HELIXMITH

Protocol VMDN-003

Protocol Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Participants with Painful Diabetic Peripheral Neuropathy

Protocol Number: VMDN-003; Version H

NCT Number: NCT02427464

Document Date: 05 September 2019

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-003 / H

September 5, 2019

Sponsor
Helixmith Co., Ltd.

[redacted]

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

[redacted] [redacted] 05-09-2019

Signature *Date (DD-MM-YYYY)*

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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.
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- 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. 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	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
STUDY PHASE	III
INVESTIGATIONAL AGENT	VM202
DOSE	16 mg of VM202 administered as a divided dose at Day 0 and Day 14, with a second treatment of 16 mg VM202 at 3 months administered as a divided dose at Day 90 and Day 104, for a final total dose of 32 mg VM202 administered per subject.
POPULATION	Subjects aged ≥ 18 years to ≤ 75 years diagnosed with painful diabetic neuropathy in both lower extremities.
STUDY DESIGN	A phase III, double-blind, randomized, placebo-controlled, multicenter, 9-month study designed to assess the safety and efficacy of bilateral intramuscular (IM) injection of VM202 in the calves of subjects with painful diabetic peripheral neuropathy (DPN). A total of 477 subjects will be randomized in a 2:1 ratio to one of two treatment groups: Treatment - VM202 - 318 subjects Control - Placebo (VM202 suspension medium) - 159 subjects Randomization will be stratified by current use of gabapentin and/or pregabalin. Up to 30 sites in the US and Korea will participate in the study. 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 efficacy of IM administration of VM202 in subjects with painful DPN in the lower extremities, when compared with placebo, on pain. • To evaluate the safety of IM administration of VM202 in subjects with painful DPN in lower extremities.

INCLUSION CRITERIA	1. Age ≥ 18 years to ≤ 75 years; 2. Documented history of Type I or II diabetes with current treatment control (glycosylated hemoglobin A_{1c} of ≤ 10.0% at Screening) and currently on medication for diabetes (oral, injectable and / or insulin); 3. No significant changes anticipated in diabetes medication regimen; 4. No new symptoms associated with diabetes within the last 3 months prior to study entry†; 5. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities; 6. Lower extremity pain for at least 6 months; 7. Visual analog scale (VAS) score of ≥ 40 mm at Initial Screening (0 mm = no pain – 100 mm very severe pain); 8. Symptoms from the Brief Peripheral Neuropathy Screening (BPNS) is ≤ 5-point difference between legs at Initial Screening; 9. The average daily pain intensity score of the Daily Pain and Sleep Interference Diary completed after medication wash-out is ≥ 4 with a standard deviation ≤ 2; 10. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Initial Screening; 11. Subjects on gabapentin (Neurontin), pregabalin (Lyrica), duloxetine (Cymbalta) for painful DPN at study entry† must be on stable regimen of these treatments for at least 3 months prior to study entry†; and 12. If female of childbearing potential, negative urine pregnancy test at screening and using acceptable method of birth control during the study.
EXCLUSION CRITERIA	1. Peripheral neuropathy caused by condition other than diabetes; 2. Other pain more severe than neuropathic pain that would prevent assessment of DPN; 3. Progressive or degenerative neurological disorder; 4. Myopathy; 5. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease); 6. Active infection; 7. Chronic inflammatory disease (e.g., Crohn's disease, rheumatoid arthritis); 8. Positive HIV or HTLV at Screening; 9. Active Hepatitis B or C as determined by Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B surface antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening;

† Study entry is defined as the date of signing informed consent.

10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy;
11. Stroke or myocardial infarction within last 3 months;
12. Clinically significant laboratory values at Screening (e.g., Hemoglobin < 8.0 g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm^3, Creatinine > 2.0 mg/dL; AST and/or ALT > 3 times the upper limit of normal or any other clinically significant lab abnormality) which, in the opinion of the investigator should be exclusionary;
13. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
14. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at Screening;
15. Subjects with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence for one year); subjects with medical history and/or family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
16. Use of the following drugs / therapeutics is **PROHIBITED**. Subjects may participate in the study if they are willing to discontinue use of these drugs / therapeutics ***7 days prior to starting the Daily Pain and Sleep Interference Diary***. Subjects must refrain from taking these drugs or undergoing these therapies for the duration of the study:

    - skeletal muscle relaxants, opioids, benzodiazepines (except for stable bedtime dose),
    - capsaicin, local anesthetic creams (except for Lidocaine cream prior to IM injections) and patches, isosorbide dinitrate (ISDN) spray,
    - transcutaneous electrical nerve stimulation (TENS), acupuncture

17. If not using gabapentin (Neurontin) or pregabalin (Lyrica), subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on these medications at study entry[†] must maintain a stable dose until Day 180 visit of the study;
18. If not using duloxetine (Cymbalta), any antidepressants (e.g. amitriptyline and venlafaxine), any other antiepileptics (e.g., valproic acid, carbamazepine, vigabatrin), subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on

these medications at study entry† must maintain a stable dose until Day 180 visit of the study;

19. Subjects requiring > 81 mg daily of acetylsalicylic acid; subjects may be enrolled if willing/able to switch to ≤ 81 mg daily of acetylsalicylic acid or to another medication;
20. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or steroids (except inhaled steroids or ocular steroids); subjects may be enrolled if willing/able to undergo medication wash-out prior to the first dosing and to refrain from taking these drugs until Day 180 visit of the study;
21. Major psychiatric disorder within last 6 months that would interfere with study participation;
22. Body mass index (BMI) > 45 kg/m^2 at Screening;
23. Any lower extremity amputation due to diabetic complications;
24. Use of an investigational drug or treatment in past 6 months or prior participation in any study of VM202; and
25. Unable or unwilling to give informed consent.

STUDY PROCEDURES

Screening should be completed within the 90 days prior to Day 0 (day of injection). Prior to screening, subjects will give informed consent and then be initially screened using the VAS, the symptoms portion of the BPNS and the entire MNSI. Only subjects with a VAS score of ≥ 40 mm, a ≤ 5-point difference in symptoms of the BPNS between legs and physical examination component of MNSI of ≥ 3 will be allowed to proceed with the full screening procedures. All other assessments other than the completion of the Diary may be scheduled during medication washout. Screening will include assessment of study eligibility, medical history, vital signs, physical exam, concomitant medications, cancer screening tests, retinal fundoscopy, viral screening, 12 lead EKG, serum chemistry and hematology including HbA1c, and urine pregnancy test (women of childbearing potential only).

