Protocol VMDN-003b

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**
Protocol Number:	VMDN-003b; Version C
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Document Date:	30 July 2019

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

Protocol VMDN-003b/C

July 30, 2019

Sponsor

[redacted]

[redacted]

DISCLOSURE STATEMENT

This document contains information that is confidential and proprietary to Helixmith Co., Ltd. This information is being provided to you solely for the purpose of evaluating or conducting a clinical study for Helixmith Co., Ltd. You may disclose the contents of this document only to study personnel under your supervision who need to know the contents for this purpose and to your Institutional Review Board (IRB), otherwise the contents of this document may not be disclosed without the prior authorization from Helixmith Co., Ltd. The foregoing shall not apply to disclosure required by governmental regulations or laws. Any supplemental information that may be added to this document also is confidential and proprietary to Helixmith Co., Ltd and must be kept in confidence in the same manner as the contents of this document.

SIGNATURE PAGE

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

[redacted] 08-August-2019

Signature *Date (DD-MM-YYYY)*

[redacted]

Signature *Date (DD-MM-YYYY)*

SIGNATURE PAGE

We, the undersigned, confirm that we have read and are in agreement with the contents of this document.

[redacted]

Signature *Date (DD-MM-YYYY)*

[redacted]

[redacted]

Signature

07-Aug-2019

Date (DD-MM-YYYY)

INVESTIGATOR'S AGREEMENT

I, the undersigned, am responsible for the conduct of the study at the site below and agree to the following:

- I understand that this protocol is a confidential document. I agree that the information within it will not be disclosed to anyone without prior written authority from the sponsor, Helixmith Co., Ltd, except to the extent necessary to conduct this study and obtain approval from the Institutional Review Board or other approving body.
- I understand and will conduct the study according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board, except where necessary to prevent any immediate danger to the subject.
- I have read and understand fully the Investigator Brochure.
- I have sufficient time to properly conduct and complete the study within the agreed study period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.
- I will ensure that any staff members at my site(s) who are involved in the study conduct are adequately trained regarding this trial's operations, the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the sponsor with a delegation of investigators responsibilities log.
- I understand that the study may be terminated or enrollment may be suspended at any time by Helixmith Co., Ltd, Inc. with or without cause, or by me or my institution if it becomes necessary to protect the best interest of the study subjects.

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

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
PURPOSE AND RATIONALE	Purpose is to explore the overall safety profile and durability of efficacy of VM202 in painful diabetic peripheral neuropathy.
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.
POPULATION	This study will include subjects who were 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.
STUDY DESIGN	All subjects still in follow-up for the VMDN-003 study or who have completed the Day 270 visit within the prior 90 days will be approached to enroll in the long-term safety extension study. Subjects will be requested to complete a 7-Day Daily Pain and Sleep Interference diary and one visit 365 ± 14 days after their VMDN-003 Day 0 visit. All 24 sites in the US who recruited subjects for the VMDN-003 study will be invited to participate in this long-term extension trial. Safety will be monitored throughout the study and assessed regularly by an independent Data Safety Monitoring Board (DSMB) throughout the study.
STUDY OBJECTIVES	• To evaluate the long-term safety of IM administration of VM202 in subjects with painful DPN in the lower extremities. • To evaluate the durability of efficacy of IM administration of VM202 in subjects with painful DPN in the lower extremities.
INCLUSION CRITERIA	1. Subjects randomized and dosed in the VMDN-003 study; 2. Having received all intramuscular injections of study drug on Days 0, 14, 90, and 104 in the VMDN-003 study; 3. Currently in follow-up for the VMDN-003 study or having completed Day 270 within the last 90 days prior to signing consent.

EXCLUSION CRITERIA	1. Current use of an investigational drug or treatment; and 2. Unable or unwilling to give informed consent.
STUDY PROCEDURES	Subjects currently in follow-up in the VMDN-003 study or having completed Day 270 within the last 90 days will be invited to enroll in the safety extension. Subjects willing to participate with be asked to complete a 7-Day Daily Pain and Sleep Interference diary within 14 days before a visit scheduled 365 ± 14 days after their Day 0 visit for the VMDN-003 study. Diaries will be collected at the visit, along with vital signs, concomitant medications, adverse events, and the Patient's Global Impression of Change (PGIC) questionnaire.

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ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CDRC	Clinical Data Review Committee
CFR	Code of Federal Regulation
CRO	Clinical Research Organization
CS	Clinically Significant
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capturing
ER	Extended Release
FDA	Food and Drug Administration
HGF	Hepatocyte Growth Factor
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
IND	Investigational New Drug
MRC	Medical Research Council
NCS	Not Clinically Significant
PGIC	Patients' Global Impression of Change
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

PERSONNEL AND FACILITIES

STUDY SPONSOR

Helixmith Co., Ltd
[redacted]

MEDICAL MONITOR

[redacted]

INVESTIGATORS

Principal Investigator (for entire study):
John A. Kessler, M.D.
Davee Professor of Stem Cell Biology, Director, Feinberg Clinical Neuroscience Institute, Director, Northwestern University Stem Cell Institute
303 East Chicago Avenue
Chicago, Illinois 60611-3008

Principal Investigators by site:

