be based on this ITT population.

9.2 Safety Population

The safety population will contain all enrolled Participants. Participants in the Safety population will be analyzed according to actual treatment received in Study VMDN-003-2, regardless of original treatment assigned.

9.3 Modified Intent-to-Treat (mITT) Population

The modified ITT (mITT) population includes all participants that meet the following:

- Underwent (any) injections in Study VMDN-003-2
- Correctly completed the BPI-DPN eDiary at Baseline and the 12-month follow-up (with at least 5 of 7 days of BPI-DPN eDiary collected prior to Day 365 Visit) in Study VMDN-003-2b. 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.

9.4 Per Protocol (PP) Populations

The Per Protocol population is a subset of mITT. It includes all mITT participants who meet all of the following criteria for Study VMDN-003-2 and Study VMDN-003-2b:

- The participant meets major protocol eligibility criteria determined by Clinical Data Review Committee (CDRC) prior to database lock and breaking the randomization codes.
- The participant received all 32 injections from each visit (Day 0, Day 14, Day 90 and Day 104) in Study VMDN-003-2, based on the randomized treatments and had a Day 365 Visit, including a 7-day ADPS (with at least 5 of 7 days of BPI-DPN eDiary collected prior to Day 365 Visit).

The CDRC, which is blinded to the treatment information of each participant, may determine additional criteria, if any, before unblinding the randomization code.

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

10.0 Conventions and Derivations

Data screening will be conducted in a blinded fashion periodically during the conduct of the study. The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. The designated Contract Research Organization (CRO) will be responsible for data cleaning and dictionary coding of AEs, medical history, and medications. Any questionable values or situations will be reported to the CDRC for final review and confirmation.

10.1 Study Day

Because VMDN-003-2b is a 6-month extension study following Study VMDN-003-2, Study Day 0 is defined as the date of first dose in the main study VMDN-003-2. Study Day 180 is defined as the completion of the Day 180 Visit of Study VMDN-003-2 and enrollment into extension study VMDN-003-2b. Subsequent visits in extension study will be counted from Study Day 180.

10.2 Baseline Definition

Unless specified otherwise, the baseline value for each variable is the value recorded at the last visit on or before start of dosing in Study VMDN-003-2.

For the pain scores from the BPI-DPN eDiary, the baseline value is the Average Daily Pain Score prior to the Day 0 visit from the main study.

Note that, for eligibility, the mean of Average Daily Pain Scores of the BPI-DPN eDiary should be ≥ 4 during the 7 days prior to Day 0. For the Average Daily Pain Score calculation, at least five (5) days need to have the available scores.

10.3 Visit Windows

Data at each scheduled follow-up visit will be analyzed according to the nominal visit identified on the data record.

In case of multiple different visits with the same nominal visit designation, the visit with the visit date closest to the target days of each protocol-specified visit schedule will be used for the efficacy analyses. For visits with the same distance to the target days, the later nominal visit record will be used. Data from all visits will be provided in the data listings.

If a subject fails to complete a study visit but provides necessary eDiary data during the time period expected for that visit (i.e. based on study day relative to the date of the first dose in VMDN-003-2), those eDiary data will be used to derive applicable endpoints. Day 270 endpoint would be derived by the eDiaries recorded 7 days up to 270 days from the date of first dose in VMDN-003-2. Similarly, Day 365 endpoint would be derived by the eDiaries recorded 7 days up to 365 days from the date of first dose in VMDN-003-2. Otherwise, if subject completes study visit, then date of visit will be used to derive applicable endpoints.

10.4 Unmasking of Randomization Codes

Following database lock of this extension study, the randomization code will be unmasked to the project team for all subjects in the extension study and concurrently for Study VMDN-003-2. During the study, the randomization code will be unmasked to the Data Safety Monitoring Board (DSMB; Section 7.5) members and the CRO that will prepare the unmasking summary tables for the DSMB meetings. However, to prevent bias, the unmasking detailed data summaries will not be shared with the sponsor management team, the CDRC, or the team that is monitoring the clinical data collection. The participant and study personnel, including core lab, principal investigator, co-investigators, study coordinators, study monitors and study director will remain blinded to individual data and group results until all data has been entered into the database and the database is locked.

