Statistical Analysis Plan

Protocol Title:	**Long-Term, Prospective, Non-Interventional, Safety Extension of a Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects with Painful Diabetic Peripheral Neuropathy**
SAP Version:	VMDN-003b SAP; Version A
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Statistical Analysis Plan

[redacted]

Sponsor	Helixmith Co., Ltd.
Protocol Title:	LONG-TERM, PROSPECTIVE, NON-INTERVENTIONAL, SAFETY EXTENSION OF A PHASE III, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF VM202 IN SUBJECTS WITH PAINFUL DIABETIC NEUROPATHY
Protocol Number:	VMDN-003b
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Document Date:	07-Aug-2019

Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
Biostatistician	Print Name: [redacted] Sign Name:	
Helixmith Co., Ltd. Representative	Print Name: [redacted] Sign Name:	

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Biostatistician	Print Name: [redacted] Sign Name:	
Helixmith Co., Ltd. Representative	Print Name: [redacted] Sign Name: [redacted]	07-Aug-2019

[redacted]

Document History

Not applicable. This is the first SAP (Version A) corresponding to Protocol VMDN-003b/C.

[redacted]

Table of Contents

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Helixmith Co., Ltd. protocol number VMDN-003b (long-term, prospective, non-interventional, safety extension of a phase III, double-blind, randomized, placebo-controlled, multicenter study to assess the safety and efficacy of VM202 in subjects with painful diabetic neuropathy), version C, dated 30-Jul-2019. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Helixmith Co., Ltd.'s study VMDN-003b.

2. Study Objectives and Endpoints

2.1. Study Objectives

To explore the overall safety profile of VM202 over the long-term as well as the durability of pain relief in subjects enrolled in the VMDN-003 trial.

- To evaluate the long-term safety of IM administration of VM202 in subjects with painful diabetic neuropathy (DPN)
- To evaluate the durability of efficacy of IM administration of VM202 in subjects with painful DPN in the lower extremities.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The primary endpoint is the difference in long-term safety – defined as occurrence of adverse events – observed between subjects receiving VM202 versus subjects receiving placebo in the VMDN-003 study.

2.2.2. Efficacy Endpoints

The secondary efficacy endpoints are:

- 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 change in the average 24-hour pain score from the Day 270 to the Day 365 follow-up from the Daily Pain and Sleep Interference Diary
- Patient's Global Impression of Change (PGIC) at the Day 365 follow-up

3. Overall Study Design and Plan

This is a prospective, observational, non-interventional study for long-term follow-up of subjects enrolled in the VMDN-003 study: a phase III, double-blind, randomized, placebo-controlled, multicenter, 9-month study designed to assess the safety and efficacy of VM202 in subjects with painful DPN. Subjects currently enrolled or having recently completed the VMDN-003 trial will be invited to provide informed consent and enroll in this extension study.

After providing consent, subjects will be asked to complete a 7-Day Daily Pain and Sleep Interference diary and one visit 365 ± 14 days after their VMDN-003 Day 0 visit. Diaries will be collected at the visit, along with vital signs, concomitant medications, adverse events, and the PGIC questionnaire.

3.1. Overall Design

3.2. Sample Size and Power

This study was not designed with statistical power in mind and will enroll as many VMDN-003 subjects as possible.

3.3. Study Population

This study will include subjects who are randomized and administered study drug in the VMDN-003 trial, and who are still currently enrolled or within 90 days of having completed the Day 270 visit.

3.4. Treatments Administered

Not applicable.

3.5. Method of Assigning Subjects to Treatment Groups

In the safety outputs, subjects will be analyzed using the treatment they received in the VMDN-003 study. Subjects will be analyzed according to treatment received, regardless of original treatment assigned.

In the efficacy outputs, subjects will be analyzed according to randomized treatment on the VMDN-003 study.

3.6. Blinding and Unblinding

Not applicable.

[redacted]

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

[redacted]

Table 1: Schedule of Events

PROCEDURE	Day 270 Up to 14 D prior to Day 365	12M Day 365 ± 14 D
Informed Consent	✓	
Safety and Efficacy Parameters		
Vital Signs		✓
Concomitant Medications		✓
Daily Pain and Sleep Interference Diary		✓
PGIC		✓
Adverse Events		✓

4. Statistical Analysis and Reporting

This SAP is based on the approved clinical study protocol, version C, dated 30-Jul-2019.

This SAP addresses the safety and efficacy objectives of the study and describes the statistical methods that are to be used for the final analysis of the completed study.

The reader of this SAP is encouraged to also read the clinical protocol, DSMB charter, and all other identified documents, for details on the planned conduct of the study. Operation aspects related to the collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum. Other statistics such as coefficient of variation (%CV), quartiles, confidence intervals (CIs), and number of missing values may be added as appropriate.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data, unless that precision exceeds two decimal places. If the precision does exceed two decimal places, the minimum and maximum will be reported with two decimal places. Measures of location (mean and median) will be reported to one degree of precision more than the observed data and measures of spread (SD) will be reported to two degrees of precision more than the observed data.

Percentages will be presented to one decimal place, unless otherwise specified.

Summary tables will present results by treatment group (i.e., VM202 and Placebo) both within and across the randomization stratification factor (i.e., baseline use of gabapentin and/or pregabalin) values.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *P* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

The independent safety monitoring board (DSMB) will periodically review a limited set of un-blinded tables, listings, and/or datasets, including all reported AEs, as per its responsibilities described in the DSMB Charter. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to study sponsor regarding the safety of VM202. The data analyses for the DSMB meetings will be provided to the DSMB members and other participants of the DSMB meeting. For additional information, please see the DSMB Charter.

5. Analysis Populations

- The **safety population (SAF)** will include all subjects who sign consent for the safety extension study. Subjects in the analysis population will be analyzed according to the treatment received in the VMDN-003 study, regardless of the treatment assigned at randomization. Subjects that sign informed consent but screen fail will still be considered part of the safety population and will have their collected safety data summarized.
- The **intent-to-treat (ITT) population** will include all subjects who sign consent for the safety extension study and who were randomized on the VMDN-003 study. The ITT population will be the primary population used for the efficacy analyses. In such analyses, subjects will be randomized according to their randomized treatment on the VMDN-003 study.
- The **modified intent-to-treat (mITT) population** will include all subjects who sign consent for the safety extension study and complete the Day 365 visit.

6. General Issues for Statistical Analysis

All safety outputs will be based on the safety population and all listings will be presented by actual treatment received. All efficacy outputs will be presented by randomized treatment on the VMDN-003 study. Unless otherwise stated, table outputs will contain a placebo column and a VM202 column. Table and figure outputs based on the baseline use of gabapentin/pregabalin stratification group will also be provided.

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

In general, the last observation recorded prior to the first dose of study drug in the VMDN-003 study will be used as the baseline observation for all calculations of change from baseline.

The baseline average value of the Daily Pain and Sleep Interference Diary is based on the assessments recorded prior to the screening visit.

6.1.2. Adjustments for Covariates

Not applicable.

6.1.3. Multiple Comparisons

Not applicable.

6.1.4. Handling of Dropouts or Missing Data

The Daily Pain and Sleep Interference Diary is to be completed within 14 days of the 12-month visit. The average 24-hour pain score for a visit will be considered as missing if fewer than 5 of 7 days of Daily Pain and Sleep Interference Diary entries are provided. Sensitivity analyses for the mean change in the average 24-hour pain score will include the following imputation approaches for missing values at 3, 6, 9, or 12 months. It is important to note that over-stratification may result when the total list of pre-specified factors is considered. Under this scenario, the least represented factor will be removed and the imputation will be re-run. This process will be followed until the imputed dataset is complete.

- Multiple imputation: Each missing pain score will be imputed ten times to generate ten imputed complete data sets based on the Markov Chain Monte Carlo (MCMC) method with baseline pain score, 3-month and 6-month pain score, and categorical covariates of baseline use of gabapentin and/or pregabalin, baseline HbA1c, gender, and age. The imputed score will be rounded to the first decimal point. The results of the ten tests from the continuous Repeated Measures Model using these data will be combined.

- Mean of the other group (MOTH)[1] as follows:

    1. For a subject with a missing 3-month or 6-month average 24-hour pain score, identify the subject's following baseline characteristics:
        - Study treatment group
        - Baseline use of gabapentin and/or pregabalin.
        - Baseline average 24-hour pain score (< median or ≥ median)
        - HbA1c (< median or ≥ median)
        - Gender (male or female)
        - Age (<65 years and ≥ 65 years).

        The median subgroups will be based on the median of ITT subjects in the VMDN-003 study such that VMDN-003b subjects remain in the same subgroups across studies.

    2. The missing 3-month, 6-month, 9-month, or 12-month average 24-hour pain score will be imputed by using the mean average 24-hour pain score obtained at the same time point of those subjects in the other treatment group who match the subject's baseline characteristics. For example, for the missing pain scores of the VM202 subjects, the mean pain scores of the placebo subjects within the same

covariate groups will be used to impute the missing pain scores.

3. The baseline characteristics will be re-examined for appropriateness and may be re-categorized (due to small sample size) before unblinding the study.

4. The imputed score will be rounded to the first decimal point. The imputed scores will be included in the continuous Repeated Measures Model analysis.

Sensitivity analyses for the percentage of subjects with a reduction in the average 24-hour pain score of at least 50% will include the following imputation approaches for missing values at 3 or 6 months.

- Imputed average 24-hour pain scores at 3, 6, 9, and 12 months from the multiply-imputed pain score datasets described above. The results of the ten tests from the categorical Repeated Measures Model will be combined.