SITE NUMBER	CONTACT INFORMATION
01	Senda Ajroud-Driss, MD Northwestern University Department of Neurology [redacted] Chicago, Illinois 60611-3008 [redacted]
02	Aziz Shaibani, MD, FACP, FAAN Nerve and Muscle Center of Texas [redacted] Houston, TX 77030 [redacted]
03	Mark Christiansen, MD Diablo Clinical Research [redacted] Walnut Creek CA 94598 [redacted]

SITE NUMBER	CONTACT INFORMATION
04	Judith L. White, MD Compass Research, LLC [redacted] Orlando, FL 32806 [redacted]
05	Aaron Vinik, MD East Virginia Medical School Strelitz Diabetes Center [redacted] Norfolk VA 23510 [redacted]
06	Gordon Smith, MD University of Utah [redacted] Salt Lake City UT 84132 [redacted]
07	David Kudrow, MD Neurological Research Institute [redacted] Santa Monica, CA 90404 [redacted]
08	Lon D. Lynn, DO Clinical Research of West Florida [redacted] Tampa, FL 33603 [redacted]
09	Alexander Reyzelman, DPM Center for Clinical Research [redacted] San Francisco, CA 94115 [redacted]
10	Mazen Dimachkie, MD U. of Kansas Clinical Research Center [redacted] Fairway, KS 66205 [redacted]
11	Jeffrey Allen, MD University of Minnesota Department of Neurology [redacted] Minneapolis, MN 55455 [redacted]

SITE NUMBER	CONTACT INFORMATION
12	James Wymer, MD University of Florida McKnight Brain Institute, L3-100 [redacted] Gainesville, FL 32611 [redacted]
13	Victor Biton, MD Clinical Trials, Inc. [redacted] Little Rock, AR 72205 [redacted]
14	Michael Bowman, MD Raleigh Neurology Associates, PA [redacted] Raleigh, NC 27607 [redacted]
15	Miguel Trevino, MD Innovative Research of West Florida [redacted] Clearwater, FL 33756 [redacted]
16	Joseph S. Gimbel, MD Arizona Research Center [redacted] Phoenix, AZ 85023 [redacted]
17	Leslie Klaff, MD, PhD Rainier Clinical Research Center, Inc. [redacted] Renton, WA 98057 [redacted]
18	Richard S. Cherlin, MD [redacted] Los Gatos, CA 95032 [redacted]
19	Joe Chehade, MD UF Health College of Med., Jacksonville [redacted] Jacksonville, FL 32207 [redacted]

SITE NUMBER	CONTACT INFORMATION
20	Thomas Brannagan, MD Columbia University Medical Center Department of Neurology [redacted] New York, NY 10032 [redacted]
21	Thomas Toothaker, MD Associated Neurologists of Southern CT, PC [redacted] Fairfield, CT 06824 [redacted]
22	Douglas Young, MD Northern California Research [redacted] Sacramento, CA 95821 [redacted]
24	Maria Kasper, DPM Martin Foot and Ankle [redacted] York, PA 17402 [redacted]
25	Christine N. Sang, MD, MPH Brigham and Women's Hospital Dept. of Anesthesia [redacted] Boston, MA 02115 [redacted]

CLINICAL RESEARCH ORGANIZATION (CRO)

[redacted]

1. BACKGROUND

Diabetic peripheral neuropathy (DPN) is one of the most commonly encountered neuropathic pain syndromes in clinical practice, and is a particularly debilitating complication of diabetes. According to both the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Disease, 60 to 70 percent of diabetics will eventually develop some form of diabetic neuropathy. Today, it is estimated that 3 to 6 million patients with diabetes have painful DPN.[1,2] The total annual cost of DPN and its complications in the U.S. is estimated to be between $4.6 and $13.7 billion.[3-5]

Currently, there are only three drugs approved by FDA specifically for the treatment of the symptoms of DPN: Nucynta ER – (tapentadol), an opioid medication; Cymbalta – (duloxetine), a serotonin and norepinephrine reuptake inhibitor; and Lyrica – (pregabalin), an anticonvulsant drug. All are prescribed for the management of pain associated with diabetic peripheral neuropathy.

Hepatocyte growth factor (HGF) has been shown to be a potent angiogenic growth factor, stimulating the growth of endothelial cells and migration of vascular smooth muscle cells.[6,7] Recent research also indicates that HGF can function as a neurotrophic factor.[8] It is proposed that administration of HGF may promote axonal growth and regeneration. As loss of microvasculature in diabetic neuropathy has also been implicated in acceleration of neuronal loss and pain symptoms,[9] HGF may be an ideally suited candidate for the treatment this condition.

VM202 is a DNA plasmid that contains novel genomic cDNA hybrid human hepatocyte growth factor (HGF) coding sequence [redacted] expressing two isoforms of HGF, [redacted]. VM202 has been used in phase I and II studies for painful diabetic peripheral neuropathy (PDPN) with significant efficacy on pain.

In the phase III VMDN-003 study, subjects received 2 treatments of either VM202 or placebo administered as intramuscular (IM) injections into bilateral calves on Days 0 and 14, and Days 90 and 104. Primary efficacy was evaluated 90 days following the first injection. The growth potential for HGF make long-term follow-up important both for safety and efficacy: in order for VM202 to be a candidate for chronic treatment of PDPN, it must be demonstrated not to induce unexpected adverse events with repeated dosing; and the potential for reversal or stabilization of diabetic neuropathy using only one or two treatments of VM202 may make it especially attractive compared to current treatments which must be taken daily for the duration of the disease. A safety extension to the VMDN-003 study is therefore warranted.