10.5 Data Safety Monitoring Board

An independent DSMB will periodically review a limited set of unblinded tables and/or listings, including all reported AEs. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to the study sponsor regarding the safety of the Engensis. The data analyses for the DSMB meetings will be directly provided to the DSMB members and no data will be released to the study sponsor and blinded designees. There will be no adjustment for multiple testing due to the DSMB data review. The DSMB may be asked to review and provide guidance regarding protocol deviations that may affect the determination of the PP populations. Further details of DSMB responsibilities are included in the DSMB Charter.

10.6 Handling of Missing and Incomplete Data

Participants may have missing specific data points for a variety of reasons. In general, data may be missing due to a participant's early withdrawal from study, a missed visit, or a clinical parameter not measured at a particular point in time. The general procedures outlined below describe how missing data will be addressed in the analyses.

10.6.1 Missing Pain Scores for the Average Scores from BPI-DPN

The means of the Average Daily Pain Scores (Question 5 from the BPI-DPN) for a visit will be considered as missing if fewer than 5 of 7 days of BPI-DPN eDiary entries are provided. Any missing mean pain score of ADPS will be imputed using the methods described below.

Multiple Imputation (MI) method:

- Step 1: Intermittent missing values will first be imputed by treatment group using the Markov Chain Monte Carlo (MCMC) method, resulting in data with a monotone pattern.
- Step 2: Multiple imputation by treatment group using linear mixed model regression with factors of baseline pain score, baseline HbA1c, gender, and age at informed consent (Study VMDN-003-2) will be applied to the data obtained from the MCMC step. The imputed score will be rounded to the first decimal point.

The entire procedure will be repeated 10 times, and 10 complete datasets will be used for the analysis.

10.6.2 Addressing Missing Data for the Secondary and Exploratory Efficacy

Missing individual item scores of the full BPI-DPN will be imputed for the calculation of the average score within a domain using the average score across the non-missing items within the domain at a subject's visit provided that the proportion of missing items scores within that domain is less than 25%; otherwise, the domain score at that visit is missing.

The same method as the full BPI-DPN will be used when addressing the missing data for SF-36 and EQ-5D.

Individual item scores on the MNSI (both physical assessment and history) questionnaire will not be imputed. The total MNSI scores will be imputed using a "worst-case" imputation approach. Missing individual items will be imputed as the category corresponding to the largest number of points in the total score calculation. This equates to a response of "Yes" to questions 1-3, 5-6, 8-9, 11-12, and 14-15 and "No" to questions 7 and 13 on the history assessment. On the physical assessment, it equates to a response of "No" on the "Appearance of Feet" question, a response of "Present" on the "Ulceration" question, and a response of "Absent" on the "Ankle Reflexes", "Vibration perception at great toe", and "Monofilament" questions.

Missing PGIC and BST scores and the use of rescue medication will not be imputed.

10.6.3 Missing Dates

If a start or stop date for an adverse event or a concomitant medication use is completely missing, it will not be imputed. If it is partially missing, imputed dates in accordance with Table 1 will be used to derive the duration of the adverse event or the duration of the medication use. Missing years will not be estimated under any conditions. Missing dates of medical history will not be imputed.

Table 1: Imputation Rules for Partial Adverse Event or Concomitant Medication Start and Stop Dates

	Missing	Imputation	Exception
Start Date	Day	01	Default to Study Day 180 +1 (first date in extension study) if an event starts in the same year and month as Study Day 180

	Day/Month	01JAN	Default to Study Day 180 + 1 if an event starts in the same year as Day 180
Start Date			If the start date is completely missing and stop date is either after the date of Study Day 180 + 1 or completely missing, then the start date will be estimated to be equal to Study Day 180 + 1. Otherwise, the start date will be estimated to be the first day of the same year as the stop date.
Stop Date	Day	Last day of the month	Default to the End of Study Date if the imputed event stop date is after the End of Study Date or before start day of the event
	Day/Month	31DEC	

11.0 Interim Analyses

There will be no interim analysis during this 6-month extension study.