- Missing pain score will be imputed from the MOTH-imputed dataset described above and the categorical Repeated Measures Model will be used for the data analyses.

- Multiple imputation for the missing responder outcomes, 1 (Yes) or 0 (No), by fully conditional specification logistic regression method: each missing responder outcome will be imputed ten times to generate ten imputed complete data sets using a logistic regression model with baseline use of gabapentin and/or pregabalin, and categorical baseline HbA1c, gender, and age as covariates. The results of the ten tests from the categorical Repeated Measures Model will be combined.

Steps to generate the MMRM analysis are presented below; different options will be used depending on the exact model being run. First the proc mixed code in section 8.1 will be run within each imputation dataset. Least square means, differences between treatments, and p-values will be combined using the following MIANALYZE code.

```
Proc Mianalyze data=[LS Mean/Difference/p-value dataset from proc mixed] ;
        by  avisitn trtn;
        modeleffects estimate;
        stderr;
Run;
```

6.1.5. Analysis Visit Windows

Analyses of all variables for this study will be done by nominal timepoint. No visit windowing will be applied.

6.1.6. Pooling of Sites

Not applicable.

6.1.7. Derived Variables

- The Average 24-hour Pain Score will be derived by taking the average of the daily pain measurements recorded by a subject prior to a visit. The score will only be derived if a subject completes at least 5 of 7 days of diary entries within the 14 days prior to the visit.

- The Average 24-hour Sleep Interference Score will be derived by taking the average of the daily sleep interference measurements recorded by a subject prior to a visit. The score will only be derived if a subject completes at least 5 of 7 days of diary entries within the 14 days prior to the visit.

- Change from baseline = value at current time point – value at baseline.

- Treatment-Emergent Adverse Event (TEAE) = All adverse events collected in the VMDN-003b clinical database with a start date after the last visit on the VMDN-003 study will be considered treatment-emergent.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Adverse events will be coded using the MedDRA version 21.0 thesaurus.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) (March 2018).

A treatment related AE is any AE with a relationship to the study drug of possibly, probably, or definitely.

The date and time of the first dose of study drug will be the date and time of the first dose of study drug in the VMDN-003 study.

For partial medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, or medication is ongoing, then impute as the month and day of the first dose date. If this produces a date after the medication end date, assign 01 January.
    - Otherwise if the year does not match the year of the first dose date, assign 01 January.
- If the year and month are known, but the day is unknown, then:

- If the month and year match the month and year of the first dose date, then impute as the day of the first dose date. If this produces a date after the medication end date, assign 01.
- Otherwise, if the month and year do not match the month and year of the first dose date, assign 01.

For partial medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known but the month or month and day is unknown, then:
  - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
  - Otherwise, assign 31 December.
- If the year and month are known, but day is unknown, then:
  - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
  - Otherwise, assign the last day of the month.

For partial AE start dates:

- When the year is known, but the month and day is unknown, then:
  - If the year matches the year of first dose date and the end date (if present) is after first dose date, or AE is ongoing, then impute as the month and day of the first dose date.
  - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- When the year and day are present and the month is missing:
  - If the year of AE onset = the year of initiation of the treatment, then the month will be set to the month of initiation of the treatment.
  - If the year of AE onset < the year of initiation of the treatment, then the month will be set to December.
- If the year and month are known, but the day is unknown, then:
  - If the year of AE onset = the year of initiation of the treatment and:
    - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.

- if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.

- If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month.
- If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of month.

If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.

If an AE has a missing severity, it will be considered severe. If an AE has a missing relationship to study medication, injection procedure, or underlying disease, it will be considered related.

Baseline gabapentin/pregabalin use will be set based on the baseline gabapentin/pregabalin use from the VMDN-003 study.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

The number of subjects in each treatment group will be summarized. The number and percentage of subjects who complete the study and who screen fail will be summarized by treatment group. The reasons for screen failure will also be summarized. The number and percentage of subjects in the safety population will be summarized by treatment group.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Demographic variables collected in the VMDN-003 study such as age, gender, ethnicity, and race, and baseline characteristics such as height, weight, body mass index (BMI), baseline gabapentin/pregabalin use, and diabetes type will be summarized by treatment group and by treatment group within baseline gabapentin/pregabalin use. The gabapentin/pregabalin summary will be excluded from the subgroup tables.

Categorical variables, such as gender, ethnicity, race, baseline pregabalin/gabapentin use, and diabetes type will be summarized using frequencies and percentages. Continuous variables such as age, height, weight, and BMI will be summarized using mean, standard deviation (SD), median, minimum, and maximum.

8. Efficacy Analysis

8.1. Daily Pain Diary Analysis

Descriptive summaries of observed values, changes from baseline, and changes from Day 270

will be calculated for average 24-hour pain score and average 24-hour sleep interference score at Baseline and Day 365. Observed values and changes from baseline will also be summarized at Day 90, Day 180 and Day 270. Diary results will be listed.

Since higher scores indicate worse pain, a negative value of change means an improvement, and a positive value of change means deterioration. Subjects with a percent change from baseline of ≤ -50% (i.e., reduction of at least 50%) will be classified as a responder. The means of the change in the average 24-hour pain score and the percentage of subjects with a change in the average 24-hour pain score of ≤ -50% will be compared between the two treatment groups (VM202 and placebo).

The mean change in pain score from baseline between the treatment groups will be analyzed using a linear mixed-effects model for repeated measures (hereinafter, the continuous Repeated Measures Model). The model will include treatment, visit (3-month, 6-month, 9-month, and 12-month visits), treatment-by-visit interaction, and baseline use of gabapentin and/or pregabalin as the main fixed effects, and baseline average 24-hour pain score as a covariate using an unstructured variance-covariance matrix. The point estimate for the last-squares mean of the treatment difference (VM202 – Placebo) at each visit and the corresponding 95% confidence interval and p-value will be summarized.

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

```
proc mixed data=work order=internal method = quad(Qpoint = x);
  class usubjid trtp avisitn basemed;
  model chg = trtp avisitn trtp*avisitn base basemed / 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 (Primary model will include the 3, 6, 9 and 12 month visits)
CHG: change in average pain score from baseline
BASE: baseline average pain score
BASEMED: a Y/N variable indicating if the subject took gabapentin/pregabalin at baseline.
Qpoint: Number of quadrature nodes to clarify the dimensionality

To derive the estimates comparing the 2 treatment arms for the change from day 270 to day 365, a contrast statement will be used.

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.

The model will be run using the ITT population as well as the mITT population.

Similarly, 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 subjects with a percent change in average 24-hour pain score of ≤ -50% (responder rate) between the two study treatment groups. The model will include treatment, visit, treatment-by-visit interaction, baseline use of gabapentin and/or pregabalin, and baseline average 24-hour pain scores as covariates with an unstructured variance-covariance matrix. The point estimates for the least-squares mean of the treatment difference (VM202 – Placebo) and the corresponding 95% confidence interval and p-value will be summarized.

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

```
PROC GLIMMIX DATA=work method=quad;
  class usubjid trtp avisitn basemed;
  MODEL critvar(event='Y') = trtp base avisitn basemed 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 (Primary model will include the 3, 6, 9 and 12 month visits)
CHG: change in average pain score from baseline
BASE: baseline average pain score
BASEMED: a Y/N variable indicating if the subject took gabapentin/pregabalin at baseline.
CRITVAR: a Y/N variable indicating if the subject had at least a 50% reduction in baseline pain score from baseline at that visit

To derive the estimates comparing the 2 treatment arms for the change from day 270 to day 365, a contrast statement will be used.

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.

The model will also be run comparing responder rates of 20%, 30%, 40%, 60%, and 70% reductions from baseline. Frequencies and percentages of subjects achieving those response levels within each treatment group will also be provided.

8.2. Daily Pain Diary Subgroup Analysis

The daily pain diary data will be analyzed within the below subgroups:

- Baseline HbA1c (< and ≥ median)
- Gender (male and female)
- Age (<65 years and ≥ 65 years).

For baseline HbA1c, the median will be the VMDN-003 median and subjects will be summarized within the same group as that study. For each subgroup of the ITT population, the

change in average 24-hour pain score will be summarized by treatment group and visit using descriptive statistics including mean, median, standard deviation, minimum, and maximum. The count and percentage of subjects with a change in the average 24-hour pain score will also be summarized by treatment group and visit for each subgroup of the ITT population. Both types of descriptive summaries are also provided for the subgroups of baseline use of gabapentin and/or pregabalin, study center, and VMDN-003 protocol version the subject enrolled under.

Except for the subgroups of study center and protocol version, the Repeated Measures Model analyses described in Section 8.1 will be performed within each subgroup.

A sensitivity analysis excluding subjects that took prohibited medications on more than 14 consecutive days will be presented also. Both types of descriptive summary statistics and efficacy models will be run with these subjects excluded.

Additionally, the possible treatment-by-subgroup interaction will be tested for each subgroup variable as follows:

- A subgroup variable will be included in the primary analysis models described in Section 8.1 along with its interaction with the treatment effect. If the p-value of the interaction term is ≥ 0.05, the treatment-by-subgroup interaction is not significant.
- If the interaction effect is statistically significant (i.e., p-value < 0.05), then the Gail and Simon test will be used to test for the qualitative interaction at a significance level of 0.05 and provided as an aid for interpretation.

