Statistical Analysis Plan

A PHASE II, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF VM202 IN SUBJECTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Protocol VMDN-002 (August 1, 2012)

April 9, 2014

VMDN002-SAP/A

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Revision: A

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
CSR	Clinical Study Report
DPN	Diabetic Peripheral Neuropathy
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IM	Intra-Muscular
IENFD	Intraepidermal nerve fiber density
ITT	Intent-to-Treat
MSNI	Michigan Neuropathy Screening Instrument
PGIC	Patients' Global Impression of Change
SAE	Serious AE
TEAE	Treatment-Emergent AE
VAS	Visual Analog Scale

DEFINITIONS

Adverse Event	An adverse event (AE) is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational product, whether or not it is considered causally related to the product.
Baseline	The last non-missing value prior to first dose of study drug.
Serious AE	Any untoward medical occurrence which results in death; is a life-threatening experience; requires hospitalization (admission to hospital with a stay > 24 hours) or prolongation of an existing hospitalization which is not specifically required by the protocol or is elective; Results in permanent impairment of a body function or permanent damage to a body structure; or requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of ViroMed Co., Ltd. Protocol VMDN-002 [A Phase II, Double-Blind, Randomized, Placebo-Controlled, Multi-center Study to Assess the Safety and Efficacy of VM202 in Subjects with Painful Diabetic Peripheral Neuropathy]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2. OBJECTIVES

2.1. Primary Objective

The primary objective of this analysis is to evaluate the safety of IM administration of VM202 in subjects with painful diabetic peripheral neuropathy (DPN) in lower extremities ().

2.2. Secondary Objectives

The secondary objective of the study is to evaluate potential bioactivity of intramuscular (IM) administration of VM202 in subjects with painful DPN in lower extremities, when compared to placebo, on:

- The average 24-hour pain score (obtained from the Daily Pain and Sleep Interference Diary) from baseline to the 6-month follow-up
- Visual Analogue Scale for Pain (VAS)
- Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN)
- Michigan Neuropathy Screening Instrument (MNSI)
- Patients' Global Impression Change (PGIC)
- The average 24-hour pain score interfering with sleep (obtained from the Daily Pain and Sleep Interference Diary)

The mean and mean change from baseline of these efficacy endpoints will be compared between the VM202 groups and the placebo group.

It should be noted that, in addition to the outcomes above, the evaluation of histological findings on skin biopsy will be provided by an independent lab.

3. STUDY OVERVIEW

This is a 9 month Phase II, double-blind, randomized, placebo-controlled, multi-center study designed to assess the safety and efficacy of VM202 in subjects with painful DPN.

Patients who meet the eligibility criteria will be randomized in a 2:2:1 ratio to one of three treatment arms: Low Dose (16 mg VM202), High Dose (32 mg VM202) or placebo (normal saline), respectively.

Patients in the Low Dose Group (16 mg VM202) will receive:

- Day 0: 4 mg of VM202/calf (16 injections of 0.5 ml of VM202/calf) and 16 injections of 0.5 mL of normal saline/calf.
- Day 14: 4 mg of VM202/calf (16 injections of 0.5 ml of VM202/calf) and 16 injections of 0.5 mL of normal saline/calf.

Patients in the High Dose Group (32 mg VM202) will receive:

- Day 0: 8 mg of VM202/calf (32 injections of 0.5 ml of VM202/calf)
- Day 14: 8 mg of VM202/calf (32 injections of 0.5 ml of VM202/calf)

Patients in the placebo control group will receive 32 injections/calf of 0.5 ml normal saline at each visit.

Table 1 lists the final dose and dose per visit to be administered by each study arm.

Table 1. VM202 administration for each study arm

TREATMENT GROUP	DOSE VM202 (mg) / VISIT / LEG		FINAL DOSE VM202 / LEG (mg)	FINAL DOSE VM202 / PATIENT (mg)
	DAY 0	DAY 14		
Low Dose	4	4	8	16
High Dose	8	8	16	32
Placebo	0	0	0	0

0 indicates injections of normal saline only

The schedule of study visits and the clinical parameters that will be measured at the visits are summarized in Table 2 below.