12.0 Statistical Methods

The primary analysis for this study will be performed and summarized after all randomized participants have had an opportunity to complete their 12-month follow-up visit.

The Safety Analysis will be based on the Safety population. The primary analyses of the efficacy endpoints will be based on the ITT population. Additional sensitivity analyses for the primary and secondary efficacy endpoints will be performed to further assess the effects of the treatment (Section 8.4.2 and 8.4.4).

The statistical analyses will be reported using summary tables, figures and listings. Continuous variables will be summarized with mean, standard deviation, median, minimum, maximum, 25th percentile, 75th percentile, and number of non-missing observations for each treatment group.

Categorical variables will be summarized by counts and by the percentage of participants in corresponding categories.

All inferential statistical analyses will be performed with a two-sided confidence level of 95% or a two-sided significance level of 0.05 unless otherwise noted.

All analyses and tabulations will be performed using SAS Version 9.4 or higher on a Server platform.

12.1 Subject Disposition

Participant disposition will be summarized for all enrolled participants. The summary including the number and percentage (based on total number of participants enrolled) of participants in each of the following categories will be prepared:

- Completing 12-month blinded assessment based on the ITT population
- Early Termination based on the ITT population
- Safety population, ITT, mITT, and PP populations

A Participant is considered to have completed the study if the Participant completes the Day 365 Visit and has at least 5 days of the most recent 7 days with electronic diary (eDiary) entries prior to the Day 365 Visit. Major protocol deviations for participants not in the PP populations will be listed. Major protocol deviations will be summarized for the ITT population.

12.2 Demographic and Baseline Characteristics

The following outcomes will be summarized by the standard methods for continuous and categorical variables described in Section 8.1.

The demographics include the following parameters:

- Age at informed consent of main study
- Sex
- Race
- Ethnicity
- Vital signs: height, weight, BMI,

The baseline characteristics include the following:

- Baseline Average Daily Pain Score from the 7 days prior to the Day 0 Visit obtained from the BPI-DPN eDiary
- Vital signs: blood pressure, heart rate, respiration rate, temperature
- Diabetes type
- 12-lead electrocardiogram (ECG): Normal, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS)

These parameters will be summarized by treatment group for the ITT and included in data listings. The demographic and selected baseline characteristics (diabetes type and specific medical history items of interest) will also be summarized for each level of the stratification variable.

12.3 Prior and Concomitant Medications

Prior medications are those with a stop date before the first day of treatment during main study (VMDN-003-2) or have missing stop date but are not marked as ongoing. Concomitant medications are those medications taken after the initial dose of study drug in the main study (VMDN-003-2). A medication with a missing start date and a stop date that is either missing or on or after the treatment start date will be considered as concomitant. All prior and concomitant medications will be assigned WHO drug names using the WHO Drug Dictionary (March 2018 version or later). Prior and concomitant medications will be summarized separately for each treatment group by preferred names. These summaries will present the number and percentage of participants using each medication.

12.4 Important Protocol Deviations

A Clinical data Review Committee (CDRC) will review all subjects to evaluate whether subjects meet major protocol eligibility criteria prior to database lock and breaking the randomization codes.

12.5 Efficacy Analyses

12.5.1 Primary Analysis of the Primary Efficacy Endpoint

The primary analysis for comparing the change in mean Average Daily Pain Scores at the Day 365 visit from Baseline between the treatment groups will be analyzed using the MI method for handling the missing data as specified in Section 10.6.1. A linear mixed-effects model for repeated measures (hereinafter, the continuous Repeated Measures Model) will be used to analyze each complete dataset. The model will include treatment, visit (Day 90 and Day 180 from main study, Day 270 and 365 from extension study), treatment-by-visit interaction, and baseline (Study VMDN-003-2) Average Daily Pain Score as a covariate using an unstructured variance- covariance matrix. Then the Proc MIANALYZE procedures will be used to generate the point estimate for the least-squares mean of the treatment difference (Engensis – Placebo)

and the corresponding 95% confidence interval. LSMEANS, differences and p values compared to baseline will be presented for Day 90 and Day 180 visits from the main study, and Day 270 and Day 365 at the extension study.