If applicable, the subject will be washed out of prohibited medications prior to initiation of the Daily Pain and Sleep Interference Diary; the Diary must be completed within 14 days prior to Day 0. At least 5 days of the diary must be completed. The average pain score of the Daily Pain and Sleep Interference Diary must be ≥ 4 with a standard deviation ≤ 2 in order to be eligible for study participation. Eligible subjects will be randomly assigned in 2:1 ratio to the VM202 treatment group or to the placebo group.

A single treatment with VM202 is delivered as an equally divided dose administered two weeks apart. Subjects will receive VM202 or placebo (VM202 vehicle) by intramuscular injections in both legs (in the calf) on Day 0 and Day

† Study entry is defined as the date of signing informed consent.

14. Subjects will receive a second treatment on Day 90 and Day 104. Injections will be administered as follows:

First Treatment: Days 0, 14

TREATMENT GROUP	DOSE VM202 (mg) / VISIT / LEG		FINAL DOSE VM202 / LEG (mg)	FINAL DOSE VM202 / SUBJECT / TREATMENT (mg)
	DAY 0	DAY 14		
VM202	4	4	8	16
Placebo	0	0	0	0

0 = injections of VM202 vehicle

Second Treatment: Days 90, 104

TREATMENT GROUP	DOSE VM202 (mg) / VISIT / LEG		FINAL DOSE VM202 / LEG (mg)	FINAL DOSE VM202 / SUBJECT / TREATMENT (mg)
	DAY 90	DAY 104		
VM202	4	4	8	16
Placebo	0	0	0	0

0 = injections of VM202 vehicle

VM202 is delivered in a solution of 0.5mg VM202 / mL. All subjects will receive sixteen (16) 0.5 mL injections of VM202 or placebo evenly distributed over each calf at each treatment visit.

Subjects randomized to the VM202 treatment arm will receive the following intramuscular injections in each calf:

- Day 0 – 16 injections of 0.5mL of VM202 / calf
- Day 14 – 16 injections of 0.5mL of VM202 / calf

- Day 90 – 16 injections of 0.5mL of VM202 / calf
- Day 104 – 16 injections of 0.5mL of VM202 / calf

Subjects in the placebo control group will receive the following intramuscular injections in each calf:

- Day 0 – 16 injections of 0.5mL of VM202 vehicle / calf
- Day 14 – 16 injections of 0.5mL of VM202 vehicle / calf

- Day 90 – 16 injections of 0.5mL of VM202 vehicle / calf
- Day 104 – 16 injections of 0.5mL of VM202 vehicle / calf

Note: Visually, VM202 vehicle is indistinguishable from reconstituted VM202. The subject and clinician will not be able to distinguish placebo from VM202 injections.

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 21, Day 60, immediately pre-treatment on Day 90, immediately pre-treatment on Day 104, Day 111, Day 150, Day 180, and Day 270.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 21, Day 60, at Day 90 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 104 (pre-injection, and 2 hours [± 1 hour] post injection), Day 111, Day 150, Day 180, and Day 270.

Nerve conduction studies will be conducted pre-treatment on Day 0, Day 180 and Day 270 at selected sites.

Serum chemistry, hematology and HbA1c will be determined on Day 0, Day 90, Day 180, and Day 270.

VAS, Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), and Semmes-Weinstein monofilament testing will be recorded at Day 0, Day 90, Day 180, and Day 270. Patients' Global Impression of Change (PGIC) will be recorded at Day 90, Day 180 and Day 270. MNSI will be conducted at Day 180 and Day 270 to track disease progression.

Retinal fundoscopy will be conducted on Day 180 and Day 270.

The Daily Pain and Sleep Interference Diary will be completed by subjects before the Day 90, Day 180, and Day 270 visits.

Rescue medication (i.e., Acetaminophen [Tylenol]) taken for DPN pain will be dispensed on Day 0 and use of Tylenol will be documented through the 9-month follow-up visit.

Adverse events, concomitant medications and vital signs will be recorded throughout the 9-month follow-up period, while injection site reactions will be assessed starting on Day 0 through Day 150.

CONCOMITANT MEDICATIONS

COX-1 and COX-2 inhibiting drugs, and steroids (except inhaled steroids or ocular steroids) may interfere with the bioactivity of VM202, and are therefore prohibited from use during the study. Other than the maximal 81 mg daily dose of aspirin (acetylsalicylic acid), subjects must agree not to take any of these drugs until Day 180 visit of the study.

Several medications used to manage neuropathic pain will be excluded from use during the study. Subjects must discontinue use of the

following drugs / therapeutics listed below. Subjects may participate in the study if they are willing to discontinue use of these drugs / therapeutics ***7 days prior to starting the Daily Pain and Sleep Interference Diary***. Subjects must refrain from taking these drugs or undergoing these therapies for the duration of the study:

- skeletal muscle relaxants, opioids, benzodiazepines (except for stable bedtime dose),
- capsaicin, local anesthetic creams and patches (except for Lidocaine cream prior to IM injection), isosorbide dinitrate (ISDN) spray,
- transcutaneous electrical nerve stimulation (TENS), acupuncture

If not using gabapentin (Neurontin) or pregabalin (Lyrica), subjects must agree not to start these drugs for the first 6 months of the study. Subjects on these medications must be on stable regimen of these treatments for at least 3 months at study entry[†] and must maintain the stable dose until Day 180 visit of the study.

If not using duloxetine (Cymbalta), any antidepressants (e.g. amitriptyline and venlafaxine), any other antiepileptics (e.g., valproic acid, carbamazepine, vigabatrin) at screening, subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on these medications at study entry must maintain a stable dose until Day 180 visit of the study.

Acetaminophen (Tylenol) is the only rescue medication allowed in this study. Up to 3 grams / day will be allowed.

SCHEDULE OF EXAMINATIONS

Screening (Day -90 to Day 0)
Day 0
Day 14 ± 1 day
Day 21 ± 3 days
Day 60 ± 3 days
Day 90 ± 7 days
Day 104 – 13 to15 days after Day 90 Visit
Day 111 – 4 to 10 days after the Day 104 visit
Day 150 ± 7 days
Day 180 ± 7 days
Day 270 ± 14 days

STUDY ENDPOINTS

There are two primary efficacy endpoints that will be evaluated in sequential order.