The Repeated Measures Model analyses described in Section 8.1 already accounts for the subgroups of baseline use of gabapentin and/or pregabalin (i.e., Yes and No groups). For evaluating the interaction between treatment and baseline use of gabapentin and/or pregabalin, the interaction effect will be added to the primary analysis models. If the interaction effect is significant, then the Gail and Simon test will be used to test for the qualitative interaction at a significance level of 0.05.

8.3. Daily Sleep Interference Diary Analysis

The daily sleep interference diary data will be analyzed using the continuous Repeated Measures Model described in section 8.1. A descriptive summary will also be presented.

This data will also be listed.

8.4. Patient's Global Impression of Change (PGIC)

Patient's Global Impression of Change (PGIC) results will be summarized at Day 365. The change will be assessed relative to the VMDN-003 baseline. The results will be summarized by the following three categories:

- Very Much Improved or Much Improved
- Minimally Improved/Worsened or No Change

- Much Worse or Very Much Worse

PGIC will be analyzed by Cochran-Mantel-Haenszel (CMH) test to account for the stratification variable and row means scores differ statistic (row variable: treatment group, column variable: 3-category data of PGIC) will be used.

PGIC results will be listed.

Efficacy data will be summarized by treatment group and by treatment group within baseline gabapentin and pregabalin use.

9. Safety and Tolerability Analysis

Safety assessments will be collected at the Day 365 visit and include adverse events, concomitant medications, and vital signs.

All safety analyses will be performed on the safety population by actual treatment received in the VMDN-003 study.

9.1. Adverse Events

Adverse events will be coded using the MedDRA coding thesaurus (version 21.0). All AEs recorded in the clinical database starting after the last visit on the VMDN-003 study will be considered a treatment-emergent adverse event (TEAE). All AE summary tables will include the number and percentage of subjects with an AE within a category, system organ class (SOC), and preferred term.

An overall summary of the number and percentage of subjects with TEAEs will be provided by treatment group. Frequencies and percentages of the following will be included: subjects with any TEAE, subjects with a related TEAE, subjects with any TEAE leading to discontinuation, subjects with any TEAE leading to death, and subjects with any serious treatment-emergent AE (SAE).

The incidence of TEAEs will be summarized with frequencies and percentages by the following:

- SOC and PT
- SOC and PT by maximum severity
- SOC and PT by relationship to study medication
- SOC and PT by relationship to injection procedure.
- SAEs by SOC and PT
- AEs of special interest by SOC and PT

There are 4 types of AEs of special interest (AESI):

- Ophthalmological events that could potentially suggest causality related to HGF and its angiogenic potential
- Acute cardiac events

- Foot ulcers
- AEs related to pregabalin or gabapentin and their occurrence rates with in conjunction with VM202

Adverse event data will be summarized by treatment group and by treatment group within baseline gabapentin and pregabalin use.

All adverse events will be presented in a listing.

9.1.1. Adverse Events Leading to Withdrawal

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

9.2. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, weight, heart rate, respiration rate, temperature, and body mass index (BMI).

The height collected in the VMDN-003 study will be used to derive the BMI at the Day 365 visit based on the weight collected at the Day 365 visit.

Vital signs data will be summarized by treatment group and by treatment group within baseline gabapentin and pregabalin use.

All vital signs data will be listed.

9.3. Concomitant Medication

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) (Version March 01, 2018 or later) thesaurus.

Frequencies and percentages of subjects taking concomitant medications will be presented by anatomic therapeutic class (ATC) level 3 and preferred base name. Concomitant medication data will be summarized by treatment group and by treatment group within baseline gabapentin and pregabalin use.

A medication will be considered concomitant if the subject started taking it after the last visit on the VMDN-003 study. Subjects will be counted once for each ATC and PT.

All medications will be listed.

10. Changes from Planned Analysis

Not applicable.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Not applicable.

12. References

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. FDA Guidance for Industry (1998). E9 Statistical Principles for Clinical Trials (ICH). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Available at: www.fda.gov/media/71336/download. Accessed July 15, 2019.

13. Tables, Listings, and Figures

This section presents the shells for the planned Tables, Listings, and Figures (TLFs) to be programmed. This section provides guidance on the programming specifications (shells) for the planned outputs. After the programming begins, it may be necessary to modify table titles or footnotes or the order of rows or columns. Minor, cosmetic changes such as these will not require a modification to the final SAP.

General Reporting Conventions

- All tables and data listings will be developed in landscape orientation.
- Header and footer rows for tables will repeat on all pages of the table.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing.
- A blank row will be included between subjects in the listings.
- In the listings, if text will be repeated on multiple rows for a subject, it will only be displayed in the first row. If the repeated rows cover multiple pages, the text will also be displayed in the first row of each new page.
- Programming notes may be inserted into the shells, these notes will not appear in the final output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxxx), where appropriate.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however, counts and percentages of missing values may be needed.
- All population summaries for continuous variables will include: N, mean, SD, median, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, median, quartiles, 95% CIs, and coefficient of variation [CV] or % CV) may be used as appropriate. The precision of the maximum and minimum will match the maximum precision in the data. The mean and median will have one additional decimal place. The SD will have two additional decimal places.
- All percentages are rounded and reported to a single decimal point (xx.x %)

13.1. Planned Table Descriptions

The following are planned summary tables for protocol number VMDN-003b. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

The following standard layout will be applied to all Tables, Listings, and Figures in support of this study. Note that programming notes may be added if appropriate after each TLF shell.

Figure 1: Standardized Layout

Helixmith Co., Ltd. Page xx of xx

Protocol: VMDN-003b <version>

<Table, Listing, Figure> xx.x.x

<Title of Table Listing or Figure>

<Study Population and if applicable subgroup Description>

Body of Table, Listing or Figure

Note: *<Note: if directly applicable>*

Abbreviation(s): *<if applicable>*

Footnote 1 *<if applicable>*

Footnote 2 *<if applicable>*

Footnote n *<if applicable>*

14.2. Planned Table Shells

See Figure 2 below.

Figure 2. Planned Table Shells

Table 14.1.1.1
Subject Disposition
All Subjects

Status	Placebo	VM202	Overall
Screened			XX
Completed Day 365 Visit	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Screen Failed	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Reason for Discontinuation:			
Adverse Event	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Lost to Follow-up	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Withdrew Consent	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Did Not Meet Elig bility Criteria	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Safety Population [1]	XX	XX	XX
Intent-to-treat Population [2]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Modified intent-to-treat Population [3]	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: Percentages are based on the number of subjects in the safety population.
[1] The safety population consists of all subjects who sign informed consent for the VMDN-003b study.
[2] The intent-to-treat population consists of all subjects who sign informed consent and who were randomized in the VMDN-003 study.
[3] The modified intent-to-treat population consists of all subjects who sign informed consent and complete the day 365 visit.
SOURCE: Listing 16.2.1.1

Figure 2 (continued)

Table 14.1.1.2
Ineligibility Summary of Screen Failures
Screen Failures

Inclusion/Exclusion Criteria	Overall (N=XX) n (%)
Number of subjects failing any eligibility criteria	XX (XX.X%)
Number of Subjects Failing any Inclusion Criteria [1]	XX (XX.X%)
Inclusion Criteria 1	XX (XX.X%)
Inclusion Criteria 2	XX (XX.X%)
Inclusion Criteria 3	XX (XX.X%)
Number of Subjects Satisfying any Exclusion Criteria [1]	XX (XX.X%)
Exclusion Criteria 1	XX (XX.X%)
Exclusion Criteria 2	XX (XX.X%)

Note: The denominator for percentage corresponds to the N in each column. N is the number of screen failures.
[1] Subjects may be counted in more than one category.
SOURCE: Listing 16.2.1.2.1

Figure 2 (continued)

Table 14.1.2.1
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Placebo (N=XX)	VM202 (N=XX)	Overall (N=XX)
Age (years)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Less than 65 years	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
65 years or more	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Gender			
Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Ethnicity			
Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Hispanic or Latino	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Race			
White	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Black or African American	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Asian	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Native Hawaiian or Other Pacific Islander	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
American Indian or Alaska Native	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Unknown	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the safety population. Subjects are summarized by treatment received in the VMDN-003 study. Age is calculated from the date of birth to the date of informed consent in the VMDN-003 study. Baseline information is relative to baseline in the VMDN-003 study.

Table 14.1.2.1 (Cont.)
Demographics and Baseline Characteristics
Safety Population

Variable Statistic or Category	Placebo (N=XX)	VM202 (N=XX)	Overall (N=XX)
Height (cm)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Weight (kg)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX
BMI (kg/m^2)			
n	XX	XX	XX
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX
Gabapentin and/or Pregabalin Use			
No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Diabetes Type			
Type I	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Type II	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Continue for baseline HbA1c

Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the safety population. Subjects are summarized by treatment received in the VMDN-003 study. Age is calculated from the date of birth to the date of informed consent in the VMDN-003 study. Baseline information is relative to baseline in the VMDN-003 study.

Figure 2 (continued)

Table 14.1.2.2
Demographics and Baseline Characteristics by Gabapentin and or Pregabalin use at Baseline
Safety Population

Same shell as 14.1.6.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.2.1.1.1
Summary of Change from Baseline in Average 24-hour Pain Score
ITT Population

Study Visit		Placebo (N=XX)			VM202 (N=XX)		
Statistic	Observed	CFB	%CFB	Observed	CFB	%CFB
Baseline [1]						
n	XX			XX		
Mean (SD)	XX.X (XX.XX)			XX.X (XX.XX)		
Median	XX.X			XX.X		
Q1, Q3	XX.X, XX.X			XX.X, XX.X		
Min, Max	XX, XX			XX, XX		
Day 90						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Day 180						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

Continue for 'Day 270' and Day 365 visit.