The SAS code to be used to for the continuous repeated measure model is presented below:

proc mixed data=work order=internal method = REML;

class usubjid trtp avisitn;

*model chg = trtp avisitn trtp*avisitn base / ddfm=KR;*

repeated avisitn /subject = usubjid type = un;

*lsmeans trtp trtp*avisitn / pdiff cl;*

run;

where

USUBJID: subject ID TRTP: treatment

AVISITN: variable representing visits

CHG: change in the Average Daily Pain Score from baseline(Study VMDN-003-2)

BASE: baseline (Study VMDN-003-2) Average Daily Pain Score (continuous variable)

Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options will be substituted based on the lowest Akaike information criterion (AIC) if convergence problems arise.

The primary efficacy analysis will be performed for ITT population.

12.5.1.1 Sensitivity Analyses

The primary endpoint will be also analyzed for mITT and PP using the same continuous Repeated Measure Model described in Section 12.5.1.

In addition, there will be a sensitivity analysis accounting for the individual pain scores influenced by the protocol-prohibited concomitant medications. In this analysis, the pain scores after receiving protocol-prohibited concomitant medication will be replaced with the baseline value only if a prohibited medication was used during the 10 days prior to Day 90 visit, Day 180 visit, Day 270 visit or Day 365 visit.

12.5.2 Analysis of the Secondary Efficacy Endpoints

12.5.2.1 Change from Baseline in the means of Worst Pain Scores at Day 365 Visit

The change from Baseline (Study VMDN-003-2) in mean worst pain score at the Day 365 visit will be analyzed using the same linear mixed method described in Section 8.4.1 for the ITT population. Missing data will be handled according to the method pre-specified in Section 12.5.1

12.5.2.2 Proportion of Responders (≥50% reduction in mean ADPS) on Day 365

Responders will be defined as participants with at least 50% reduction from Baseline in the mean ADPS at the Day 365 visit. The percent reduction will be computed as follows:

$$\%Change = \frac{Day\ 365\ mean\ ADPS - Baseline\ mean\ ADPS}{Baseline\ mean\ ADPS} X\ 100$$

For each 10 completed datasets imputed using the MI method, a generalized linear mixed-effects model for repeated measures based on a logit link function (hereinafter, the categorical Repeated Measures Model) will be used for comparing the percentage of responders between the two study treatment groups. The model will include treatment, visit, treatment-by-visit interaction, and baseline (Study VMDN-003-2) Average Daily Pain Score as covariates with an unstructured variance-covariance matrix. Then the Proc MIANALYZE procedures will be used to generate the point estimate and the corresponding 95% confidence interval. Study visits from main study will include Baseline and Day 180 and extension study Day 270 and Day 365 will be included.

The SAS code to be used to conduct the analysis is presented below:

PROC GLIMMIX DATA=work method=*REML;*

class usubjid trtp avisitn;

*MODEL critvar(event='Y') = trtp base avisitn trtp*avisitn / DIST=binary LINK=LOGIT SOLUTION;*

random INTERCEPT / SUBJECT=usubjid type=un;

*lsmeans trtp *avisitn / diff cl; RUN;*

where

USUBJID: subject ID TRTP: treatment

AVISITN: variable representing visits

CHG: change in Average Daily Pain Score from baseline(Study VMDN-003-2)

BASE: (Study VMDN-003-2) Average Daily Pain Score (continuous variable)

CRITVAR: a Y/N variable indicating if the participant had at least a 50% reduction in Average Daily Pain Score from baseline (Study VMDN-003-2) at that visit

Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options will be substituted based on the lowest AIC if convergence problems arise.

12.5.2.3 Other Analysis of the Secondary Efficacy Endpoints

The secondary endpoints (not including PGIC endpoints) will be also analyzed for mITT and PP using the same analysis method described in Section 12.5.1. PGIC endpoint will be summarized by treatment group.