2. GOOD CLINICAL PRACTICES (GCP) STATEMENT

This trial will be conducted in compliance with all applicable federal regulations pertaining to investigational drugs and devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 312, and GCP standards. This trial will be conducted in compliance with the protocol as approved by an Institutional Review Board (IRB). Any deviations from the protocol that may affect the safety and welfare of study participants will be immediately reported to the Sponsor and to the IRB per each institution's guidelines.

3. INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

The objective of this safety extension study is to evaluate the long term safety and efficacy of IM administration of VM202 in subjects with painful DPN in the lower extremities.

3.2. STUDY DESIGN

This is a prospective, observational, non-interventional study for long-term follow-up of subjects previously 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.

3.3. SUBJECT POPULATION

Subjects currently in follow-up in the VMDN-003 study or having completed Day 270 within the last 90 days will be invited to enroll in this safety extension study.

3.3.1. INCLUSION CRITERIA

Subjects must satisfy all of the following criteria to be included in the study:

1. Subjects randomized and dosed in the VMDN-003 study;
2. Having received all intramuscular injections of study drug on Days 0, 14, 90, and 104 in the VMDN-003 study;
3. Currently in follow-up for the VMDN-003 study or having completed Day 270 within the last 90 days prior to signing consent.

3.3.2. EXCLUSION CRITERIA

Subjects ***will not be eligible for the study*** if any of the following criteria are present:

1. Current use of an investigational drug or treatment; and

2. Unable or unwilling to give informed consent.

3.4. STUDY PROCEDURES

Prior to recruitment of any subjects into the study, written approval of the protocol and informed consent must be obtained from the IRB.

3.4.1. INFORMED CONSENT

The investigator or designee will explain the study purpose, procedures, and subject's responsibilities to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained (Appendix 1). The subject will sign and date the informed consent form. The investigator or designee will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject.

3.4.2. SUBJECT IDENTIFICATION

To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form. All subjects that give informed consent (sign the informed consent form) will be assigned the same unique identifier that they were given for VMDN-003 in the following format: XX-YYY-ZZZ. XX is the 2 digit assigned site number, YYY is the subject ID number, and ZZZ are the subject initials (initials of first name/middle name (if applicable)/last name).

3.4.3. DAY 270 UP TO 14 DAYS PRIOR TO SCHEDULED DAY 365 VISIT

- Informed consent

Study subjects may sign the informed consent form for the extension study after completing Day 270 assessments for study VMDN-003. Alternatively, subjects may return to the research center at any time following Day 270 but no later than 14 days prior to their scheduled Day 365 visit to sign the informed consent form.

3.4.4. DAY 365 ± 14 DAYS

The only study visit will be scheduled 365 days ± 14 days after the subject's VMDN-003 Day 0 visit.

- *The subject will be asked to completed the Daily Pain and Sleep Interference Diary within 14 days prior to the Day 365 visit*

3.4.4.1. STUDY VISIT PROCEDURES

- *Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to the visit*
- Vital Signs
- Concomitant Medications
- PGIC
- Adverse event assessment

3.5. STUDY COMPLETION

3.5.1. COMPLETED SUBJECTS

Each subject in the study will be considered completed when all Day 365 assessments have been performed in accordance with the study protocol.

3.5.2. NON-PARTICIPATING SUBJECTS

Any subject eligible for the long-term safety extension may elect not to participate. If possible, the reason(s) for the subject not participating should be recorded on the study worksheets.

Possible reasons for not participating in the extension study include the following:

- Adverse events (AEs).
- The subject is lost to follow-up.
- Subject decision (specify).
- Investigator decision (specify).
- Other reason (specify).

3.5.3. PREMATURE STUDY TERMINATION

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

4. EXAMINATIONS AND EVALUATIONS

4.1. CONCOMITANT MEDICATIONS

All concomitant medications (taken since completion of Day 270 of the VMDN-003 study) will be recorded at each study visit. For each medication taken, the following information will be collected:

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

4.2. VITAL SIGNS

Vital signs consisting of blood pressure (while subject is sitting), temperature, weight, heart rate, and respiratory rate will be measured and recorded.

4.3. DAILY PAIN AND SLEEP INTERFERENCE DIARY

Subjects will be asked to keep a Daily Pain and Sleep Interference Diary (see Appendix 2). Subjects will be asked to rate their 24-hour average daily pain intensity score using an 11-point numerical rating scale from 0 (no pain) to 10 (worst possible pain). The effect of pain on the subject's ability to sleep will be assessed

using the sleep interference score. Like the pain intensity score, the sleep interference score is an 11-point numerical rating scale from 0 (pain did not interfere with sleep) to 10 (pain completely interfered; subject was not able to sleep due to pain).

The diary will be completed within 14 days prior to the Day 365 visit. To increase compliance, the Diary will be FedExed to the subject 2 weeks prior to the scheduled visit. The FedEx shipping bill will become part of the subject's source documents. Ten days prior to the scheduled visit, the study coordinator will call the subject to remind the subject of their upcoming visit at Day 365, and the requirement to complete the diary starting within 14 days of the visit. The phone call will be documented on the source document worksheets. One day prior to the visit, the site study coordinator will call the subjects to confirm their upcoming visit and to remind the subject to bring the completed Diary. If the subject arrives at the clinic without the completed diary, the visit will be rescheduled as soon as possible.