Abbreviations: CFB = change from baseline.
Note: A negative value of change means an improvement, and a positive value of change means deterioration. N is the number of subjects in the ITT population. Subjects are summarized by randomized treatment.
[1] The baseline value is the average 24-hour pain score from the diary collected prior to the Day 0 visit.
SOURCE: Listing 16.2.6.1

Figure 2 (continued)

Table 14.2.1.1.2
Summary of Change from Baseline Average 24-hour Pain Score by Gabapentin and/or Pregabalin use at Baseline
ITT Population

Same shell as Table 14.2.1.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.2.1.1.3
Summary of Change from Day 270 Average 24-hour Pain Score
ITT Population

Same shell as Table 14.2.1.1, only include Day 270 and Day 365 timepoints. Update headers from 'CFB' to 'CFD270' and '%CFD270'. Drop the [1] footnote. Update abbreviation footnote to say CFD270 = change from day 270 visit.

Table 14.2.1.1.4
Summary of Change from Day 270 Average 24-hour Pain Score by Gabapentin and/or Pregabalin use at Baseline
ITT Population

Same shell as Table 14.2.1.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.2.1.1.5
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Study Visit Statistic [1]	Placebo (N=XX)	VM202 (N=XX)
Day 90		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Day 180		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX

Continue for Day 270 and Day 365

Abbreviation: CI = confidence interval; LS = least squares; SE = standard error.
Note: A negative value of change means an improvement, and a positive value of change means deterioration. Subjects are summarized by randomized treatment.
The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
[1] Estimates for LS means and accompanying 95% CIs and P values are from a linear mixed-effects model for repeated measures (MMRM) with treatment, visit (3-month, 6-month, 9-month, and 12-month visit), treatment-by-visit interaction, and baseline use of gabapentin and/or pregabalin as the main fixed effects, and baseline average 24-hour pain score as a covariate. An unstructured covariance matrix was used to model the within subject correlation.
[2] P value for testing mean change from baseline is zero.
[3] P value for testing difference (VM202 minus Placebo) in mean change from baseline from is zero.
SOURCE: Listing 16.2.6.1
Programming note: *Check convergence per Section 8.1 of the SAP. Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options may be substituted if convergence problems arise. Update footnote accordingly.*

Figure 2 (continued)

Table 14.2.1.2.1
Summary of Change from Baseline in Average 24-hour Pain Score
Multiple Imputation
ITT Population

Same shell as 14.2.1.1.1, add the following to footnote "Each missing pain score was imputed ten times to generate ten imputed complete data sets based on the Markov Chain Monte Carlo (MCMC) method with categorical covariates of baseline use of gabapentin/pregabalin, baseline hbA1c, gender, race, and age."

Table 14.2.1.2.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM using Multiple Imputation
ITT Population

Same shell as 14.2.1.1.5, add the following to footnote [1] "Each missing pain score was imputed ten times to generate ten imputed complete data sets based on the Markov Chain Monte Carlo (MCMC) method with categorical covariates of baseline use of gabapentin/pregabalin, baseline hbA1c, gender, race, and age"

Table 14.2.1.3.1
Summary of Change from Baseline in Average 24-hour Pain Score
MOTH Imputation
ITT Population

Same shell as 14.2.1.1.1, add the following to footnote "Each missing 3-month or 6-month average 24-hour pain score was imputed using the mean average 24-hour pain score obtained at the same time point of those subjects in the other treatment group who match the subject's baseline characteristics. Characteristics considered are baseline use of gabapentin/pregabalin, baseline average 24 hour pain score (less than median; more than or equal to median), HbA1c (less than median; more than or equal to median), gender, race (white; non-white), and age (less than median; more than or equal to median)."

Table 14.2.1.3.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM using MOTH Imputation
ITT Population

Same shell as 14.2.1.1.5, add the following to footnote [1] "Each missing 3-month or 6-month average 24-hour pain score was imputed using the mean average 24-hour pain score obtained at the same time point of those subjects in the other treatment group who match the subject's baseline characteristics. Characteristics considered are baseline use of gabapentin/pregabalin, baseline average 24 hour pain score (less than median; more than or equal to median), HbA1c (less than median; more than or equal to median), gender, race (white; non-white), and age (less than median; more than or equal to median)." Add the following Abbreviation: MOTH = Mean of the Other Group.

Table 14.2.1.4.1
Summary of Change from Baseline in Average 24-hour Pain Score
mITT Population

Same shell as 14.2.1.1.1

Table 14.2.1.4.2

Figure 2 (continued)

Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM using Observed Values
mITT Population

Same shell as 14.2.1.1.5

Figure 2 (continued)

Table 14.2.1.5.1
Summary of Change from Baseline in Average 24-hour Pain Score
ITT Population Excluding Scores Influenced by Prohibited Concomitant Medications

Same shell as 14.2.1.1.1

Table 14.2.1.5.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM
ITT Population Excluding Scores Influenced by Prohibited Concomitant Medications

Same shell as 14.2.1.1.5

Table 14.2.1.6.1
Summary of Change from Baseline in Average 24-hour Pain Score
mITT Population Excluding Scores Influenced by Prohibited Concomitant Medications

Same shell as 14.2.1.1.1

Table 14.2.1.6.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM
mITT Population Excluding Scores Influenced by Prohibited Concomitant Medications

Same shell as 14.2.1.1.5

Table 14.2.1.7.1
Summary of Change from Baseline in Average 24-hour Pain Score by Hb1Ac
ITT Population

Same shell as 14.2.1.1.1, add a row at the top of table reading "Group: HbA1c < Median". Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: < Median and >= Median. Populate Median with actual value.

Table 14.2.1.7.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and HbA1c
Tabulation of Fitted Summary Statistics from MMRM
ITT Population
Same shell as 14.2.1.1.5, add a row at the top of table reading "Group: HbA1c < Median". Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: < Median and >= Median. Populate Median with actual value.

Table 14.2.1.8.3
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with HbA1c-by-Treatment Interaction
ITT Population

Study Visit Statistic [1]	Placebo (N=XX)	VM202 (N=XX)
Day 90		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Day 180		
n	XX	XX
LS Mean Change from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Overall		
P value for HbA1c-by-Treatment Interaction		X.XXXX
P value for Gail and Simon Test [4]		X.XXXX

Abbreviation: CI = confidence interval; LS = least squares; SE = standard error.
Note: A negative value of change means an improvement, and a positive value of change means deterioration. Subjects are summarized by randomized treatment.
The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
[1] Estimates for LS means (change from baseline and difference from placebo [ie, change from baseline for VM202 minus change from baseline for Placebo]) and accompanying 95% CIs and P values are from a linear mixed-effects model for repeated measures (MMRM) with treatment, visit (3-month, 6-month, 9-month, and 12-month visit), treatment-by-visit interaction, and baseline use of gabapentin and/or pregabalin as the main fixed effects, baseline average 24-hour pain score, HbA1c, and HbA1C-by-Treatment interaction as covariates. An unstructured covariance matrix was used to model the within subject correlation.
[2] P value for testing mean change from baseline is zero.
[3] P value for testing difference (VM202 minus Placebo) in mean change from baseline is zero.
[4] P value for Gail and Simon test of no qualitative interaction

Figure 2 (continued)

SOURCE: Listing 16.2.6.1

Programming note: *Check convergence per Section 8.4.2 of the SAP. Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options may be substituted if convergence problems arise. Update footnote accordingly. Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: <Median and >= Median. Populate Median with actual value. Add HbA1c and HbA1c-by-Treatment interaction as covariates in the model and in footnote [1]. Add 16.2.8.1 to SOURCE. Only add a line for the Gail and Simon p-value if the interaction term is significant. Add/remove footnote [4] as appropriate.*

Table 14.2.1.8.4
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with HbA1c Covariate
ITT Population
Same shell as 14.2.1.1.5. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup. Add HbA1c <Median and >= Median subgroups as a covariate in the model and in footnote [1].

Table 14.2.1.9.1
Summary of Change from Baseline in Average 24-hour Pain Score by Gender
ITT Population

Same shell as 14.2.1.1.1, add a row at the top of table reading "Group: Male". Once all records from group are summarized, update row text for the Female group and start table on a new page. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup. Add 16.2.4 to SOURCE.

Table 14.2.1.9.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and Gender
Tabulation of Fitted Summary Statistics from MMRM
ITT Population
Same shell as 14.2.1.1.5, add a row at the top of table reading "Group: Male". Once all records from group are summarized, update row text for the Female group and start table on a new page. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup. Add 16.2.4 to SOURCE.

Table 14.2.1.9.3
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with Gender-by-Treatment Interaction
ITT Population
Same shell as 14.2.1.10.3. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup. Add Gender and Gender-by-Treatment interaction as covariates in the model and in footnote [1]. Only add a line for the Gail and Simon p-value if the interaction term is significant. Add/remove footnote [4] as appropriate.

Table 14.2.1.9.4
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with Gender Covariate
ITT Population
Same shell as 14.2.1.10.2. Add Gender as a covariate in the model and in footnote [1].

Table 14.2.1.10.1
Summary of Change from Baseline in Average 24-hour Pain Score by Age Category

Figure 2 (continued)

ITT Population

Same shell as 14.2.1.1.1, add a row at the top of table reading "Group: Age < 65". Once all records from group are summarized, update row text for Age ≥65 and start table on a new page. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup.