In addition, there will be a sensitivity analysis accounting for the individual pain scores influenced by the protocol-prohibited concomitant medications. In this analysis, the pain scores after receiving protocol-prohibited concomitant medication will be replaced with the baseline value only if a prohibited medication was used during the 10 days prior to Day 90 visit, Day 180 visit, Day 270 visit or the Day 365 visit.

12.5.3 Subgroup Analysis of Primary and Secondary Efficacy Endpoints

The subgroup analysis for the primary and secondary endpoints will be performed for the following factors:

- Baseline pain score of main study
- Baseline HbA1c of main study (< and ≥ median of main study)
- Gender (male and female)
- Age at informed consent (Study VMDN-003-2) (<65 years and ≥ 65 years)

For each subgroup of the ITT population, the primary and secondary endpoints will be summarized by treatment group and visit using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum for the continuous variable and frequency and percentage for the categorical variable). Both types of descriptive summaries are also provided for the subgroups of study center and protocol version.

Participants will be assigned to a protocol version based on their randomization date and the date of Institutional Review Board (IRB) approval at their site.

The main analysis method described above for the primary and secondary endpoints will be used to analyze the treatment effect within each subgroup. Additionally, the possible treatment-by-subgroup interaction will be tested for each subgroup variable as follows:

- The interaction term for the subgroup variable and treatment group will be included in the analysis model. If the p-value of the interaction term is ≥ 0.05, the treatment-by-subgroup interaction will be considered not statistically significant.

[redacted]

12.6 Safety Analyses

Safety analyses in this study will evaluate the safety profile of Engensis as compared with control. No formal statistical testing will be conducted for the safety analyses. The following sections summarize the descriptive analysis methods for these safety endpoints. All participants in the Safety population will be included in these analyses. Participants will be grouped by treatment administered. All summaries will be derived based on available data in the extension study only. No imputation will be performed for missing values.

12.6.1 Adverse Events

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as AEs that occur the day after Day 180 visit (Day 180 visit date +1) or are pre-existing medical conditions that worsen following Day 180 visit. AEs that occurred after dosing until the Day 180 visit will be summarized in VMDN-003-2 study. AE with a missing start date and a stop date that is either missing or after Day 180 visit (Day 180 visit date + 1) will be considered as a TEAE. For summary purposes, verbatim

terms reported by the study centers will be mapped to MedDRA (v21.0 or later) system organ classes (SOC) and preferred terms by the CRO and approved by the CDRC. It should be noted that only AEs that occurred after the first injection will be collected during the study.

The adverse event listings will be displayed by treatment group. The number of participants experiencing a particular event, the percentage of participants experiencing the event, and the total number of events will be presented. The following summaries will be created:

- TEAE by SOC and preferred term
- TEAE by SOC, preferred term and maximum severity. At the across-SOC and preferred term levels of participant summarization, a participant is classified according to the highest severity if the participant reported one or more events; severity within an SOC is not summarized. AEs with missing severity will be considered severe for this summary.
- TEAE by SOC, preferred term and closest relationship to study treatment (Related/Not Related). At each level of participant summarization, a participant is classified according to the closest relationship if the participant reported one or more events. AEs with a missing relationship will be considered related for this summary; events classified as "possibly," "probably," or "definitely" will be considered "related."
- Serious TEAEs by SOC and preferred term
- TEAEs leading to study discontinuation by SOC and preferred term
- Adverse events of special interest (AESI) by preferred term. An Excel spread sheet/listing will be generated for all TEAEs/TESAEs designated to be AESIs in the EDC database and sent to the Medical Monitors for review. The Medical Monitors will be blinded while reviewing the AESIs and will assign each AESI to one of the three main categories, including the subcategories for angiogenesis and AESIs related to other medical problems. When all AESIs have been assigned to a category by the Medical Monitors, the Excel spreadsheet/listing will be returned to the statistician. The statistician will break the blind and assign the participants with each of these AESIs to the appropriate treatment group and then, will generate appropriate tables and listings.

AESI summary tables will also be presented separately for each level of the randomization stratification factor.