Upon completion of the Diary, the study coordinator will check the Diary for completeness. Any omissions or ambiguous answers will be clarified by the subject prior to leaving the clinic. Note, the subject will be required to initial each page of the diary.

4.4. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC)

The patient's global impression of change after treatment will be measured using the Patient's Global Impression of Change (PGIC) questionnaire.[10] This questionnaire measures a patient's perception of how treatment has affected their level of activity, symptoms, emotions, and overall quality of life. Each descriptor is ranked on an intensity scale of 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse 7 = Very Much Worse. This test will be self-administered during study visits on Day 365.

Upon completion of the questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the subject prior to leaving the clinic. The PGIC can be found in Appendix 3. Note, the subject will be required to initial and date the PGIC.

5. EVALUATION OF ADVERSE EVENTS

5.1. DEFINITIONS

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 considered causally related to the product.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).

Conditions or diseases that are chronic but stable should not be recorded as an AE. Changes in a chronic condition or disease that are consistent with natural disease progression are NOT considered AEs and also should not be recorded on AE worksheets. These medical conditions should be adequately documented on the appropriate page of the study worksheet (relevant medical history and/or physical examination). However, medical conditions present at enrollment that worsen in intensity or frequency in a manner inconsistent with the natural course of the disease during the treatment or post-treatment periods should be reported and recorded as AEs.

An **adverse reaction** means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

A **serious adverse event (SAE)** is any untoward medical occurrence which:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of 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.

Additionally, important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when they jeopardize the subject or require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

Life-threatening means that the subject is, in the view of the investigator, at immediate risk of death from the AE as it occurred. It does not include an AE which, had it occurred in a more serious form, might have caused death.

Persistent or significant disability/incapacity means that the event resulted in permanent or significant and substantial disruption of the subjects' ability to carry out normal life functions.

An **unexpected AE** is an AE, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved product). Expected means that the event has been previously observed with the test article and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications. It is expected that certain disease states will have reoccurring adverse events some of which may be considered expected over time.

5.2. ASSESSMENT OF AEs

All AEs, regardless of severity, occurring following study drug administration by a subject must be recorded on the AE worksheet. This will include the following information:

- Description of the AE
- Date of onset
- Duration
- Frequency
- Severity
- Seriousness (yes/no)
- Treatment
- Outcome
- Relationship to study medication, injection procedure and/or underlying disease

All AEs and SAEs must be followed until resolution, or the condition stabilizes. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The Sponsor or its designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations.

5.2.1. AE CAUSALITY

The study investigator will determine whether an AE is related or unrelated to study medication, the procedure (intramuscular injection) and / or the underlying disease using the following criteria:

Not related: An adverse event that is not related to the use of the test article or administration procedure.

Possibly related: An adverse event that might be due to the use of the test article or administration procedure. An alternative explanation, e.g., concomitant study

product(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, a causal relationship cannot be excluded.

Probably related: An adverse event that might be due to the use of the test article or administration procedure. The relationship in time is suggestive. An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Definitely related: An AE that is due to the use of the test article or administration procedure. The event cannot be reasonably explained by an alternative explanation – e.g., concomitant drug(s), concomitant disease(s).

5.2.2. AE INTENSITY

The intensity of the AE/SAE will be defined by the following criteria:

Mild:	The AE is noticeable to the subject but does not interfere with routine activity.
Moderate:	The AE is discomforting and interferes with routine activity.
Severe:	The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy.

5.3. REPORTING/RECORDING OF AES

Throughout the course of the study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing appropriate medical intervention. The period of observation for collection of AEs starts during the first intramuscular injection procedure (Day 0) until the Day 365 follow-up safety extension visit. Any AE should be recorded on the appropriate study worksheet.

5.4. REPORTING / RECORDING OF SAES

5.4.1. INVESTIGATOR'S RESPONSIBILITY

SAEs will be recorded following the first study drug administration through the Day 365 safety extension follow-up visit. Any serious adverse event or unexpected adverse event that occurs during this investigation, whether or not related to the study medication, must be reported as soon as possible but no later than 3 working days after the investigator first learns of the event to the Sponsor and the designated CRO by completing the SAE form and the AE information in the EDC and selecting appropriate criteria that classifies the AE as serious and/or unexpected. In order to have the Investigator's signature on file, the signed SAE form needs to be uploaded to the EDC at the time of initial data entry.

Each SAE must be followed with appropriate medical management until resolved or assessed as chronic or stable regardless of whether or not, in the opinion of the Investigator, the event is thought to be related to the study medication.

The Investigator will be required to provide complete information (including the Investigator's opinion of the relationship of the SAE to the study medication) concerning each SAE to the CRO and Sponsor within 5 working days of first learning of the event. This information must be recorded in the subject's medical record and then entered into the EDC. Copies of related source documentation such as results/reports, hospitalization records, and other relevant information must be obtained if possible.

In the event of an SAE leading to hospitalization, every effort will be made by the investigational site to obtain medical records, including a hospital discharge summary. In the event of a fatal AE, documentation of any available postmortem findings, including autopsy, will be provided to the Sponsor or their designee. In any event, the Investigator will provide a narrative summary of circumstances, events related to the death, and cause of death, if known.