Table 14.2.1.10.2
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and Age Category
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Same shell as 14.2.1.1.2, add a row at the top of table reading "Group: Age < 65". Once all records from group are summarized, update row text for Age ≥65 and start table on a new page. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup.

Table 14.2.1.10.3
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with Age Category-by-Treatment Interaction
ITT Population

Same shell as 14.2.1.10.2. Per Section 6.5 of SAP, If there are <10% of subjects within each subgroup, do not perform the analysis for that subgroup. Add Age Category and Age Category-by-Treatment interaction as covariates in the model and in footnote [1]. Only add a line for the Gail and Simon p-value if the interaction term is significant. Add/remove footnote [4] as appropriate.

Table 14.2.1.10.4
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM with Age Category Covariate
ITT Population

Same shell as 14.2.1.10.2. Add Age (less than 65 years; more than or equal to 65 years) as a covariate in the model and in footnote [1].

Table 14.2.1.11
Summary of Change from Baseline in Average 24-hour Pain Score by Baseline Use of Gabapentin and/or Pregabalin
ITT Population

Same shell as 14.2.1.1.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text for No Gabapentin and/or Pregabalin Use and start table on a new page.

Table 14.2.1.12
Summary of Change from Baseline in Average 24-hour Pain Score by Study Center
ITT Population

Same shell as 14.2.1.1.1, add a row at the top of table reading "Group: Study Center" Once all records from group are summarized, update row text for the next study center and start table on a new page. Add 16.2.1.1 to SOURCE.

Table 14.2.1.13
Summary of Change from Baseline in Average 24-hour Pain Score by VMDN-003 Protocol Version
ITT Population

Same shell as 14.2.1.1.1.1, add a row at the top of table reading "Group: Protocol Version C". Once all records from group are summarized, update row text for

Figure 2 (continued)

the next group and start table on a new page. Groups will be: C, D, and E. Add 16.2.1.1 to SOURCE.

Table 14.2.1.14
Mean Change from Baseline in Average 24-hour Pain Score by Study Visit and Treatment Adjusted for Covariates
Tabulation of Fitted Summary Statistics from MMRM
ITT Population
Same shell as 14.2.1.1.1.2. Add all 4 covariates (HbA1c, Gender, and Age (with 65 years as the cutoff) as covariates in the model and in footnote [1]. Add 16.2.4

Figure 2 (continued)

Table 14.2.2.1
Summary of Subjects with at least a 50% Reduction from Baseline in the Average 24-hour Pain Score
ITT Population

Study Visit Statistic	Placebo (N=XX)	VM202 (N=XX)
Day 90		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 180		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 270		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 365		
Number of Responders	XX (XX.X%)	XX (XX.X%)

Note: Subjects with a percent change of ≤ -50% from baseline (i.e., reduction of at least 50%) will be classified as a responder at the respective visit. The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
SOURCE: Listing 16.2.6.1

Figure 2 (continued)

Table 14.2.2.2
Analysis of Responder Rate of at least a 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
ITT Population

Study Visit Statistic [1]	Placebo (N=XX)	VM202 (N=XX)
Day 90		
n	XX	XX
LS Mean Responder Rate (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Responder Rate)	(XX.X, XX.X)	(XX.X, XX.X)
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [2]		X.XXXX
Day 180		
n	XX	XX
LS Mean Responder Rate (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Responder Rate)	(XX.X, XX.X)	(XX.X, XX.X)
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [2]		X.XXXX

Continue for Day 270 and Day 365

Abbreviation: CI = confidence interval; LS = least squares; SE = standard error.
Note: Subjects are summarized by randomized treatment. Subjects with a percent change of ≤ -50% from baseline (i.e., reduction of at least 50%) will be classified as a responder at the respective visit. The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
[1] Estimates for LS means and accompanying 95% CIs and P values are from a generalized linear mixed-effects model for repeated measures (GLMM) based on a logit link function. The model included treatment, visit, treatment-by-visit interaction, baseline use of gabapentin and/or pregabalin, and baseline average 24-hour pain scores as covariates. An unstructured covariance matrix was used to model the within subject correlation.
[2] P value for testing for difference in responder rate between treatments at the specified visit.
SOURCE: Listing 16.2.6.1
Programming note: *Check convergence per Section 8.1 of the SAP. Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options may be substituted if convergence problems arise. Update footnotes accordingly.*

Figure 2 (continued)

Table 14.2.2.3
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures using Multiple Imputation
ITT Population

Same shell as 14.2.1.2.2, add the following to footnote [1] "Each missing pain score was imputed ten times to generate ten imputed complete data sets based on the Markov Chain Monte Carlo (MCMC) method with categorical covariates of baseline use of gabapentin/pregabalin, baseline hbA1c, gender, race, and age."

Table 14.2.2.4
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures using MOTH Imputation
ITT Population

Same shell as 14.2.1.2.2, add the following to footnote [1] "Each missing 3-month or 6-month average 24-hour pain score was imputed using the mean average 24-hour pain score obtained at the same time point of those subjects in the other treatment group who match the subject's baseline characteristics. Characteristics considered are baseline use of gabapentin/pregabalin, baseline average 24 hour pain score (less than median; more than or equal to median), HbA1c (less than median; more than or equal to median), gender, race (white; non-white), and age (less than 65 years; more than or equal to 65 years)." ."

Table 14.2.2.5
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures using Fully Conditional Logistic Regression Imputation
ITT Population

Same shell as 14.2.1.2.2, add the following to footnote [1] "Each missing responder outcome will be imputed ten times to generate ten imputed complete data sets using a logistic regression model with baseline use of gabapentin and/or pregabalin, and categorical baseline HbA1c, gender, race, and age as covariates."

Table 14.2.2.6
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
ITT Population Excluding Scores Influenced by Prohibited Concomitant Medications

Same shell as 14.2.1.2.2

Table 14.2.2.7.1
Summary of Subjects with at least 50% Reduction from Baseline in the Average 24-hour Pain Score by Hb1Ac
ITT Population

Same shell as 14.2.2.1, add a row at the top of table reading "Group: HbA1c < Median". Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: < Median and >= Median. Populate Median with actual value.

Figure 2 (continued)

Table 14.2.2.7.2
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and HbA1c
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
ITT Population

Same shell as 14.2.2.2, add a row at the top of table reading "Group: HbA1c < Median". Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: < Median and >= Median. Populate Median with actual value.

Figure 2 (continued)

Table 14.2.2.7.3
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with HbA1c-by-Treatment Interaction
ITT Population

Study Visit Statistic [1]	Placebo (N=XX)	VM202 (N=XX)
Day 90		
n	XX	XX
LS Mean Change in Responder Rate from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change in Responder Rate from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change in Responder Rate from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Day 180		
n	XX	XX
LS Mean Change in Responder Rate from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change in Responder Rate from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
P value for LS Mean Change in Responder Rate from Baseline) [2]	X.XXXX	X.XXXX
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Continue for Day 270 and Day 365		
Overall		
P value for HbA1c-by-Treatment Interaction		X.XXXX
P value for Gail and Simon Test [4]		X.XXXX

Abbreviation: CI = confidence interval; LS = least squares; SE = standard error.
Note: Subjects are summarized by randomized treatment. Subjects with a percent change of ≤ -50% from baseline (i.e., reduction of at least 50%) will be classified as a responder at the respective visit. The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
[1] Estimates for LS means and accompanying 95% CIs and P values are from a generalized linear mixed-effects model for repeated measures (GLMM) based on a logit link function. The model included treatment, visit, treatment-by-visit interaction, baseline use of gabapentin and/or pregabalin, baseline average 24-hour pain scores, HbA1c subgroup, and HbA1c-by-Treatment interaction as covariates. An unstructured covariance matrix was used to model the within subject correlation.
[2] P value for testing for difference in responder rate between baseline and the specified visit.
[3] P value for testing for difference in responder rate between treatments at the specified visit.
[4] P value for Gail and Simon test of no qualitative interaction
SOURCE: Listing 16.2.6.1
Programming note: *Check convergence per Section 8.1 of the SAP. Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options may be substituted if convergence problems arise. Update footnotes accordingly.*

Figure 2 (continued)

Table 14.2.2.7.4
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with HbA1c Covariate
ITT Population

Same shell as 14.2.1.2.2. HbA1c as a covariate in the model and in footnote [1].

Table 14.2.2.8.1
Summary of Subjects with at least 50% Reduction from Baseline in Average 24-hour Pain Score by Gender
ITT Population

Same shell as 14.2.1.2.1, add a row at the top of table reading "Group: Male". Once all records from group are summarized, update row text for the Female group and start table on a new page. Add 16.2.4 to SOURCE.

Table 14.2.2.8.2
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and Gender
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
ITT Population
Same shell as 14.2.1.2.2, add a row at the top of table reading "Group: Male". Once all records from group are summarized, update row text for the Female group and start table on a new page. Add 16.2.4 to SOURCE.

Table 14.2.2.8.3
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with Gender-by-Treatment Interaction
ITT Population

Same shell as 14.2.1.2.12.3. Add Gender and gender-by-Treatment interaction to the model and to footnote [1]. Add 16.2.4 to SOURCE.

Table 14.2.2.8.4
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with Gender Covariate
ITT Population

Same shell as 14.2.2.2. Add Gender to the model and to footnote [1]. Add 16.2.4 to SOURCE.

Table 14.2.2.9.1
Summary of Subjects with at least 50% Reduction from Baseline in Average 24-hour Pain Score by Age Category
ITT Population

Same shell as 14.2.2.1, add a row at the top of table reading "Group: Age < 65". Once all records from group are summarized, update row text for Age ≥65 and start table on a new page. Add 16.2.4 to SOURCE.