12.6.2 Vital Signs

Vital signs and change from baseline will be summarized descriptively at each visit by treatment group. Additionally the number of subjects with the following vital signs of special interest will be summarized descriptively by treatment group:

- Systolic BP levels ≥180 mmHg
- Diastolic BP levels ≥100 mmHg
- Heart rate ≥180 beats/min
- Heart rate ≤60 beats/min

12.6.3 HbA1c, Serum Chemistry, and Hematology

Central laboratory results will be summarized using International System (SI) of units. The laboratory results will be summarized by treatment and visit. The parameters within each panel are outlined in section 8.3.5.1 of the trial protocol, and lab panels for hematology and serum chemistry will be included.

Shift tables (i.e., low, normal, high at baseline versus low, normal, high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up result at each scheduled follow-up visit. The counts and percentage of participants with each of the 9 possible "shift" outcomes will be calculated by treatment group. Individual laboratory data from scheduled and unscheduled visits will be listed.

Additionally the number of subjects with the following lab parameters of special interest will be summarized descriptively by treatment group:

- Glucose levels: critically high > 320 mg/dL (logic: 2-hour PP level for patients >60 years old is 160 mg/dl)
- Triglyceride levels: critically high ≥ 500 mg/dL
- LDL cholesterol levels: critically high ≥ 189 mg/dL
- Potassium levels: critically high ≥ 5.5 mmol/L
- Hemoglobin levels: critically low ≤ 6 g/dL
  critically high ≥ 20 g/dL
- WBC counts: critically low ≤ 1,500/uL (1.5 x 10^9 / L)
  critically high ≥ 20,000/uL (20.0 x 10^9 / L)
- Platelet count: critically low ≤ 50,000/uL (50.0 x 10^9 / L)
  critically high ≥ 400,000/uL (400.0 x10^9 / L)
- Creatinine level: critically high ≥ 2 mg/dL
- AST: critically high ≥ 10 x ULN (upper limit of normal reference range)
- ALT: critically high ≥ 10 x ULN (upper limit of normal reference range)
- Total bilirubin: critically high ≥ 3 mg/dL

12.6.4 Retinal Fundoscopy

Retinal fundoscopy findings in each eye (presence or absence of proliferative retinopathy, other finding) at screening (Baseline - Study VMDN-003-2) and the Day 365 visit and any changes from the baseline at the follow-up visits will be summarized descriptively by treatment group.

12.6.5 Electrocardiogram (ECG)

The collected ECG values will be listed.

12.6.6 Total Acetaminophen (Rescue Medication) Dose

The number and percentage of participants taking acetaminophen between baseline (Study VMDN-003-2) and up to but not including Day 270, Day 270 and up to but not including Day 365 and baseline (Study VMDN-003-2) and up to but not including Day 365 will be calculated by the treatment group. The number and percentage of participants taking acetaminophen between baseline (Study VMDN-003-2) and Day 270, Day 270 and Day 365 and baseline (Study VMDN-003-2) and Day 365 will be summarized by the treatment group. The mean, standard deviation, minimum, maximum, median, and 1st and 3rd quartiles of days to the first start date of the acetaminophen will be summarized by the treatment group using observed data; participants not taking acetaminophen will not be included in these descriptive statistics. The total dose of acetaminophen of each participant between baseline (Study VMDN-003-2) and Day 270, Day 270 and Day 365 and baseline (Study VMDN-003-2) and Day 365 will be summarized by the treatment group. These analyses will be based on the ITT and PP population.

13.0 References

See Section 11 in trial protocol.

14.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
ADPS	Average Daily Pain Score
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
CDRC	Clinical Data Review Committee
CRO	Clinical Research Organization
CS	clinically significant
CSR	clinical study report
DPN	diabetic peripheral neuropathy
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
HEENT	head, eyes, ears, nose, and throat
HGF	hepatocyte growth factor
IDMC	Independent Data Monitoring Committee
IM	intramuscular
IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent-to-treat
mITT	modified intent-to-treat
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Affairs
MOTH	Mean of the Other Group
MNSI	Michigan Neuropathy Screening Instrument
NCS	not clinically significant
PGIC	Patients' Global Impression of Change
PP	per protocol
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WHODrug	World Health Organization Drug Dictionary