TABLE 2 SCHEDULE OF EVALUATIONS AND VISITS

Procedure	Screening / Baseline (-60 – 0 D)	1st Injection Day 0		2nd Injection Day 14 ± 1 D		Day 21 ± 3 D	Day 30 ± 3 D	Day 60 ± 3 D	Day 90 ± 7 D	6 months ± 1 mo	9 months ± 1 mo	Early Withdrawal
		Pre-dose	Post-dose	Pre-dose	Post-dose							
Baseline Evaluation												
Informed Consent	✓											
Complete Medical History	✓											
Complete Physical Exam	✓											
Cancer screening†	✓											
Viral screening – HIV, HTLV, HBV, HCV	✓											
Urinalysis	✓											
EKG	✓											
Pregnancy test	✓											
Safety and Efficacy Parameters												
VAS	✓	✓					✓	✓	✓	✓	✓	
MNSI ††	✓									✓	✓	
Symptoms of BPNS	✓									✓		
Retinal Fundoscopy	✓										✓	✓
Daily Pain and Sleep Interference Diary	✓								✓	✓	✓	
Concomitant Medications	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PGIC *							✓	✓	✓	✓	✓	
BPI-DPN**		✓					✓	✓	✓	✓	✓	
Serum Chemistry and Hematology	✓	✓					✓		✓		✓	✓
HbA1c	✓								✓	✓	✓	✓
Serum HGF		✓		✓			✓	✓	✓			✓[1]
Copies of VM202 in whole blood		✓	✓***	✓	✓***	✓	✓	✓	✓			✓[1]
Skin biopsy		✓								✓		
Treatment												
Injection site reaction assessment			✓	✓	✓	✓	✓	✓				✓[2]
Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

† Cancer screening: chest X-ray or chest CT scan if subject has a previous history of tobacco use within 3 months; pap smear and mammogram within past 12 months (females only); PSA within past 3 month (males only); for subjects ≥ 50 years old, colonoscopy within past 10 years; for subjects with a first degree relative with colon cancer, colonoscopy within past 12 months.

†† MNSI - Michigan Neuropathy Screening Instrument

1. If withdrawal occurred before Day 90 Visit
2. If withdrawal occurred before Day 60 Visit

* PGIC - Patient's Global Impression of Change

** BPI-DPN - Brief Pain Inventory, diabetic neuropathy specific test

*** 2 hours after injection (± 1 hour)

4. SAMPLE SIZE JUSTIFICATION

The sample size for this Phase 2 study was chosen to estimate effect sizes and variability for a pivotal study. Based on the 12 subjects in the Phase I study (Protocol VMDN-001), the overall mean VAS reduction from baseline to 6 months is about 23 mm with a standard deviation of about 25 mm.

This Phase II study has two VM202 dose groups (16 mg and 32 mg) and a placebo group. The study goal is to identify any difference in mean reduction in pain as measured by the Daily Pain and Sleep Interference Diary between each of the two VM202 groups against the placebo group. Based on the two-sided two-sample t-test with a significance level of 0.025 (per the Bonferroni adjustment for multiple comparisons) and an assumption of a standard deviation of 25 mm, a sample size of 40 subjects versus 20 subjects has a statistical power of 80% to detect a mean difference of 21.5 mm, a statistical power of 70% to detect a mean difference 19.5 mm, and a statistical power of 60% to detect a mean difference of 17.5 mm. Therefore, the sample size for Protocol VMDN-002 is determined to be 40 subjects in the VM202 16 mg group, 40 subjects in the VM202 32 mg group, and 20 subjects in the placebo group.

5. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, figures, and data listings. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums for each treatment arm. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories.

All analyses and tabulations will be performed using SAS® Version 9.2 or higher on a PC platform.

It should be noted that this Phase II study is for planning the future Phase III studies, therefore the p-values of the statistical tests should be used descriptively with clinically interpretation.

5.1. Visit Windows

Data at each scheduled follow up visit will be analyzed according to the nominal visit identified on the CRF, regardless of the actual elapsed time since treatment.