The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB), and Institutional Biosafety Committee (IBC) if applicable. Upon receipt from the Sponsor of an initial or follow-up IND Safety Report or other safety information, the Investigator must promptly notify his or her IRB, and IBC (if applicable).

5.4.2. SPONSOR'S RESPONSIBILITY

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

All serious, unexpected adverse reactions and suspected adverse reactions will be reported to FDA and to all participating investigators as an IND Safety Report within 15 calendar days of the event after the sponsor determines that the suspected adverse reaction qualifies for reporting (21 CFR §312.32). Any unexpected fatal or life-threatening AEs will be reported to the Agency within 7 calendar days after the sponsor's initial receipt of the information.

The Sponsor will notify all participating investigators of any new safety information that alters the current risk-benefit assessment of the study medication or that would be sufficient to consider changes in VM202 administration or in the overall conduct of the trial.

5.5. ANALYSIS POPULATION

The analysis population will be the safety population, and will include all subjects who sign consent for the safety extension study. Subjects in the analysis population

will be analyzed according to treatment received, regardless of original treatment assignment. The primary analyses of the primary and secondary endpoints will be based on the analysis population.

5.6. STUDY ENDPOINTS

5.6.1. PRIMARY 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.

5.6.2. SECONDARY ENDPOINTS

The secondary efficacy endpoints are:

1. 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;
2. The change in the average 24-hour pain score from Day 270 to the Day 365 follow-up from the Daily Pain and Sleep Interference Diary; and
3. Patient's Global Impression of Change (PGIC) at the Day 365 follow-up.

5.6.3. ANALYSIS METHODS

The statistical analyses will be descriptive only and reported using summary tables, figures, and listings. All summaries will be derived based on available data. 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. No imputation will be performed for missing values. 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. Continuous variables will be summarized using the number of non-missing values, mean, standard deviation, median, minimum and maximum values. Categorical data will be summarized using the number of observations and percentages. Summary plots of efficacy data will present mean values with standard error bars.

5.6.4. DATA SAFETY MONITORING BOARD (DSMB)

The independent data safety monitoring board (DSMB) for the VMDN-003 study will periodically review a limited set of un-blinded tables and/or listings, 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 the VM202. The data analyses for the DSMB meetings will be provided to the DSMB members and other participants of the DSMB meeting.

6. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

The Sponsor has designated consultants to monitor the progress of this study. The clinical monitor, as a representative of the Sponsor, has the obligation to follow this study closely.

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

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

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

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

7. QUALITY CONTROL AND ASSURANCE

The Sponsor employees and/or their contracted representatives utilize Standard Operating Procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and Good Clinical Practice guidance.

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

8. INSTITUTIONAL REVIEW BOARD

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

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to the Sponsor or its designee for approval prior to IRB submission.

The investigator is responsible for notifying the IRB of any serious adverse events as required by the IRB.

Status reports must be submitted to the IRB at least once a year (or more frequently as required by the IRB) and the IRB must be notified of completion or termination of the study. A final report must be provided to the IRB and the Sponsor within 1 month of study completion or termination. This report should include: any deviations from the protocol, the number of participants evaluated, the number of participants who withdrew or were withdrawn and the reasons for withdrawal, any significant adverse events and the investigator's summation of the study.

9. INFORMED CONSENT PROCESS

It is the responsibility of the investigator or designee to inform each subject, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. A sample informed consent form containing the required elements of informed consent is provided in Appendix 1. Any changes made to this sample must be approved by the Sponsor or its designee, prior to submission to an IRB. After approval by the Sponsor or its designee, the informed consent must be submitted to and approved by an IRB. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the informed consent form. The person executing the consent must also sign and date the final consent form page. One original informed consent form is to be retained by the study site and a copy is to be given to the subject. The informed consent process must be documented in the subject's medical record.

The informed consent must be written in a language in which the subject is fluent. If a foreign language translation is required, a statement of certification of the translation must be issued. Regulations require that foreign language informed consent forms be submitted to the IRB for approval. The investigator must forward a copy of the consent form, the certified foreign language translation and an IRB approval letter to the Sponsor or its designee.

10. CONFIDENTIALITY

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

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

11. PROTOCOL AMENDMENTS

The Sponsor will document modifications to the protocol in the form of a written amendment. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB before implementation. In the case of a medical emergency, to remove immediate apparent hazard to subjects, a change may be made preferably after discussion with the Sponsor or its designee. In these instances, the IRB and FDA will be notified as soon as possible.

12. DATA MANAGEMENT

Electronic data capture (EDC) will be utilized for this study. Study worksheets will be provided by the Sponsor or its designee to the site before data collection. In order to facilitate data entry, the worksheets coincide with the data entry pages in the EDC system. The design of the data entry screens will follow the same flow as the provided worksheets in order to insure minimal issues during data entry. If the site elects to use the worksheets, appropriate worksheets will be completed and initialed or signed where indicated at each examination. All worksheets will be completed in a legible manner in black/blue ink. Alternatively, the site may elect to use their own source documents. It is expected there will be source data for all entries in the EDC.

Any corrections to the worksheets will be made by drawing a single line through the incorrect entry, recording the correct information, and initialing and dating the change.

The study worksheets and data entered in the EDC system will be audited by the Study Monitor.