The first primary efficacy endpoint is the change in the average 24-hour pain score from baseline to the 3-month follow-up [Day 90] obtained from the Daily Pain and Sleep Interference Diary. The difference in the

mean of the change in the average 24-hour pain score will be compared between the treatment group and the placebo arm to determine the treatment effect in the efficacy analysis populations.
The second primary efficacy endpoint is the outcome of at least a 50% reduction (i.e. ≥ 50%) in the average 24-hour pain score from baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary. The responder success rate will be compared between the treatment group and the placebo arm to determine the treatment effect in the efficacy analysis populations.

The secondary efficacy endpoints will be based on the change in the average 24-hour pain score from baseline to the 6-month follow-up [Day 180] (3 months after the Day 90 injection) obtained from the Daily Pain and Sleep Interference Diary. The difference in the mean of the change in the average 24-hour pain score will be compared between the treatment group and the placebo arm to determine the treatment effect in the efficacy populations. The proportion of subjects with at least a ≥ 50% reduction in the average 24-hour pain score from baseline to the 6-month follow-up [Day 180] (3 months after the Day 90 injection) will be compared between the two study groups.

All other efficacy endpoints will be exploratory.

SAFETY

Any subject who receives study injections (VM202 or placebo) will be included in the safety analysis population. Adverse events (including serious adverse events, and adverse events leading to treatment discontinuation) throughout the 9-month follow-up will be described according to severity and to their relationship with the study drug and injection procedure. Descriptive statistics (N, mean, median, SD, minimum and maximum values, where applicable) will be used to characterize continuous safety parameters. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories.

All subjects will undergo testing as presented in the American Cancer Society Cancer Screening Guidelines as part of their screening to rule out cancer.

PHARMACO-KINETICS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 21, Day 60, immediately pre-treatment on Day 90, immediately pre-treatment on Day 104, Day 111, Day 150, Day 180 and Day 270.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 21, Day 60, at

Day 90 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 104 (pre-injection, and 2 hours [± 1 hour] post injection), Day 111, Day 150, Day 180, and Day 270.

TABLE OF CONTENTS

Figures & Tables

Table of Appendices

ABBREVIATIONS

AE	Adverse Event
ABI	Ankle Brachial Index
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
ALT	Alanine Transaminase (SGPT)
Anti-HCV	Hepatitis C antibodies
AST	Aspartate Transaminase (SGOT)
BMI	Body Mass Index
BP	Blood Pressure
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Nephropathy
BPNS	Brief Peripheral Neuropathy Screening
BUN	Blood Urea Nitrogen
cDNA	Complementary Deoxyribonucleic Acid
CBC	Complete Blood Count
CDRC	Clinical Data Review Committee
CFR	Code of Federal Regulation
CLI	Critical Limb Ischemia
cm	Centimeter(s)
CR	Controlled Release
[redacted]	[redacted]
CRO	Clinical Research Organization
CS	Clinically Significant
DBP	Diastolic Blood Pressure
DIP	Distal Interphalangeal
DLT	Dose Limiting Toxicities
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capturing
EFFS	Efficacy Analysis Set
EKG	Electrocardiogram
ER	Extended Release
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core antibody (IgG and IgM)
HBsAb	Antibody to Hepatitis B surface antigen
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose, and Throat
Hgb	Hemoglobin

HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
IND	Investigational New Drug
ISDN	Isosorbide dinitrate
ITT	Intent-to-Treat
LLOQ	Lower limit of quantitation
mITT	Modified Intent-to-Treat
mm	millimeters
MNSI	Michigan Neuropathy Screening Instrument
MRC	Medical Research Council
NCS	Not Clinically Significant
NCV	Nerve Conduction Velocity
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
PAD	Peripheral Arterial Disease
PGIC	Patients' Global Impression of Change
PI	Principal Investigator
PP	Per Protocol
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cells
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGPT	Serum Glutamic Pyruvic Transaminase (same as ALT)
SNRI	Serotonin–Norepinephrine Reuptake Inhibitors
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitors
TAR	Treatment Authorization Request
TBI	Toe Brachial Index
TCA	Tricyclic Anti-depressants
$TcPO_2$	Transcutaneous Pressure of Oxygen
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells
WFI	Water for Injection

PERSONNEL AND FACILITIES

STUDY SPONSOR

Helixmith Co., Ltd.
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MEDICAL MONITOR

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CLINICAL RESEARCH ORGANIZATION (CRO)

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1. BACKGROUND

1.1. DIABETES

Approximately 29.1 million adults in the United States have diabetes mellitus, a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism. Diabetes can result from defects in insulin secretion (type 1), insulin action (type 2), or a combination of these factors, and is associated with a high level of morbidity and mortality. The total estimated cost of diabetes in 2012 was $245 billion, including $176 billion in excess medical expenditures and $69 billion in reduced national productivity.[†]

1.1.1. DIABETIC PERIPHERAL NEUROPATHY

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. When symptomatic, it is associated with continuous or paroxysmal pain described by patients as shooting, stabbing, or electric in nature.[1] The pain can either be triggered by an external stimulus or be independent of external input. Unlike other painful sensations which signal a warning in response to a harmful stimulus, neuropathic pain is maladaptive. DPN accounts for significant morbidity by predisposing the foot to ulceration and lower extremity amputation.[2-4]

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 - 6 million patients with diabetes have painful DPN.[5,6] The total annual cost of DPN and its complications in the U.S. is estimated to be between $4.6 and $13.7 billion.[7-9] If current health trends persist unabated, the costs associated with diabetic neuropathy will rise sharply over the coming decades.

1.1.2. PATHOPHYSIOLOGY OF DIABETIC PERIPHERAL NEUROPATHY

DPN manifests as three broad categories: sensory, motor and autonomic. The most prevalent form is somatic or sensorimotor neuropathy. Symptoms often exhibit a distal symmetric pattern, beginning distally at the base of the toes and ascending proximally up the lower leg as the disease progresses. Symptoms are described as burning, tingling, stabbing and a pins-and-needles sensation in a stocking and glove distribution. Patients may also display muscle weakness, lack of coordination and ataxia, and loss of pain perception. Loss of protective sensation can lead to the formation of foot ulcerations, infections, and amputations.

Despite being the focus of current research, the sequence of physiological events that result in this condition is poorly understood. The pathogenesis of diabetic neuropathy likely involves the interplay of hyperglycemia, ischemia, and oxidative stress.[10] Vascular dysfunction, driven by metabolic change, is thought to play a

[†] From: *National Diabetes Statistics Report*, 2014 http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

crucial role in the progression of diabetic neuropathy.[11-15] Figure 1 portrays the relationship of hyperglycemia to oxidative stress, metabolic alterations, vascular dysfunction and neural damage.