5.2. Statistical Methods

Although the detectable effect size for the mean pain score reduction is calculated by the two-sided t-test with a significance level of 0.025 per Bonferroni adjustment, the Analysis of Variance (ANOVA) will be performed to detect any difference in the 6-month mean pain score reduction (as measured using the Daily Pain and Sleep Interference Diary) among the three study groups first and, if there is a significant findings based on ANOVA,

the Dunnett's test for the multiple comparisons will be used to compare each of the two VM202 groups and the placebo group in the 6-month mean pain score. Therefore, two-sided p-values <0.05 will be considered statistically significant, unless otherwise stated. As described previously, regardless of the statistical significance, the p-values of the statistical tests should be used descriptively with clinically meaningful interpretation.

Separate statistical tests will be performed at each time point for key endpoints of interest such as Visual Analogue Scale for Pain, Brief Pain Inventory for Diabetic Peripheral Neuropathy, Michigan Neuropathy Screening Instrument, Patients' Global Impression Change, and the [redacted] No adjustment for multiplicity will be performed.

In general, an overall test to determine if there is a statistically significant difference among the three treatment arms will be conducted first. Further comparisons will be made to determine if either the low or high dose groups are statistically significantly different from the placebo group.

For continuous variables, a one-way analysis of variance (ANOVA) with treatment group (high dose, low dose, and placebo) as a factor will be used to determine if there is a significant difference among the groups. The low and high dose groups will each be compared against the placebo group using Dunnett's test. The mean difference between the VM202 groups versus placebo along with 95% confidence intervals for the mean difference will also be presented.

For categorical variables, Fisher's exact test will be used to determine if there is a significant difference among the three treatment groups. Separate Fisher's exact tests will be used to compare the low and high dose groups to the placebo group.

5.3. Unmasking of the Randomization Codes

The randomization code will be unmasked after all the data queries related to the efficacy and safety outcomes have been resolved and the corresponding data revisions have been completed in the database.

6. ANALYSIS POPULATIONS

The following subject populations will be used for analysis:

The Safety Analysis Group will include all subjects who receive one or more study injections. Data will be analyzed according to the treatment actually received. The safety analyses will be performed on the Safety Analysis Group.

The Efficacy Analysis Group will include all subjects who received injections of the correct dose of study drug medication based on randomization schedule at both Day 0 and Day 14, have the 6-month assessment, and do not have any protocol violations or major deviations. The protocol violations or major deviations will be determined in a blinded

review before database lock. Subjects will be analyzed according to the treatment to which they were randomized. Primary efficacy analyses will be performed on the Efficacy Analysis Group.

The Intent-to-Treat (ITT) Group will include all subjects who were randomized regardless receiving treatment. Subjects will be analyzed according to the treatment to which they were randomized. The ITT group will be used for summarizing the baseline characteristics and for the secondary analyses on the efficacy endpoints.

7. SUBJECT DISPOSITION

Subject disposition information will be summarized for all subjects by dose cohort. Summaries will include the number of subjects:

- enrolled
- in each analysis population
- who received all planned doses of VM202
- who completed each scheduled visit
- who completed the study
- who discontinued the study early, and their primary reason for early discontinuation.

8. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for the Safety Analysis Group, Efficacy Analysis Group and ITT population. Demographic variables include:

- age at informed consent
- sex
- race
- Height
- Weight and BMI

Age, height, weight, and BMI will be compared among treatment groups using the method for continuous variables. Sex and race will be compared among groups using the method for categorical variables.

9. BASELINE VALUES

Unless specified otherwise, the baseline value for each variable is the value recorded at the last visit on or before start of dosing.

10. PRIOR MEDICAL HISTORY

Abnormal medical history will be categorized by body system. The counts and percentages of subjects with medical history within the body system at baseline will be summarized.

11. EFFICACY ANALYSES

The primary efficacy analysis will be based on the Efficacy Analysis Group. Additional efficacy analyses will be performed on the ITT Group.

11.1. Primary Efficacy Analysis

Subjects will be asked to assess the level of pain they feel by selecting a score from 0 (No Pain) to 10 (Worst Possible Pain) in the 7-Day Daily Pain and Sleep Interference Diary 7 days before the Baseline, Day-90, 6-Month, and 9-Month Visits. The average of the pain score will be calculated for each subject at each visit.

The primary efficacy endpoint is the change in average pain score as determined by the 7-Day Daily Pain and Sleep Interference Diary between baseline and the 6-month follow-up. The change in pain will be calculated for each subject as follows:

Change = 6-month Pain Score – Baseline Pain Score

The baseline pain score is the average of average score at screening and at Day 0. Since higher scores indicate worse pain, a negative value of change means an improvement, and a positive value of change means deterioration.