Once the data is ready to be entered into the EDC System, then the site will begin entering the data into the system. Afterwards, the monitor will review the data against the source documents and/or worksheets and either approve the data records or create queries to the site for further review. If the data records are deemed "clean" with the approval of the monitor, then the investigator can e-sign the records. Finally, when the data records are ready to be locked, the data manager will perform the interim lock in the system. However, the data manager also has the right to unlock the data record if any updates to the data are necessary.

Data are protected by preventing unauthorized users from accessing the system with the use of username and password combination. In addition, each individual user will be assigned a specific role in the EDC System which will grant that user the right to view, edit and/or delete the data. Furthermore, any changes to the data are captured in the EDC System's audit trail where a reason for change is required.

All clinical data generated in the study will be submitted to the Sponsor or designated CRO for quality assurance review and statistical analysis. All worksheets and data entered into the EDC system will be reviewed for completeness and evident recording errors will be rectified by contact with the appropriate clinical site. Computerized data checks will be used to identify unusual data entries for verification prior to statistical analysis.

To minimize the amount of missing data, investigators will be trained on the deleterious effect that missing data have on trial integrity and credibility and that missing data could diminish the scientific value of all subjects' altruistic contributions.

13. RECORD KEEPING AND RETENTION

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

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

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

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

In addition to the documents listed above, the study site will also retain the following items:

- Certifications and laboratory reference ranges for all local laboratories used for this study.
- Copy of delegation of authority log.
- All original informed consent forms with required signatures.
- All IRB correspondence (i.e., informed consent [including any approved revisions], protocol, AE, advertisements, newsletters).
- Copy of the Study Monitoring Log
- Clinical and non-clinical supply shipment forms
- Copies of all pertinent correspondence pertaining to the study (except budget issues) between the Sponsor or the CRO and the site
- Copies of all SAEs reports submitted to the Sponsor or its designee
- Copies of all IND Safety Reports submitted to the site by the Sponsor or its designee
- Copies of approved package labeling

All study-related records must be maintained for at least 2 years after a marketing application (NDA/BLA) is approved for the drug; or if an application is not approved for the drug, until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified. The Sponsor will notify the principal investigator when records are no longer needed. The investigator will not discard any records without notifying the Sponsor. If the principal investigator moves from the current investigational site, the Sponsor should be notified of

the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

14. INVESTIGATOR FINAL REPORT

The investigator shall provide the IRB and the Sponsor with an accurate final report within 2 months after completion, termination or discontinuation of the study. The final report may not precede final data submission which has not been monitored.

15. STUDY REPORT AND PUBLICATION

The data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. None of the data resulting from this study will be allowed to be presented or published in any form, by the investigator or any other person, without the prior written approval of the Sponsor. At the end of the study, a clinical study report will be written by the Sponsor or its designee.

16. REFERENCES

1. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: epidemiology, natural history, early diagnosis, and treatment options. Pain Med 2008;9:660-74.
2. Hartsfield CL, Korner EJ, Ellis JL, Raebel MA, Merenich J, Brandenburg N. Painful diabetic peripheral neuropathy in a managed care setting: patient identification, prevalence estimates, and pharmacy utilization patterns. Population health management 2008;11:317-28.
3. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes care 2003;26:1790-5.
4. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. Journal of diabetes and its complications 2006;20:26-33.
5. Sadosky A, Mardekian J, Parsons B, Hopps M, Bienen EJ, Markman J. Healthcare utilization and costs in diabetes relative to the clinical spectrum of painful diabetic peripheral neuropathy. Journal of diabetes and its complications 2014.
6. Bussolino F, Di Renzo MF, Ziche M, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol 1992;119:629-41.
7. Nakagami H, Kaneda Y, Ogihara T, Morishita R. Hepatocyte growth factor as potential cardiovascular therapy. Expert Rev Cardiovasc Ther 2005;3:513-9.
8. Hashimoto N, Yamanaka H, Fukuoka T, et al. Expression of HGF and cMet in the peripheral nervous system of adult rats following sciatic nerve injury. Neuroreport 2001;12:1403-7.
9. Camera A, Hopps E, Caimi G. Diabetic microangiopathy: physiopathological, clinical and therapeutic aspects. Minerva Endocrinol 2007;32:209-29.
10. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of manipulative and physiological therapeutics 2004;27:26-35.

APPENDICES

TABLE OF APPENDICES

Appendix 1. Schedule of Evaluations

SCHEDULE OF EVALUATIONS AND VISITS

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		✓

Appendix 2. Sample Informed Consent

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 (Protocol Number: VMDN-003b)

SPONSOR: Helixmith Co., Ltd
[redacted]
www.Helixmith.com

Worldwide Headquarters:
Helixmith Co., Ltd.
[redacted]

PRINCIPAL INVESTIGATOR:	[INSERT NAME AND TITLE]
INSTITUTION:	[INSERT INSTITUTION NAME AND ADDRESS]
SUBJECT INITIALS:	[INSERT SUBJECT'S INITIALS]
SUBJECT NUMBER:	[INSERT SUBJECT'S UNIQUE STUDY NUMBER]

You are being asked to participate in a research study sponsored by Helixmith Co., Ltd. Before you decide whether to participate, it is important for you to know why the research is being done, and what it will involve. Please take your time to read the following information carefully, and feel free to discuss your decision with your family, friends, and your primary care doctor. Please ask your study doctor to explain if there is anything that is not clear or if you would like more information. If you agree to take part in this study, you need to sign this consent form. Your signature on this form means that you have been told about and understand the purpose of the study, procedures to be followed, and any benefits or risks. Your signature on this form also means that you want to take part in this study. After you agree, you will be provided with a copy of this signed form for your records.