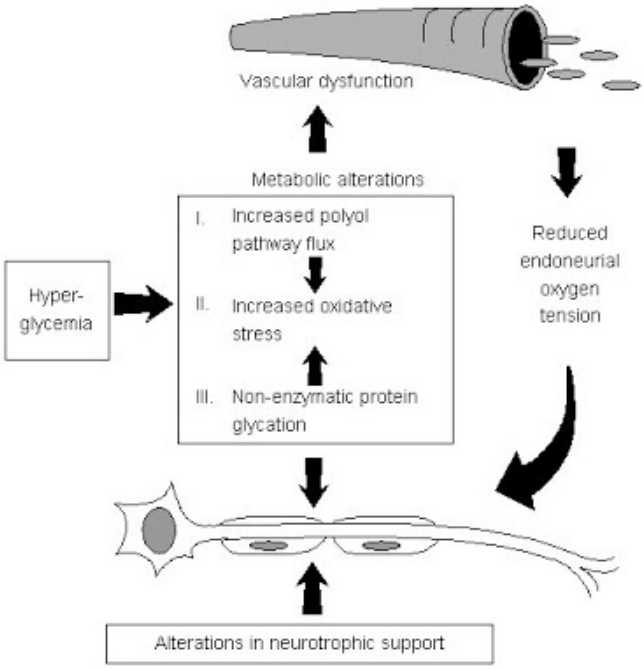

Figure 1. The neurodestructive effects of hyperglycemia

Increased polyol pathway flux. Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myoinositol, decreased membrane Na^+/K^+-ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation.[16]

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

Oxidative Stress. Glucose can cause significant oxidative stress and damage when present in excess in the body. Under physiological conditions, aerobic respiration is associated with the formation of a small amount of free radicals (ROS). In a hyperglycemic state, however, particularly in endothelial cells which do not have the ability to limit glucose entry into the cell, glucose accumulation exceeds the levels that glycolytic enzymes can handle.[17] The flood of excess glucose into endothelial

cells is shunted into alternate metabolic pathways (e.g. polyol pathway, glycosylation, hexosamine pathway, the diacylglycerol activation of protein kinase C [PKC], etc.). These pathways, particularly PKC, produce significantly larger amounts of ROS than aerobic respiration, overwhelming compensatory antioxidant mechanisms.[18-25] The resulting hyperglycemic oxidative stress contributes to endothelial dysfunction by inhibiting endothelial nitric oxide (NO) production and by initiating and promoting the deposition of modified lipids in the subendothelium. These factors accelerate atherosclerotic macrovascular disease, and is associated with the development of apoptosis in neurons and supporting glial cells.[15 26]

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

1.2. CURRENT TREATMENT OPTIONS

Currently, there are no approved drugs or interventional strategies known to halt or reverse the progression of DPN. Treatments target pain reduction, physical function improvement, reduction of psychological distress, and quality of life improvements.[5]

1.2.1. PREVENTIVE TREATMENT

Glycemic control. It is generally agreed that long-term complications of both type 1 and type 2 diabetes can be reduced by tight glycemic control. To date, this is the only intervention specifically shown to arrest or postpone the onset and severity of peripheral neuropathy.[27-29]

Modifiable risk factors. The incidence of neuropathy is also associated with potentially modifiable cardiovascular risk factors, including an elevated triglyceride level, a high body mass index (BMI), smoking, and hypertension.[30]

Foot care. Patients with diabetes also need to be educated about foot care and footwear, and about protection of hyposensitive areas and pressure points, to prevent the occurrence of ulcers and to decrease the risk of bone infection.[31]

1.2.2. MEDICAL MANAGEMENT

There are only two drugs approved by FDA specifically for the treatment of the symptoms of DPN: Cymbalta – (duloxetine), a serotonin and norepinephrine reuptake inhibitor; and Lyrica – (pregabalin), an anticonvulsant drug. Both are prescribed for the management of pain associated with diabetic peripheral neuropathy. Table 1 presents the Diabetic Peripheral Neuropathic Pain Consensus Treatment Guidelines Advisory Board's recommendations for first- and second-tier

agents to treat DPN based on the level of evidence available from clinical trials and the committee's clinical experience.[1]

Table 1. First and second tier recommendations for pain management in DPN

Agent Type	Reason for Recommendation	Agent Names
First Tier	≥2 RCTs in DPN	Duloxetine, oxycodone CR, pregabalin, TCAs
Second Tier	1 RCT in DPN; ≥1 in other painful neuropathies	Carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine ER
Topical	Mechanism of action	Capsaicin, lidocaine
Other	≥1 RCTs in other painful neuropathies or other evidence	Bupropion, citalopram, methadone, paroxetine, phenytoin, topiramate

CR = controlled release; DPN = diabetic peripheral neuropathy; ER = extended release; RCT = randomized controlled trial; TCAs = tricyclic antidepressants.

1.2.3. Other Treatment Options

α-lipoic acid. α-lipoic acid is a naturally occurring antioxidant compound that can be purchased as a dietary supplement. It is synthesized in small amounts by humans and found in various plants such as spinach and broccoli. α-lipoic acid was recently studied in a multicenter placebo-controlled trial of subjects with type 2 diabetes and symptomatic neuropathy. One hundred eighty-one (181) subjects were given a once daily oral doses of 600 mg, 1200 mg or 1800 mg of α-lipoic acid or placebo. After 5 weeks, neuropathic symptoms improved in those subjects that received α-lipoic acid. The 600 mg dose appeared to provide the optimum risk-to-benefit ratio.[32]

Nerve decompression surgery. Surgery to decompress the lower-extremity peripheral nerves in patients with DPN is still considered an experimental intervention. Results of a comprehensive meta-analysis of studies of nerve decompression in DPN subjects had mixed results.[33]

Pancreatic transplantation. Pancreatic transplantation in patients with diabetes can stabilize neuropathy and in some instances improve motor, sensory, and autonomic function.[34]

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

1.2.4. UNMET CLINICAL NEED

Peripheral neuropathy is a serious complication of diabetes. This form of neuropathy carries a high risk of pain, trophic changes and autonomic dysfunction. Treatment of DPN is based on either pathogenetic mechanisms or symptomatic relief. A number of clinical trials have established symptomatic treatment but for pathogenetic mechanisms, the only proven treatment strategy is strict glycemic control. Clearly, it would be desirable to prevent, impede, or reverse the disrupting and often life-threatening manifestations of peripheral neuropathy by stimulating growth or regeneration of peripheral nerve axons.