The mean change in pain will be compared among the three treatment groups. The statistical null and alternative hypotheses for the primary efficacy endpoint are:

Ho: $\mu_H = \mu_L = \mu_P$ and
Ha: at least one of the three μ's is different,

where μ_H, μ_L, and μ_P are mean change in pain from baseline to 6-month follow-up for VM202 high dose, VM202 low dose, and placebo groups, respectively.

The one-way Analysis of Variance (ANOVA) with treatment (VM202 high dose, VM202 low dose, and placebo) as the factor will be used to compare the mean change in pain among the three treatment groups. Dunnett's test will be used to compare the mean change in pain score between VM202 high dose to placebo and between VM202 low dose to placebo. The 95% confidence interval of the mean pain score difference between VM202 groups and placebo group will be provided.

The mean score and mean score change from baseline to Day-90, and 9 Months will also be summarized using the statistical methods described above.

11.1.1. Handling Missing Data

For ITT population, the analyses with imputation for missing data will be performed for the primary efficacy endpoint (pain score change from baseline to 6 months). For subjects without the primary efficacy endpoint, the following imputation methods will be considered:

- For subjects with an early drop-out reason not related to death or AEs, the last available value (LOCF) of the subject will be used for the missing 6-month value. For early discontinued subjects due to AEs, the maximum value of all available 6-month pain score will be imputed for the missing 6-month value. For early discontinued subjects due to death, no imputation will be performed and therefore will not be included in the 6-month analyses if they are discontinued prior to the 6-month visit.

No imputation for missing values will be performed for other variables.

11.2. Outcome of at least 50% Reduction in Average Pain Score from Baseline to 6-Month

The percent reduction in the average pain score (determined by the 7-Day Daily Pain and Sleep Interference Diary) from baseline to 6-month follow-up will be calculated for each subject as follows:

% reduction = (Baseline Pain Score – 6-month Pain Score) ÷ Baseline Pain Score × 100%.

The percentage of subjects with at least 50% reduction in pain from baseline to the 6-month follow-up and the corresponding 95% confidence intervals based on the binomial distribution will be calculated for each study group. Fisher's exact test will be used to compare the percentage of subjects with at least 50% reduction in pain among the three study groups. The comparison between the placebo group and each of the two VM202 group will also be performed by Fisher's exact test. The 95% confidence interval of the difference between placebo and each of the two VM202 group in the percentage of subjects with at least 50% reduction will be derived by the two-sample normal distribution.

The percentage of subjects with at least 20%, 30%, 40%, 60%, 70%, and 80% reduction in pain and the corresponding 95% confidence intervals based on the binomial distribution will also be provided.

11.3. Other Efficacy Variables

The analyses for the other efficacy variables will be performed based on the Efficacy Analysis Group unless specified otherwise. No imputation for the missing data will be performed for these efficacy endpoints. These efficacy endpoints include:

11.3.1. Visual Analogue Scale for Pain (VAS)

Subjects will be asked to assess the level of pain they feel by placing a perpendicular line on a scale of 0 (No Pain) to 100 mm (Very Severe Pain) at Day-0, Day-30, Day-60, Day-90, 6-Month, and 9-Month Visits at the clinic. This is a separate analysis from the 7-Day Daily Pain and Sleep Interference Diary. The subject's Visual Analogue Scale (VAS) score will be determined by where the subject places the perpendicular line. The average of the VAS measured by two readers will be calculated for each subject at each visit. The VAS measurements and change from baseline (average of VAS at screening and Day 0, or if data are missing from either, the value recorded at either visit will be summarized at each required visit by treatment arm using method for continuous variables.

11.3.2. Brief Pain Inventory for Diabetic Peripheral Nephropathy (BPI-DPN)

The pain severity and pain interference will be calculated for each subject at each required visit based on the BPI-DPN instruction. The pain severity, pain interference and their change from baseline (post-treatment – baseline) will be summarized by study visit and treatment arm using the method for continuous variables.