Do I have to take part?
Taking part in this study is entirely voluntary, and you may refuse to participate or withdraw from the study at any time without influencing your regular medical treatment and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Regardless of your decision, you will still be treated for your medical condition.

Why is this study being done?
You are being considered to participate in this research study because you are currently enrolled or have recently completed the study titled "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", also known as the VMDN-003 study.

The current study is intended to help determine the long-term safety and efficacy of VM202 in subjects with painful diabetic neuropathy. No additional administration of study drug will be performed, but you will be asked to complete one additional pain diary and return to the research clinic for one more visit to evaluate your pain and your current medical status.

Who is in charge of this study?
The Principal Investigator is [INSERT PRINCIPAL INVESTIGATOR NAME]. This study is sponsored and funded by Helixmith Co., Ltd Co., Ltd. [insert PRINCIPAL INVESTIGATOR NAME] is being paid by Helixmith Co., Ltd Co., Ltd. to conduct this study. Together with your doctor, Helixmith Co., Ltd Co., Ltd. will also use a specialized research company, called a contract research organization, in addition to specialized laboratories to manage some parts of the detailed requirements of the study.

How many people will take part in this research study?
About 157 patients who are still enrolled in the VMDN-003 study or recently finished the VMDN-003 study throughout the 24 research centers in the United States will be invited to participate.

What happens if I agree to be in this research study?
After you sign this consent form indicating you want to participate in this study, you will be asked to fill out a daily questionnaire for a week (7 days). You will be asked to assess your average pain in your feet and lower legs on a scale of 0 - 10 (with 0 = no pain, and 10 = worst possible pain) every day. You will also be asked to describe if your pain in your feet and lower legs interfered with your sleep on a scale of 0 - 10 (with 0 = pain did not interfere with sleep, and 10 = pain completely interfered; I was not able to sleep due to pain).

You will complete the daily questionnaire within 14 days of a return visit to the research clinic. The visit will be scheduled to occur approximately 1 year from the date that you received your first injections of study drug for the VMDN-003 study (365 days).

Description of the tests, procedures, and diagnostic studies to be done at the visit

Vital signs – Your doctor will measure your weight, heart rate, blood pressure, and respiratory rate.

Assessment of side effects – Your doctor will ask you about any unpleasant medical experiences, side effects, or discomforts that may have happened to you since completing the VMDN-003 study and up until this visit.

Medication review – Discussion with your doctor of what medications and dietary supplements you have taken and are currently taking since you completed the VMDN-003 study. In particular, your doctor will ask you about any new medications, dietary supplements, or therapies that you may have started for the diabetic peripheral neuropathy pain.

Questionnaires – You will be asked to complete a short questionnaire about your current health.

How long will I be in this research study?
This extension study consists of one visit during which you will be explained the study and sign the informed consent if you agree to participate, and one visit about 1 year after the date your received the first injections of study drug for the VMDN-003 study. After the 1-year visit, you will have completed the study.

What do I have to do as a participant in this study?
Participation in this study requires you to make sure that you will be able to complete the diary and attend the study visit.

You also must not participate in any other clinical trial until after you complete the study visit.

What about my rights to decline participation or withdraw from the study?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data pertain to a side effect related to the study. If such an event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care. If you do decide to stop your participation in the study, you should talk to your doctor immediately so he/she can advise you of any additional tests that may be needed for your safety. Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if he/she determines that it is no longer in your best interest to continue. The Sponsor

or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss with you other options you may have.

What are the risks of this research study?
There is very little risk to participating in this study. There is no investigational product or invasive procedure such as blood draws involved and it is unlikely that you will incur any harm from participating. However, you may discuss any concerns you have with your doctor before you start in the study.

Are there benefits to taking part in this research study?
There may be no direct benefit to you by participating in this study.

Knowledge from this study may help us better understand how the study drug used in the VMDN-003 study helps treat painful diabetic neuropathy.

What if new information becomes available?
If additional data regarding potential safety risks become available during the study, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form which will explain the new information clearly.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

Will I need to pay for the tests and procedures?
Participation in this study will be of no cost to you. All medical exams and study evaluations and procedures that are required for this research study are provided to you at no cost to you. Helixmith Co., Ltd Co., Ltd. pays for this research. However, if taking part in this study leads to procedures or care not included in this study, it may lead to added costs for you or your insurance company.

What happens if I am injured because I took part in this research study?
In the event of an injury resulting from your participation in this study, you will be provided with appropriate medical care. However, the costs incurred may, ultimately, be borne by your medical insurance. Further information concerning this and your rights as a research subject can be obtained from [INSERT NAME OF PRINCIPAL INVESTIGATOR] or by phone [INSERT PHONE NUMBER] or by mail [INSERT MAILING ADDRESS].

What are my rights if I take part in this research study?