1.3. HGF FOR THE TREATMENT OF DIABETIC 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.[35,36] It is a multi-functional mesenchyme-derived cytokine with potent angiogenic and anti-apoptotic effects [35-38] HGF stimulates DNA, RNA and protein synthesis by endothelial cells in a dose-dependent manner and attenuates high D-glucose-induced endothelial cell death. [35,37] HGF has also been shown to upregulate vascular endothelial growth factor (VEGF) expression, and has demonstrated greater mitogenic activity than that of VEGF alone in human aortic endothelial cells *in vitro*.[39,40]

Recent research also indicates that HGF can function as a neurotrophic factor.[41] Sympathetic neurons co-express bioactive HGF, its cognate receptor (the Met receptor), and localized exogenous HGF has been shown to promote the growth (but not survival) of sympathetic neurons,[42-46] and to induce the formation of collateral vessels and increased blood flow both in rat diabetic and non-diabetic hind limb ischemia models.[47,48] 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,[49] HGF may be an ideally suited candidate for the treatment this condition. Exogenous VEGF has been studied in this patient population, but with limited success.[50-53]

The challenge associated with delivering a targeted sustained dose of exogenous HGF is in overcoming the instability of HGF in blood circulation and its rapid clearance by the liver; HGF has an *in vivo* half-life of less than 15 minutes.[54,55]

One approach to increasing HGF in ischemic tissues is to develop a gene transfer strategy that would allow for persistent expression of HGF protein *in vivo*. Although plasmid DNA is one of the least efficient gene transfer systems currently in use, the fact that it is associated with limited persistence and no propensity for genomic integration, (particularly in skeletal muscle tissue) makes it an attractive option for local targeted delivery.

1.4. VM202

The investigational agent being studied in this protocol is VM202. 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].

The key feature of HGF [redacted] is that it was designed by [redacted] so that both isoforms of HGF protein are expressed simultaneously and efficiently as in the human genome. Because there is no change in the coding region of the HGF gene, HGF proteins generated from VM202 are identical to the wild-type human HGF proteins.

Figure 2. VM202 construct

Safety of VM202. The use of plasmids for targeted delivery of angiogenic factors into muscle tissue is a particularly attractive and a relatively safe therapeutic approach, because plasmids have been shown to effectively transfect postmitotic cells such as skeletal and heart muscle and to successfully express angiogenic genes with very little dissemination and persistence at distant sites. Following intramuscular injection, the plasmid that persists is extrachromosomal and integration into host DNA, if it occurs, is negligible.[56-58] This local effect of conventionally injected naked plasmid DNA is well known.[59,60]

VM202 more efficiently induced migration of human umbilical vein endothelial cells and C2C12 cells when compared to DNAs expressing either of two isoforms, and it also improved cardiac function in a rat ischemic heart disease model more efficiently than an identical vector encoding only HGF_{728}.[61,62] Consistent with these preclinical data, an open label phase I/II study in painful diabetic peripheral neuropathy and a phase I/II trial for critical limb ischemia showed that VM202 is safe and well tolerated.[63,64]

Potential Efficacy of VM202. The design of the phase II study of VM202 in patients with DPN closely followed the design of the pivotal studies used to approve Lyrica and Cymbalta, with the exception that follow-up was for 9 months after a single index administration (delivered as a divided dose on day 0 and Day 14).

Eligible subjects were randomized 2:2:1 to the low dose VM202 [redacted] mg VM202 / leg, [redacted] mg total, n=[redacted], high dose VM202 ([redacted] mg VM202 / leg, [redacted] mg total, n=[redacted]), or placebo (normal saline, n=21). Key findings from the phase II VM202 study included:

- VM202 injections were well tolerated:
  - Other than Grade 1 injection site reactions (pain, itching and / or swelling), which all resolved before the 3-month visit, there were no adverse events deemed related to the study drug or study injections.
  - There were no unanticipated serious adverse events.
  - Ten subjects experienced thirteen serious adverse events over the course of the study (10/103, 9.7%). There was no significant difference in the incidence of SAEs across treatment groups. All SAEs except one in the Placebo group (Melanoma) were resolved at study exit.
  - None of the withdrawals (n=7) were due to a study related adverse event.
- Pain reduction reported in Low Dose VM202 Group was clinically meaningful:
  - Reductions in pain (as measured by the 7 Day Pain and Sleep Interference Diary which rated pain on a 0 – 10 point scale) were of similar magnitude to those experienced in the studies of Cymbalta and Lyrica (see medical reviews in respective NDAs).
  - Mean reduction in pain for the Low Dose Group (8 mg VM202 / leg, total dose 16 mg VM202) at 3 months was -3.03 points as compared to a -1.53 point reduction in the Placebo arm, for a net treatment effect of -1.5 points ($p = 0.033$)
  - Studies that demonstrated a significant reduction in pain for both Cymbalta and Lyrica showed a net pain reduction of -1 – -1.3 (includes range of both the BOCF and LOCF analyses in medical reviews).
  - Patients in the Low Dose Group that were not on Gabapentin and Pregabalin experienced greater reductions in pain at 3 months. The net pain reduction was -2.37 ($p = 0.006$).
  - 48.4% of subjects in the Low Dose arm experienced a ≥ 50% reduction in pain at 3 Months, as compared to 17.6% of Placebo patients ($p = 0.06$), and 29.3% - 38.3% of patients in the three successful studies of Lyrica (using same definition for 'responder'). The Cymbalta studies used a less stringent definition of responder (≥ 30% reduction in pain), so we did not have the ability to directly compare the results.

A pivotal phase III study of VM202 in patients with DPN is warranted.

1.5. PRECLINICAL DATA

The non-clinical safety of VM202 has been evaluated for general toxicity following single intramuscular and intravenous doses in rats. In addition, the general toxicity of VM202 following multiple intermittent (weekly or monthly) intramuscular doses has been evaluated in rabbits and rats, respectively. The potential for genomic

integration at the injection site as well as the potential for distribution to and persistence of VM202 in reproductive tissues was evaluated in rats. The ability of VM202 to induce humoral immune responses was evaluated following intramuscular administration with or without adjuvant in mice. All species utilized for these studies (mouse, rat, and rabbit) were shown in *in vivo* experiments to be able to express the plasmid following intramuscular injection.