11.3.3. Michigan Neuropathy Screening Instrument (MNSI)

Total score of patient history and of physical assessment will be calculated for each subject at each required visit. The total score of the history, the total score of the physical assessment, and their change from baseline (post-treatment – baseline) will be summarized by study visit and treatment arm using the method for continuous variables.

11.3.4. Patients' Global Impression of Change (PGIC)

Subjects will be asked to assess the level of the change of their overall status since the start of the study (scale of 1 to 7) at Day-30, Day-60, Day-90, 6-Month, and 9-Month Visits. PGIC score will be summarized by study visit and treatment arm using the method for continuous variables.

11.3.5. Pain interference with Sleep

Subjects will be asked to rate the score of pain interfering with sleep in the 7-Day Daily Pain and Sleep Interference Diary. The average of the pain-interference score will be calculated for each subject at each required visit. The average pain-interference score and the change from baseline (post-treatment – baseline) will be summarized by study visit and treatment arm using the method for continuous variables.

11.3.6. Brief Peripheral Neuropathy Screening (BPNS)

Total score of the BPNS will be summarized at the Screening and 6-Month visits using the method for continuous variables. The change from the Screening to the 6-Month visit (6-Month – Screening) will also be summarized.

11.4. Multiplicity Adjustments

There will be no adjustments for multiple comparisons or interim analyses.

12. SAFETY ANALYSES

All subjects who received one or more study injections will be included in the safety analyses, analyzed according to the study treatment actually received.

12.1. Study Drug Exposure

Study drug exposure (number of injections and total volume administered) will be summarized by treatment arm for Day 0 and Day 14 using descriptive statistics for continuous variables.

12.2. Injection Site Reaction

Assessments of injection site reaction (None and Grade 1, 2, and 3), ulceration (None and Grade 2 to 5), and allergic reaction (None and Grade 1 to 5) are planned for Day 0 (post-dose) and Day 14 (pre- and post-dose). The number and percentage of subjects with an injection site reaction will be summarized descriptively by treatment arm and study visit.

12.3. Adverse Events

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. Verbatim terms on case report forms will be mapped to preferred terms. It should be noted that only the AEs after the first round of injection will be collected during the study.

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

- TEAE by preferred term;
- TEAE by preferred term and maximum severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject

reported one or more events. AEs with missing severity will be considered severe for this summary;

- TEAE by preferred term and closest relationship to study drug (Related/Not Related). At each level of subject summarization, a subject is 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'.
- Serious TEAEs by preferred term.

12.4. Clinical Laboratory Evaluation

Shift tables (i.e., normal, abnormal not-clinically significant, abnormal clinically significant at baseline versus normal, abnormal not-clinically significant, abnormal clinically significant at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from baseline to follow-up result. The counts and percentage of subjects with each of the 9 possible "shift" outcomes will be calculated by treatment arm.

12.5. Pharmacokinetics and Skin Biopsy

HGF serum level and copies of VM202 will be summarized by treatment arm at each visit using descriptive statistics for continuous variables. This will be performed by independent lab. An independent analyses report on the histological findings on skin biopsy will be provided by an independent lab as well.

12.6. Vital Signs

Vital signs and change from baseline will be summarized descriptively at each visit by treatment arm.

12.7. Retinal Fundoscopy

A retinal fundoscopy of each eye will be performed at Screening and at 9 Months (or last available visit for early withdraw). Each eye will be given one of the following assignments: Normal, Abnormal-Not Clinically Significant, and Abnormal-Clinically Significant. Shift tables will be provided to assess changes in retinal fundoscopy. For each of the three treatment groups, counts and percentage of subjects will be calculated for each of the 9 possible "shift" outcomes.

12.8. Prior and Concomitant Medications

Prior medications are those medications taken within 60 days prior to the initial dose of study drug. Concomitant medications are those medications taken after the initial dose of study drug. Prior and concomitant medications will be summarized for each treatment by medication name. These summaries will present the number and percentage of subjects using each medication.

12.9. Interim Analyses

An independent data safety monitoring board (DSMB) will review a limited set of un-blinded tables and listings, including all reported SAEs. There will be no adjustment for multiple testing because the results of the interim analysis will not be used to declare the study a success, the unblinded analyses will be performed by a person independent to the study project statistician, and the detailed unblinded findings will not be shared with the project team.

APPENDIX A: LIST OF TABLES

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