Table 14.2.2.9.2
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit, Treatment, and Age Category
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures

Figure 2 (continued)

ITT Population

Same shell as 14.2.2.2, add a row at the top of table reading "Group: Age < 65". Once all records from group are summarized, update row text for Age ≥65 and start table on a new page. Add 16.2.4 to SOURCE.

Table 14.2.2.9.3
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with Age Category-by-Treatment Interaction
ITT Population

Same shell as 14.2.2.8.3. Add Age Category and Age Category-by-Treatment interaction to the model and to footnote [1]. Add 16.2.4 to SOURCE.

Table 14.2.2.9.4
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures with Age Category Covariate
ITT Population

Same shell as 14.2.2.2. Add Age (less than 65 years; more than or equal to 65 years) to the model and to footnote [1]. Add 16.2.4 to SOURCE.

Table 14.2.2.10
Summary of Subjects with a 50% Reduction from Baseline in the Average 24-hour Pain Score by Baseline Use of Gabapentin and/or Pregabalin
ITT Population

Same shell as 14.2.2.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text for No Gabapentin and/or Pregabalin Use and start table on a new page.

Table 14.2.2.11
Summary of Subjects with a 50% Reduction from Baseline in the Average 24-hour Pain Score by Study Center
ITT Population

Same shell as 14.2.1.2.1, add a row at the top of table reading "Group: Study Center" Once all records from group are summarized, update row text for the next study center and start table on a new page. Add 16.2.1.1 to SOURCE.

Table 14.2.2.12
Summary of Subjects with a 50% Reduction from Baseline in the Average 24-hour Pain Score by VMDN-003 Protocol Version
ITT Population

Same shell as 14.2.1.2.1, add a row at the top of table reading "Group: Protocol Version C". Once all records from group are summarized, update row text for the next group and start table on a new page. Groups will be: C, D, and E.

Table 14.2.2.13
Analysis of Responder Rate of at least 50% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment Adjusted for Covariates
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
ITT Population

Same shell as 14.2.2.2. Add all 4 covariates (HbA1c, Gender, and Age (with 65 years as the cutoff) as covariates in the model and in footnote [1]. Add 16.2.4 to SOURCE.

Figure 2 (continued)

Table 14.2.3.1
Summary of Reduction from Baseline in the Average 24-hour Pain Score by Study Visit
ITT Population

Percent Reduction Study Visit Statistic	Placebo (N=XX)	VM202 (N=XX)
20% Reduction		
Day 90		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 180		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 270		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 365		
Number of Responders	XX (XX.X%)	XX (XX.X%)
30% Reduction		
Day 90		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 180		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 270		
Number of Responders	XX (XX.X%)	XX (XX.X%)
Day 365		
Number of Responders	XX (XX.X%)	XX (XX.X%)

Continue for 40%, 60%, and 70% reduction

Note: Subjects are summarized by randomized treatment. The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
SOURCE: Listing 16.2.6.1

Figure 2 (continued)

Table 14.2.3.2.1
Analysis of Responder Rate of at least a 20% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
mITT Population

Study Visit Statistic [1]	Placebo (N=XX)	VM202 (N=XX)
Day 90		
n	XX	XX
LS Mean Change in Responder Rate from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change in Responder Rate from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX
Day 180		
n	XX	XX
LS Mean Change in Responder Rate from Baseline (SE)	XX.X (X.XX)	XX.X (X.XX)
(95% CI for LS Mean Change in Responder Rate from Baseline)	(XX.X, XX.X)	(XX.X, XX.X)
LS Mean Difference from Placebo (SE)		XX.X (X.XX)
(95% CI for Difference from Placebo)		(XX.X, XX.X)
P value for Difference from Placebo [3]		X.XXXX

Continue for Day 270 and Day 365

Abbreviation: CI = confidence interval; LS = least squares; GLMM = generalized linear mixed-effects model; SE = standard error.
Note: Subjects are summarized by randomized treatment.
The baseline value is the average 24-hour pain score from the diary collected prior to Day 0.
[1] Estimates for LS means (percent change from baseline) and accompanying 95% CIs are from a generalized linear mixed-effects model for repeated measures (GLMM) based on a logit link function. The model included treatment, visit, treatment-by-visit interaction, baseline use of gabapentin and/or pregabalin, and baseline average 24-hour pain scores as covariates. An unstructured covariance matrix was used to model the within subject correlation.
SOURCE: Listing 16.2.6.1

Programming note: *Other variance-covariance structures selected from among compound symmetry, Toeplitz, and autoregressive (1) options may be substituted if convergence problems arise. Update footnotes accordingly.*

Figure 2 (continued)

Table 14.2.3.2.2
Analysis of Responder Rate of at least a 30% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
mITT Population

Same shell as 14.2.3.2.1

Table 14.2.3.2.3
Analysis of Responder Rate of at least a 40% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
mITT Population

Same shell as 14.2.3.2.1

Table 14.2.3.2.4
Analysis of Responder Rate of at least a 60% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
mITT Population

Same shell as 14.2.3.2.1

Table 14.2.3.2.5
Analysis of Responder Rate of at least a 70% Reduction from Baseline in Average 24-hour Pain Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from GLMM for Repeated Measures
mITT Population

Same shell as 14.2.3.2.1

Table 14.2.4.1
Summary of Change from Baseline in Average 24-hour Sleep Score
ITT Population

Same shell as Table 14.2.1.1.1.

Table 14.2.4.2
Summary of Change from Baseline in Average 24-hour Sleep Score by Gabapentin and/or Pregabalin use at Baseline
ITT Population

Same shell as Table 14.2.4.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.2.4.3
Summary of Change from Day 270 Average 24-hour Sleep Score
ITT Population

Figure 2 (continued)

Same shell as Table 14.2.4.1, only include Day 270 and Day 365 timepoints. Update headers from 'CFB' to 'CFD270' and '%CFD270'. Drop the [1] footnote. Update abbreviation footnote to say CFD270 = change from day 270 visit.

Table 14.2.4.4
Summary of Change from Day 270 Average 24-hour Sleep Score by Gabapentin and/or Pregabalin use at Baseline
ITT Population

Same shell as Table 14.2.4.3, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.2.4.5
Mean Change from Baseline in Average 24-hour Sleep Score by Study Visit and Treatment
Tabulation of Fitted Summary Statistics from MMRM
ITT Population

Same shell as 14.2.1.1.4

Figure 2 (continued)

Table 14.2.5.1
Summary of Patient's Global Impression of Change (PGIC)
ITT Population

Study Visit Statistic	Placebo (N=XX) n (%)	VM202 (N=XX) n (%)
Day 365		
1: Very Much Improved or Much Improved	XX (XX.X%)	XX (XX.X%)
0: Minimally Improved/Worsened or No Change	XX (XX.X%)	XX (XX.X%)
-1: Much Worse or Very Much Worse	XX (XX.X%)	XX (XX.X%)
P value [1]	XX (XX.X%)	XX (XX.X%)

Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the safety population. Subjects are summarized by treatment received in the VMDN-003 study.
[1] P-value from a Cochran-Mantel-Haenszel (CMH) test (stratified by baseline use of gabapentin/pregabalin) comparing VM202 to Placebo.
SOURCE: Listing 16.2.6.2

Figure 2 (continued)

Table 14.2.5.2
Summary of Patient's Global Impression of Change (PGIC) by Gabapentin and/or Pregabalin use at Baseline
mITT Population

Same shell as Table 14.2.5.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page. Do not include the CMH test or footnote.

Figure 2 (continued)

Table 14.3.1.1.1
Summary of Treatment Emergent Adverse Events
Safety Population

Category	Placebo (N=XX) n (%)	VM202 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least one TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least one TEAE related to study medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least one TEAE related to injection procedure	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least one TEAE leading to discontinuation	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least one TEAE leading to death	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Subjects with at least one SAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: PT = Preferred Term; SOC = System Organ Class; TEAE = Treatment emergent adverse event; SAE = Serious treatment emergent adverse event; N = Number of subjects in the safety population; n = Number of subjects with events.
Note: The denominator for percentage corresponds to the N in each column. Subjects are summarized by treatment received in the VMDN-003 study. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the last visit in the VMDN-003 study and pre-existing medical conditions that worsen following the last visit in the VMDN-003 study.
SOURCE: Listing 16.2.7.1

Figure 2 (continued)

Table 14.3.1.1.2
Summary of Treatment Emergent Adverse Events by Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.1.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.1.2.1
Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Placebo (N=XX) n (%)	VM202 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least one TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; N = Number of subjects in the safety population; n = Number of subjects with events.
Note: The denominator for percentage corresponds to the N in each column. Subjects are summarized by treatment received in the VMDN-003 study.
AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the last visit in the VMDN-003 study and pre-existing medical conditions that worsen following the last visit in the VMDN-003 study. Subjects are counted once for each SOC and once for each PT. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Figure 2 (continued)

Table 14.3.1.2.2
Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.2.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.1.3.1
Incidence of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class, and Preferred Term
Safety Population

System Organ Class Preferred Term Maximum Severity	Placebo (N=XX) n (%)	VM202 (N=XX) n (%), m	Overall (N=XX) n (%), m
Subjects with at least one TEAE			
Any Event (Total)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1			
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Severe	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; N = Number of subjects in the safety population.
Note: The denominator for percentage corresponds to the N in each column. Subjects are summarized by treatment received in the VMDN-003 study. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the last visit in the VMDN-003 study and pre-existing medical conditions that worsen following the last visit in the VMDN-003 study. Subjects are counted once for each SOC and once for each PT. The severity shown is the greatest severity reported for a particular subject (Severe > Moderate > Mild). AEs with a missing severity were counted as Severe. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Figure 2 (continued)