An ischemic heart disease efficacy study in a Yorkshire swine model demonstrated that intramyocardial administration of VM202 increased the capillary density and regional perfusion in ischemic myocardium and improved ischemic left ventricular function. An ischemic heart disease efficacy study in rats demonstrated that histologically identifiable capillaries increased following intramuscular administration of VM202 (versus pCK and pCK-VEGF165; $p < 0.001$).

Collectively, VM202 has been well-tolerated in all studies conducted to date, with the only evidence of toxicity consisting of mild, transient injection site irritation in rats at a dose level 11 times the clinical dose of 8 mg / leg (0.11 mg/kg for a 70 kg subject). There has been no evidence of systemic toxicity in any study and human HGF has not been detected in the sera of rats or rabbits following intramuscular injection [lower limit of quantitation (LLOQ) = 125 pg/mL]. There is no evidence of genomic integration, potential germ cell transmission, or immunostimulatory effects following intramuscular administration of VM202 to animals.

Therefore, the nonclinical efficacy and safety studies support the clinical investigation of VM202 in subjects with painful diabetic peripheral neuropathy.

1.6. CLINICAL DATA

VM202 was/is being evaluated in seven clinical trials in the US.

1.6.1. PHASE I STUDY IN CRITICAL LIMB ISCHEMIA

VM202 was evaluated for treatment of critical limb ischemia (CLI) in a prospective, dose-escalation Phase I study. The study consisted of four (4) cohorts of three (3) 'no-option' CLI subjects. Subjects received [redacted] mg, [redacted] mg, [redacted] mg, or [redacted] mg VM202. For each dose cohort, VM202 was administered as local intramuscular injections with half of the dose administered at Day 0 of the study and the second half administered 2 weeks later. Preliminary efficacy (hemodynamic assessments), safety and tolerability were evaluated at Baseline (screening) and at designated time points throughout the study. Clinical evaluations were conducted at baseline, Days 15, 28, 59, 91, 180, and 365. All dose cohorts were followed for a year from the time of the first dose of study drug administration.

Between March of 2007 and October of 2008, twelve (12) subjects participated in the study (median age, 72 years, 53% male and 75% were a current or former smoker). No deaths occurred during the 12 month follow up, but one subject underwent a major amputation. Median ankle/brachial index (ABI) and toe brachial

index (TBI) significantly increased from 0.35 to 0.52 (p=0.005) and 0.15 to 0.24 (p=0.01*)* at 12 months follow-up. Transcutaneous pressure of oxygen ($TcPO_2$) showed an improvement trend (increase). A significant reduction in pain was reported by nine of eleven subjects, with median visual analog scale (VAS) decreasing from 58 to 16 (p=0.03) at 6 months follow-up. VAS score reduction tracked well with the hemodynamic data.

In general, there was more improvement over baseline in Cohort II ([redacted] mg VM202) than in any other cohort. Cohort I ([redacted] mg of VM202) also experienced a significant reduction in pain and modest improvement in hemodynamic measurement. Interestingly, 2 subjects in each of these cohorts had diabetes, possibly suggesting some benefit of VM202 in this subpopulation. Doses of aspirin above 81 mg daily may have an inhibitory effect on the therapeutic activity of VM202.

VM202 appears to be well tolerated at doses as high as [redacted] mg. There were no unexpected adverse events in the study. None of the serious adverse events (SAEs) were directly attributable to VM202 (eight SAEs in five subjects, 5/12, 41.7%). There was one amputation caused by osteomyelitis which was assessed as unrelated to VM202. Results from this study were published in *Gene Therapy* in 2011.[64]

1.6.2. PHASE II STUDY IN CRITICAL LIMB ISCHEMIA

VM202 was evaluated for treatment of CLI in a prospective, double-blind, placebo-controlled, multicenter Phase II study. A total of 50 eligible 'no-option' CLI subjects with a Rutherford Scale score of 4 or 5 were randomized in 2:2:1 ratio to a low dose of VM202, high dose of VM202 or placebo. Subjects received a final dose of [redacted] mg VM202, [redacted] mg VM202 or placebo by IM injections in the affected, unilateral calf on Days 0, 14, 28, and 42. All subjects were followed for one year from the time of the first dose of study drug administration. Clinical evaluations were conducted at Day 0 (baseline), 14, 28, 42, 49, 90, 180, 270, and 365.

Efficacy was evaluated in the Efficacy Population (n = 50, defined as subjects that received all study injections). Improvements were statistically significant for wound healing in both treatment groups.

- Ulcers improved most in the high dose group when compared to placebo. The average decrease in wound area in the high dose group was 2.8 cm^2 (SD 0.3 cm^2). Nine of the 14 ulcers present at baseline in the high dose group completely healed (9/14, 64.3%); all but one ulcer that did not completely heal showed improvement.
- Fourteen of 27 (14/27, 51.9%) ulcers in the low dose group healed; of the 13 that did not completely heal, 8 (8/13, 61.5%) improved (average decrease 1.3 cm^2, SD 1.1 cm^2).
- Only one ulcer present at baseline in the placebo group healed (1/9, 11.1%). The average *increase* in wound area in the placebo group was 4.3 cm^2 (SD 12.6 cm^2).

Improvements in skin perfusion (as measured by $TcPO_2$) in both treatment groups were also significantly improved in the dorsum foot when compared to placebo in

both treatment arms (low dose, p = 0.0299; high dose, p = 0.0681; treatment groups combined, p = 0.0475).

By the 3-month study visit, all three study arms experienced a reduction in pain with sustained reductions over the 12 month follow-up period, but only the two treatment arms had a statistically significant reduction compared to baseline. There was a greater relative reduction in pain from baseline in the high dose group at 6 and 9 months (-21.8, p=0.008, and -33.4, p=0.0018, respectively).

ABI and TBI trended towards improvement over the course of the study in all three study arms, but there were no statistically significant differences between treatment groups.

There was no statistically significant difference in Rutherford scores across treatment groups at any time, but a pairwise comparison to baseline in the low dose group demonstrated a statistically significant improvement at 6, 9 and 12 months (p = 0.0016, p = 0.0012, p = 0008, respectively).

When considering the biological activity of VM202, amputation rates were lower in the low dose and high dose groups (2.5%) as compared to the placebo group (20%).

Intramuscular injections of VM202 in the lower leg were well tolerated. There were no unexpected adverse events in the study. Overall, 26 subjects experienced 67 serious adverse events over the course of the study (26/52, 50%). With the exception of thrombosis in the high dose group (placebo = 0%, low dose = 0%, high dose = 15%), there was no significant difference in the incidence of SAEs across treatment groups. One incident of peroneal deep vein thrombosis was categorized as possibly related to the study injection. All other SAEs were deemed unrelated to the study drug / placebo. The majority of SAEs were related to the natural progression of peripheral arterial disease (PAD).