You have the right to refuse to sign this consent. Taking part in this research study does not take away any other rights or benefits you might have if you did not take part in the study. Taking part in this study does not give you any special privileges. You will not be penalized in any way if you decide not to take part or if you stop after you start the study. Specifically, you do not have to be in this study to receive or continue to receive medical care from your doctor. If you stop the study you would still receive medical care for your condition.

For any questions pertaining to your rights as a research subject, you may contact [PROVIDE CONTACT NAME] of the Institutional Review Board [PROVIDE NAME OF IRB AND CONTACT PHONE NUMBER].

What about confidentiality?

The personal information obtained about you during the course of this study will remain confidential. When recording the results of the study you will be referred to only by a unique subject identifier code number and your initials. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records.

Your records may be reviewed in order to meet Federal Food and Drug Administration (US FDA) regulations, or other national and/or local health regulatory authorities. Your records may be copied by, or for these groups. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Copies of the study records that do not include your name, but may be traced back to you may also be given to the groups listed below. The Sponsor may send a copy of the records to the FDA or other regulatory agencies.

By agreeing to participate in this research study, you consent to give representatives of the following entities access to your research-related medical records to ensure the proper conduct of the research and verify the accuracy of the collected data. Clinical monitors, auditors, IRB members, and regulatory authorities will be granted access to your original medical records for verification of clinical trial procedures and/or data, without violating your confidentiality, to the extent permitted by the applicable laws and regulations.

Reviewers for the study may include the Sponsor (Helixmith Co., Ltd.), or its representatives such as members of the Data Safety Monitoring Committee, the Contract Research Organization, and the IRB or other Research Committee(s) that approve and oversee research in the hospitals and clinics. Additionally, representatives of national regulatory authorities (for example the Food and Drug Administration in the USA) and other representatives as designated by the Sponsor who will have a role in the handling and analysis of the study data or in trial operations.

Complete confidentiality cannot be promised because information needs to be shared as described. However, information will be collected and shared following professional standards of confidentiality.

What will happen to the results of this study?
The results of this research study will be used to support an application to regulatory agencies that approve drugs for use on prescription. In addition, the results may be used in scientific publications or presented at medical meetings. Your identity as a participant will not be revealed.

Who has reviewed this study?
The study has been reviewed by the FDA, and an IRB (research ethics committee).

Who can answer my questions?
You may talk to the study doctor or IRB at any time about any questions or concerns you have on this study. A copy of this form will be placed in your medical record. A copy of this form will also be given to you.

What alternatives are there to participation in this study?
You do not have to take part in this study to receive treatment for your condition. Your doctor may suggest that you use a topical over the counter medication for pain relief (such as lidocaine or capsaicin) and may suggest taking nutritional supplements such as α-lipoic acid (a chemical found naturally in various plants such as spinach and broccoli).

There are only two drugs approved by FDA specifically for the treatment of the (nerve) pain associated with DPN: Cymbalta – (duloxetine); and Lyrica - (pregabalin). In addition, gabapentin (Neurontin) may be prescribed.

STATEMENT OF CONSENT

I confirm that I have read and understand this consent form. I confirm that the purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have decided of my own free will to agree to take part in this study.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.

I understand that sections of any or all of my medical records may be reviewed by representatives of the Sponsor, Helixmith Co., Ltd, its subcontractors, or by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that I will not be referred to by name in any report concerning the study. I understand that a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify me. I agree to disclosure of such records and any results to the regulatory authorities. I understand that I will be provided clinically appropriate medical care and that I have access to my doctor in case of any injury or deterioration in my health or well-being caused directly by my participation in this study.

(Printed Name of Participating Subject)		
(Signature of Participating Subject)	Date	: Time
(Printed Name of Physician or his/her Representative Obtaining Consent		
(Signature of Physician or his/her Representative Obtaining Consent)	Date	: Time

Original copy for site file; 1 copy for subject.

Appendix 3. Daily Pain and Sleep Interference Diary – One Day Sample

Please complete one form (a + b + c) each day starting on the day indicated by the clinic ***around 8 pm every night.***

Question 1a: indicate the day of the week, the date and time.
Return the completed forms to the clinic at your next visit.

Please ***circle*** *a number from 0 to 10 that best describes your status using a fine or medium point pen.*

1a. _____ **DAY** (Day of week) **Date:** _ _ / _ _ _ / _ _ _ _ **Time**: ___ ___ am / pm (circle one)
DD MMM YYYY

1b. Please rate your average pain in your legs (below the knee, this includes pain in your foot) during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain					Moderate Pain					Worst possible pain

1c. Please rate how much your pain in your legs (below the knee, this includes pain in your foot) interfered with sleep during the past night.

0	1	2	3	4	5	6	7	8	9	10
Did not interfere with sleep										Completely interfered with sleep

Patient's Initials: _____

The study coordinator will check the diary for completeness. Any omissions or ambiguous answers will be clarified by the subject prior to leaving the clinic. Note, the subject will be required to initial and date each page of the diary.

Appendix 4. Patient's Global Impression of Change

Patient Global Impression of Change (PGIC) Scale

Since the start of the study, my overall status is:

Check (✓) one box only:

Very Much Improved	☐ 1
Much Improved	☐ 2
Minimally Improved	☐ 3
No Change	☐ 4
Minimally Worse	☐ 5
Much Worse	☐ 6
Very Much Worse	☐ 7

Patient's Initials: _____ **Date:** _____