Table 14.3.1.3.2
Incidence of Treatment Emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term, and Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.3.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.1.4.1
Incidence of Treatment Emergent Adverse Events by Relationship to Study Medication, System Organ Class, and Preferred Term
Safety Population

System Organ Class Preferred Term Maximum Severity	Placebo (N=XX) n (%)	VM202 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least one TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Any Event (Total)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
System Organ Class 1			
Any Event (Total)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Term 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Not Related	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: TEAE = Treatment emergent adverse event; N = Number of subjects in the safety population; n = Number of subjects with events.
Note: The denominator for percentage corresponds to the N in each column. Subjects are summarized by treatment received in the VMDN-003 study. AEs were coded using MedDRA version 21.0. A TEAE is any AE that occurs after the last visit in the VMDN-003 study and pre-existing medical conditions that worsen following the last visit in the VMDN-003 study. Subjects are counted once for each SOC and once for each PT. Subjects are classified according to the closest relationship if the subject 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'. AEs are displayed by descending frequency of SOC, then PT within SOC, and then alphabetically by PT.
SOURCE: Listing 16.2.7.1

Figure 2 (continued)

Table 14.3.1.4.2
Incidence of Treatment Emergent Adverse Events by Relationship to Study Medication, SOC, PT, and Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.4.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.3.1.5.1
Incidence of Treatment Emergent Adverse Events by Relationship to Injection Procedure, System Organ Class, and Preferred Term
Safety Population

Same shell as Table 14.3.1.4.1

Table 14.3.1.5.2
Incidence of Treatment Emergent Adverse Events by Relationship to Injection Procedure SOC, PT, and Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.4.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Table 14.3.2.1.1
Incidence of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

Same shell as Table 14.3.1.2.1, update first line to say 'Subjects with at least one SAE'. Add 'SAE = Serious treatment emergent adverse event' to the abbreviation footnote.

Table 14.3.2.1.2
Incidence of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term, and Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.2.1, update first line to say 'Subjects with at least one SAE'. Add 'SAE = Serious treatment emergent adverse event' to the abbreviation footnote. Add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.3.1.1
Incidence of Serious Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term
Safety Population

Same shell as Table 14.3.1.2.1, update first line to say 'Subjects with at least one SAE'. Add 'SAE = Serious treatment emergent adverse event' to the abbreviation footnote.

Table 14.3.3.1.2
Incidence of Serious Treatment Emergent Adverse Events of Special Interest, by SOC, PT, and Gabapentin and/or Pregabalin use at Baseline
Safety Population

Same shell as Table 14.3.1.2.1, update first line to say 'Subjects with at least one SAE'. Add 'SAE = Serious treatment emergent adverse event' to the abbreviation footnote. Add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.6.1
Summary of Vital Signs
Safety Population

Parameter: XXXXXXXXX

Study Visit / Timepoint	Placebo (N=XX)		VM202 (N=XX)		Overall (N=XX)	
Statistic	Observed	CFB	Observed	CFB	Observed	CFB
Baseline [1]						
n	XX		XX		XX	
Mean (SD)	XX.X (XX.XX)		XX.X (XX.XX)		XX.X (XX.XX)	
Median	XX.X		XX.X		XX.X	
Q1, Q3	XX.X, XX.X		XX.X, XX.X		XX.X, XX.X	
Min, Max	XX, XX		XX, XX		XX, XX	
Day 365						
n	XX	XX	XX	XX	XX	XX
Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Q1, Q3	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X	XX.X, XX.X
Min, Max	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

***Continue for all* parameters include Sitting Systolic Blood Pressure (mmHg), Sitting Diastolic Blood Pressure (mmHg), Weight (kg), Heart Rate (beats/min), Respiration Rate (breaths/min), Temperature (C), Body Mass Index (kg/m2). Sort parameters based on CRF form order.**

Abbreviations: CFB = change from baseline.
Note: N is the number of subjects in the safety population. Subjects are summarized by treatment received in the VMDN-003 study.
[1] The baseline value for each variable is the value recorded at the last visit on or before start of dosing in the VMDN-003 study.
SOURCE: Listing 16.2.8

Figure 2 (continued)

Table 14.3.6.2
Summary of Vital Signs by Gabapentin and/or Pregabalin Use at Baseline
Safety Population

Same shell as Table 14.3.3.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

Figure 2 (continued)

Table 14.3.7.1
Summary of Concomitant Medications by ATC Class Level 3 and Preferred Base Name
Safety Population

Anatomical Therapeutic Chemical Preferred Base Name	Placebo (N=XX) n (%)	VM202 (N=XX) n (%)	Overall (N=XX) n (%)
Subjects with at least 1 Concomitant Medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC Class 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 2	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Preferred Base Name 3	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Abbreviations: ATC = Anatomical therapeutic chemical
Note: The denominator for percentage corresponds to the N in each column. N is the number of subjects in the safety population. Subjects are summarized by treatment received in the VMDN-003 study. Medications were coded using WHO-DDE version March 2018. Concomitant medications are all medications that started after the last visit on the VMDN-003 study. 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. Medications are displayed by descending frequency of Anatomical Therapeutic Chemical (ATC) Level 3 classification, by preferred base name within ATC, and then alphabetically. Subjects were counted only once for each ATC class and preferred base name.
SOURCE: Listing 16.2.9

Programming note: *Ensure correct WHODrug version is printed in footnote.*

Figure 2 (continued)

Table 14.3.7.2
Summary of Concomitant Medications by ATC Class Level 3, Preferred Base Name, and Gabapentin and/or Pregabalin Use at Baseline
Safety Population

Same shell as Table 14.3.4.1, add a row at the top of table reading "Group: Gabapentin and/or Pregabalin Use". Once all records from group are summarized, update row text to "Group: No Gabapentin and/or Pregabalin Use" and start table on a new page.

14.3. Planned Listing Shells

Listing 16.2.1.1
Subject Disposition

Subject ID	Study Center	Date of Exit	Completed Through Day 365?			Last Visit Performed	Data Entry Complete?	Study Procedures Completed	Taking gabapentin and/or pregabalin at time of VMDN-003 Randomization?
			Yes/No	If No, Reason	If No, Explanation				
XXXXXX	XXXXXXX	DDMMMYYYY	Yes				XX	Informed Consent Form; Vital Signs; AE/SAE Collection; Concomitant Medications; PGIC, Daily Pain and Sleep Interference Diary	Yes
XXXXXX	XXXXXX	DDMMMYYYY	Yes				XX	Informed Consent Form; Vital Signs; AE/SAE Collection; Concomitant Medications; PGIC, Daily Pain and Sleep Interference Diary	No
XXXXXX	XXXXXXX	DDMMMYYYY	No	XXXXXXXX	XXXXXXXXXXXX	XXXXXXXX X	XX	Informed Consent Form, AE/SAE Collection	No
XXXXXX	XXXXXXXX	DDMMMYYYY	Yes				XX	Informed Consent Form; Vital Signs; AE/SAE Collection; Concomitant Medications; PGIC, Daily Pain and Sleep Interference Diary	Yes
XXXXXX	XXXXX	DDMMMYYYY	Yes				XX	Informed Consent Form; Vital Signs; AE/SAE Collection; Concomitant Medications; PGIC, Daily Pain and Sleep Interference Diary	No

Listing 16.2.1.2.1
Inclusion and Exclusion Criteria

Subject ID	Date of: Screening	Informed Consent	HIPAA	Informed Consent Process [1]	All Inclusion Criteria Met? [2]	Any Exclusion Criteria Met? [3]	Screen Failure?
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	1	Yes	No	No
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	1	No: 01, 02	No	Yes
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	3	No: 03	No	Yes
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	1	Yes	Yes: 01	Yes
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	2	Yes	Yes: 02	Yes
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	2	Yes	No	No

[1] 1 = The subject was informed of study requirements as described in the protocol; 2 = Informed consent was obtained prior to any study-related procedures; 3 = A copy of the signed and dated consent was given to subject.
[2] 01 = subject randomized and dosed in the VMDN-003 study; 02 = Received Day 0, 14, 90, and 104 injections in VMDN-003 study; 03 = Currently in follow-up for the VMDN-003 study or having completed Day 270 within the last 90 days
[3] 01 = Current use of an investigational drug or treatment; 02 = Unable or unwilling to give informed consent.