In conclusion, VM202 significantly improved wound healing, improved skin perfusion (as measured by TcPO2), and reduced pain. Positive trends were seen in Rutherford classification and in measureable pressures (ABI/TBI). There appeared to be a significant dose response. The number and types of adverse events seen in this study were consistent with those reported in the literature for other interventional studies in patients with CLI. VM202 continues to demonstrate an excellent safety profile.

1.6.3. PHASE I/II STUDY IN SUBJECTS WITH PAINFUL DPN

VM202 was evaluated for treatment of DPN in a prospective, dose-escalation Phase I study. The study consisted of three (3) cohorts of four (4) subjects. Subjects received [redacted] mg, [redacted] mg, or [redacted] mg VM202 unilaterally in a calf. For each dose cohort, VM202 was administered as local intramuscular injections with half of the dose administered at Day 0 of the study and the second half administered 2 weeks later.

Preliminary efficacy (hemodynamic assessments), safety and tolerability were evaluated at Baseline (screening) and at designated time points throughout the study. All 3 dose cohorts were followed for one year from the time of the first dose of study drug administration. Between June 2010 and March 2011, twelve (12) subjects were enrolled in the study, and enrollment and follow-up are complete.

Ten out of 12 subjects (10/12, 83%) experienced a reduction in pain at their 6-month visit. One subject each in Cohort I and Cohort II did not experience a reduction in pain. At 6 months, mean change in VAS was -8.2 in Cohort I, -31.6 in Cohort II and -25 in Cohort III.

At 12 months, 9 out of 12 subjects (9/12, 75%) experienced a reduction in pain. The same 2 subjects, one each in Cohort I and Cohort II did not experience a reduction in pain, and one subject in Cohort III returned to baseline levels at 12 months. At 12 months, mean change in VAS was -12.0 in Cohort I, -32.8 in Cohort II and -18.5 in Cohort III. VAS scores also tracked well with other quality of life measures (Brief Pain Inventory for Diabetic Peripheral Nephropathy [BPI-DPN]).

Intramuscular injections of VM202 appear to be well tolerated at doses as high as [redacted] mg in subjects with DPN. There were no incidents of dose limiting toxicities (DLT). There have been no serious or unexpected adverse events in the study. The level of VM202 DNA was below the LLOQ in all 12 subjects by day 90. Circulating HGF levels remained relatively constant throughout the study, suggesting that the plasmid remained active only at the injection site. Results from this study were published in *Molecular Therapy* in 2013.[63]

1.6.4. PHASE II STUDY IN SUBJECTS WITH PAINFUL DPN

VM202 was evaluated for treatment of DPN in a multi-center, phase II, double-blind, randomized, placebo-controlled, study. The study enrolled subjects with DPN with significant pain at study entry. Pain was evaluated at initial screening using the VAS. A score of ≥ 4 cm (scale 0 - 10cm) was required for continued screening. Pain levels were confirmed by completion of a Daily Pain and Sleep Interference Diary after prohibited medication wash-out. DPN was verified, as in other studies, symptomatically, using the Michigan Neuropathy Screening Instrument (MNSI). The Brief Peripheral Neuropathy Screening (BPNS) was used to confirm bilateral involvement.

Eligible subjects were randomized 2:2:1 to the low dose VM202 ([redacted] mg VM202 / leg, [redacted] mg total, n=40), high dose VM202 ([redacted] mg VM202 / leg, [redacted] mg total, n=[redacted]), or placebo (normal saline, n=21). Clinical assessments were performed at Day 0 (baseline), Day 14, Day 21, Day 30, Day 60, 3 Months, 6 Months, and 9 Months.

Subjects that received VM202 injections improved more than subjects that received only placebo injections in most efficacy measures. Subjects in the low dose VM202 arm improved the most in all efficacy measures. Improvements were statistically significant when compared to placebo at 3 months for the mean reduction in pain (as

measured by the 7 Day Pain and Sleep Interference Diary, p = 0.033), and were of similar magnitude as improvements demonstrated in studies of pregabalin.

48.4% of subjects in the low dose VM202 arm experienced a ≥ 50% reduction in pain at 3 months, as compared to 17.6% of placebo subjects (p = 0.06). The low dose VM202 arm demonstrated significant improvements as measured by the BPI-DPN quality of life measure at 3 months and 6 months in both sections of this instrument: pain severity, p = 0.064 and p = 0.053, respectively; and pain interference, p = 0.046, p = 0.046, respectively.

The low dose VM202 arm showed significant improvements in the questionnaire portion of the MNSI at 6 months (p = 0.024). Although there were no significant differences between study groups in the physical assessment portion of the MNSI, when the monofilament testing was examined, as a stand-alone evaluation, there was an improvement trend in the low dose VM202 arm at 6 months, with continued improvement at 9 months. The low dose VM202 group maintained or improved sensitivity in the foot two-fold over placebo.

An important, unanticipated finding in the study was that subjects not on pregabalin or gabapentin during the study experienced even greater improvements in pain reduction at all time-points for both doses of VM202 (although the low dose VM202 was still superior to the high dose VM202).

Intramuscular injections of VM202 were well tolerated. No deaths or unanticipated adverse events were reported. Over the course of the study, ten (10) subjects in the as-treated (safety) population experienced 13 SAEs. Four subjects in the high dose VM202 group experienced 5 SAEs (4/43, 9.3%); 3 subjects in the low dose VM202 group experienced 3 SAEs (3/39, 7.7%); and 3 subjects in the placebo group experienced 5 SAEs (3/21, 14.3%). All SAEs were classified as unrelated to study drug / placebo.

A total of 45 Grade 1 minor injection site reactions (i.e., pain, itching, erythema, and/or bruising) were reported. Over the course of the study, 202 non-serious adverse events (AEs) were reported for 69 subjects (69/103, 67%). Most non-serious AEs (150/202, 74%) were resolved at study closure and the majority of the non-serious AEs (126/202, 62%) were considered mild in severity.

Copies of VM202 in whole blood were greatly reduced or completely negative within one week after final VM202 dosing (Day 21). Serum HGF levels remained relatively constant throughout the study.

The results from this study suggest that VM202 provides the same magnitude of pain relief as reported with pregabalin or gabapentin. A pivotal study in subjects with DPN is warranted.