Programming note: *If more than 1 inclusion or exclusion criterion number exists, concatenate with a comma as shown above. Decode any relevant criteria in the footnotes as shown in the example. If no criteria are present for a column, remove the [2] and/or [3] from the column header.*

Listing 16.2.1.2.2
Day 365 Visit Window

Subject ID	VMDN-003 Day 0 Visit Date	Target Day 365 Date	Day 365 Visit Window Start Date	Day 365 Visit Window End Date
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
XXXXXX	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY

Listing 16.2.2
Protocol Deviations

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	Date of Visit (Visit)	Deviation; Specify	Category; Specify	Reported to the IRB?	Reason for Deviation
XXXXXX	DDMMMYYYY (XXXXXXX)	XXXXXXXXXXX; XXXXXXXXXXXXX	XXXXXX; XXXXXX	Y/N	XXXXXXX
		XXXXXXXXXXXXXX; XXXXXXXXXX	XXXXXX; XXXXXX	Y/N	XXXXXXXXXXXXXXX
XXXXXX	DDMMMYYYY (XXXXXXX)	XXXXXXXXXXXX; XXXXXXXXXX	XXXXXX; XXXXXX	Y/N	XXXXXXXXXXXXXXXXXX
		XXXXXXXXXXXXXXXX; XXXXXXX	XXXXXX; XXXXXX	Y/N	XXXXXXXXXXX
XXXXXX	DDMMMYYYY (XXXXXXX)	XXXXXXXXXXXX; XXXXXXXXXXX	XXXXXX; XXXXXX	Y/N	XXXXXXXXXXXXXXXXXX

Programming note: *If deviation affected eligibility, category will be inclusion or exclusion, and the criterion number will follow the semicolon.*

Listing 16.2.3
Analysis Populations

VMDN003 Treatment Received: XXXXXXXX				
	Safety [1]	ITT [2]	mITT [3]	Primary Reason(s) for Exclusion
XXXXXX	Yes	Yes	No	Day 365 visit not completed.
XXXXXX	Yes	Yes	Yes	
XXXXXX	Yes	Yes	No	Day 365 visit not completed.

[1] The safety population includes all subjects that sign informed consent for the VMDN-003b study.
[2] The ITT population includes all subjects that sign informed consent for the VMDN-003b study and who were randomized on the VMDN-003 study.
[3] The mITT population includes all subjects that sign informed consent for the VMDN-003b study and who complete the day 365 visit.

Listing 16.2.4
Demographics and Baseline Characteristics

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	Sex	Date of Birth	Age (years)	Ethnicity	Race	Height (cm)	BMI (kg/m2)
XXXXXX	XXXX	DDMMMYYY	XX	XXXXXXX	XXXXXXX	XX	XX
XXXXXX	XXXXXX	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX	XX
XXXXXX	XXXXXX	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX	XX
XXXXXX	XXXX	DDMMMYYY	XX	XXXXXXX	XXXXX	XX	XX
XXXXXX	XXXXXX	DDMMMYYY	XX	XXXXXXX	XXXXXX	XX	XX
XXXXXX	XXXX	DDMMMYYY	XX	XXXXXX	XXXXXX	XX	XX

Note: Baseline values relative to the VMDN-003 baseline are listed.

Programming Note: *If subject has multiple races, concatenate them. If subject has a race of 'Other', concatenate specify text with 'Other: '.*

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Listing 16.2.6.1
Daily Pain and Sleep Interference Diary

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	Visit	Was Diary Completed?	Diary Date/Time (Study Day)	Pain Score	Sleep Interference Score	Mean Pain Score [1]	Mean Sleep Interference Score [1]
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX	XX	XX
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX	XX	XX
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX		
		Yes/No	DDMMMYYYY:HH:MM (XX)	XX	XX	XX	XX

Note: Study day is calculated relative to the date of first study injection in the VMDN-003 study.
[1] The mean pain and scores are derived if at least 5 of 7 measurements prior to a visit are collected.

Programming Note: *Mean score will be printed on row for the last diary entry for each visit. Screening, Day 270, and Day 365 should be listed.*

Listing 16.2.6.2
Patient's Global Impression of Change (PGIC)

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	Visit	Was PGIC Completed?	Date of Assessment (Study Day)	Overall Status
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY (XX)	XXXXXX
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY (XX)	XXXXXX
XXXXXX	XXXXXX	Yes/No	DDMMMYYYY (XX)	XXXXXX

Note: Study day is calculated relative to the date of first study injection in the VMDN-003 study.

Listing 16.2.7.1
Adverse Events

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	AE Number	Date of Onset (Study Day)/ End Date (Study Day)	System Organ Class/ Preferred Term/ Verbatim Term	Outcome	Worst Intensity/ Frequency of Event	Serious?/ Criteria Met	Unexpected?	Action Taken/Action Taken with Study Drug	Relationship to Study Medication	Relationship to Injection Procedure	Relationship to Underlying Disease
XXXXX	XX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	XXXXXX; XXXXX	XXXXXXXXX/ XXXXXXXXXX	XX	XX	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX
XXXXX	XX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXXXXX XXXXXXXXXXXXX	XXXXXX	XXXXXXXXX/ XXXXXXXXXX	XX	XX	XXXXXXXXX/ XXXXXXXXXX	XXXXXXXXX	XXXXXXXXX	XXXXXXXXX

Note: Study day is calculated relative to the date of first study injection in the VMDN-003 study. AEs were coded using MedDRA version 21.0.

Programming note: *If Serious? is Yes, concatenate all serious criteria marked as Yes with a semicolon. If no events meet the criteria for display, present "No events are reported." SOC & PT text should be in proper case in table, as shown in the shell. If event is ongoing, display "ongoing" for End Date. If no comments are entered, do not display the row. If multiple outcomes exist, concatenate all outcomes with a semicolon.*

Listing 16.2.7.2
Adverse Events Leading to Discontinuation of Study Drug

Same shell as 16.2.7.1, only include AEs with an action taken of discontinued study drug.

Listing 16.2.7.3
Adverse Events Leading to Death

Same shell as 16.2.7.1, only include AEs leading to death.

Listing 16.2.9.1
Vital Signs

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	Visit	Date of Collection (Study Day)	Parameter	Units	Result
XXXXX	XXXXXX	DDMMMYYYY (XX)	Sitting Systolic Blood Pressure	mmHg	XX
			Sitting Diastolic Blood Pressure	mmHg	XX
			Weight	b/kg	XX
			Heart Rate	BEATS/MIN	XX
			Respiration Rate	BREATHS/MIN	XX
			Temperature	F/C	XX

Note: Study day is calculated relative to the date of first study injection in the VMDN-003 study.

Listing 16.2.9.2
Prior and Concomitant Medications

VMDN-003 Treatment Received: XXXXXXXXX

Subject ID	ATC Class Level 3/ Preferred Base Name/ Trade Name of Medication	Indication	Taken for AE?	Start Date (Study Day)/ End Date (Study Day)	Dose/Unit	Route; Specify	Frequency	Ongoing?
XXXXXX	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	XXXXXXX	XXX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXX	XXXXXXX; XXXXXX	XXXXXXX	XX
	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	XXXXXXX	XXX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXX	XXXXXXX	XXXXXXX	XX
	XXXXXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXX	XXXXXXX	XXX	DDMMMYYYY (X)/ DDMMMYYYY (X)	XXX	XXXXXXX;XXXXXX	XXXXXXX	XX

Abbreviation: ATC = anatomical therapeutic chemical; NA = Not applicable.
Note: Study day is calculated relative to the date of first study injection in the VMDN-003 study. Medications were coded using WHO-DDE March 2018 version.

Appendix 1: [redacted] Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AD	associated documents
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BRD	business requirements document
BSL	biostatistician lead
CCGs	CRF completion guidelines
CD	compact disc
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CIOMS	council for international organizations of medical sciences
CIP	clinical investigational plan

Abbreviation	Definition
CM	clinical manager
CMP	clinical monitoring plan
COV	close out visit
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSM	clinical supply manager
CSR	clinical study report
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DBP	diastolic blood pressure
DCRF	data change request form
DDE	drug dispensing error form
DEA	drug enforcement administration
DIA	drug information association
DIS	data integration specification
DLT	dose limiting toxicity

Abbreviation	Definition
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DML	data management lead
DMP	data management plan
DNA	deoxyribonucleic acid
DOB	date of birth
DS	document specialist
DSG	drug safety group
DSM	drug supply management (drug distributor)
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
DTS	data transfer specification
DVD	digital video disk
EC	ethics committee
ECD	edit check and derivation specifications
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency

Abbreviation	Definition
eTMF	electronic trial master file
EU	European Union
FA	full analysis
FDA	food and drug administration
FMP	file management plan
FPFV	first patient first visit
FPI	first patient in
GCP	good clinical practice
GMP	good manufacturing practices
GPV	global pharmacovigilance
HR	heart rate
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
IDM	independent drug monitoring
IEC	independent ethics committee
IM	investigator meeting
IMV	interim monitoring visit
IND	investigational new drug
INDSR	investigational new drug safety reports

Abbreviation	Definition
IP	investigational product
IRB	institutional review board
IRF	inventory release file
IRR	infusion related reactions
IRT	interactive response technology
ISF	investigator site file
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	interactive voice/web response system
KPI	key performance indicator
LAN	local area network
LDM	lead data manager
LMS	learning management system
LLOQ	lower limit of quantification
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MAAP	medical affairs and pharmacovigilance teams
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities

Abbreviation	Definition
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
MTD	maximum tolerated dose
MVR	monitoring visit report
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PGIC	Patients' Global Impression of Change
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol

Abbreviation	Definition
[redacted]	[redacted]
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
ROT	record of training
RR	respiratory rate or relative rate
RSM	regional site monitor
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SC	study coordinator
SCR	software change request
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SDV	source data verification

Abbreviation	Definition
SECC	self-evident correction conventions
SECP	self-evident correction plan
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SLA	service level agreement
SMP	safety management plan
SOC	system organ class
SOP	standard operating procedure
SOW	statement of work
SQV	site qualification visit
SUA	start-up associate
SUSAR	suspected, unexpected, serious adverse (drug) reaction
TA	trial assistant
TEAE	treatment-emergent adverse event
TMF	trial master file
TOM	task ownership matrix
UAT	user acceptance testing
USA	United States of America
UTC	universal coordinated time
WAN	wide area network

Abbreviation	Definition
WAR	work at risk
WG	working guideline
WHO	world health organization
WHO-DD	world health organization drug dictionary