1.6.5. PHASE I/II STUDY IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Helixmith Co., Ltd is currently conducting a Phase I/II, open label, single center study to assess the safety and tolerability of VM202 in 18 subjects diagnosed with clinically definite, clinically probable, or clinically probable-laboratory supported ALS. Enrollment is complete and follow-up is ongoing. Prior to injections on Day 0, subjects were assessed using the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), the Medical Research Council (MRC) scale for muscle strength testing, dynamometry, forced vital capacity (FVC), and muscle circumference.

All subjects received a total of [redacted] mg of VM202 IM in the upper limbs (abductor pollicis brevis, first dorsal interosseous, biceps, deltoid, extensor carpi radialis, flexor carpi ulnaris, and flexor carpi radialis) and lower limbs (quadriceps, gastrocnemius, and tibialis anterior). VM202 was administered over the course of four visits: Day 0, Day 7, Day 14, and Day 21. As in all previous VM202 studies, final dose of VM202 for each target muscle group is divided and administered 2 weeks apart. However, in order to reduce the injection burden on the ALS subject, injection of the upper limbs will be done on separate visits from injection of the lower limbs.

Post-injection, ALSFRS-R, FVC and muscle strength (as determined by the MRC scale) were/will be assessed at Day 30, Day 60, Day 90, at 6 months and 9 months. Muscle circumference and dynamometry will be conducted on Day 60, Day 90, at 6 months, and 9 months. Subjects will be followed up at 12, 18, 24, and 36 months by phone to assess survival.

As of September 9, 2015, all subjects had reached the 9-month follow-up visit, and long-term follow-up through 36 months to determine vital status is ongoing. One subject died prior to the 9-month visit, and 2 subjects died following the 9-month visit; all 3 subjects died due to respiratory failure associated with ALS. Four additional SAEs that required hospitalization were reported. All deaths and SAEs were classified as unrelated to the study drug. Injection site reactions have been limited to pain, and/or bruising.

1.6.6. CLINICAL EXPERIENCE CONCLUSIONS

Data collected to date data support the feasibility and safety of intramuscular injections of VM202 in subjects with critical limb ischemia and DPN. Results suggest that this therapeutic approach may improve functional outcomes and provide symptomatic relief. VM202 is rapidly eliminated from circulation, and appears to remain active only at the injection site. The incidence of complications did not appear to be significantly different between treatment cohorts. Continued study of VM202 in subjects with CLI and DPN is warranted.

1.7. STUDY AND DOSE RATIONALE

Diabetic peripheral neuropathy, by definition, is a bilateral neuropathy. Treating only one leg may confound patient-reported pain levels and quality of life measures. Based on the excellent safety profile of VM202 observed in the phase I and phase II CLI studies and the safety and preliminary efficacy data from the phase I/II studies of VM202 injections in subjects with DPN, we propose continued bilateral treatment in this phase III study.

One dose of VM202 will be tested against placebo (VM202 vehicle). The total dose of VM202 per leg will remain within the dosing scheme of the phase II study ([redacted] mg / leg, for a total of [redacted] mg / subject). However, instead of two treatments of intramuscular injections in the calf (on Day 0 and Day 14), as performed in the prior DPN studies, subjects will receive VM202 or placebo (VM202 vehicle) by intramuscular injections in both legs (in the calf) on Day 0, and Day 14, followed by a second treatment on Day 90 and Day 104. Studies have shown that copies of VM202 in whole blood were greatly reduced or completely negative within one week after final VM202 dosing (Day 21). Serum HGF levels remained relatively constant throughout the study. The phase II DPN study showed greater improvements at 3 months than 6 months indicating that the effects of VM202 attenuate over time justifying a second treatment in the current study.

As in all prior/ongoing studies, VM202 will be delivered in a solution of [redacted] mg VM202 / mL. Subjects will be treated with an overall final dose of [redacted] mg VM202 or placebo, dosages well within those supported by the body of pharmacology and toxicology safety studies of VM202. No toxicities were reported in the phase II DPN study. Safety studies in rabbit, rat and mouse models demonstrate that doses approximately 2½ ([redacted] mg/[redacted] kg) to 30 ([redacted] mg/[redacted] kg) times the clinical dose ([redacted] mg) proposed in this study are safe and resulted in no toxicities.

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) and an Institutional Biosafety Committee (IBC). 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 and IBC per each institution's guidelines.

3. INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

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

3.2. STUDY DESIGN

This is 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 with painful DPN will be screened for study eligibility after giving informed consent.

Initial Screening Activities. Prior to screening, subjects will provide informed consent and then be initially screened using the VAS, the symptoms portion of the BPNS and the MNSI. Only subjects with a VAS score of ≥ 40 mm, a ≤ 5-point difference in symptom of BPNS between legs and MNSI score of ≥ 3 will be allowed to proceed with the full screening procedures.

Screening. If the VAS, BPNS and MNSI criteria are met, the rest of screening will proceed. If applicable, the subject will be washed out of prohibited medications. During medication wash-out, screening procedures consisting of assessment of study eligibility, a complete medical history, vital signs, physical exam, concomitant medications, cancer screening tests, viral screening, 12 lead EKG, retinal fundoscopy, serum chemistry, hematology, including HbA1c, and urine pregnancy test (women of childbearing potential only) may occur.

If applicable, the subject will be washed out of prohibited medications 14 days prior to initiation of the 7-day Daily Pain and Sleep Interference Diary. The Daily Pain and Sleep Interference Diary must be completed within 14 days of the first injections. Subjects will be asked to rate their 24-hour average daily pain intensity score using an 11-point numerical scale with 0 = no pain – 10 = worst pain possible, and to evaluate how much their pain interferes with sleep (also an 11 point numerical rating scale from 0 (did not interfere with sleep) to 10 (completely interfered with sleep; subject was not able to sleep due to pain). The subject must record at least five assessments of the 24-hour average daily pain intensity score during the seven-day period. The mean baseline 24-hour will represent the baseline reference value. The average daily pain intensity score of the Daily Pain and Sleep Interference Diary must be ≥ 4 with a standard deviation ≤ 2 in order to be eligible for study participation.

Data from the Daily Pain and Sleep Interference Diary at screening and BPI-DPN on Day 0 will represent the baseline reference values.

All screening assessments should occur within the 90 days prior to Day 0 (day of first injections), and the diary must be completed within 14 days prior to Day 0.

Randomization. Subjects who meet the eligibility criteria will be randomly assigned in a 2:1 fashion to one of the two treatment arms: VM202 (32 mg VM202 total dose, 16 mg / leg), or placebo, respectively. Randomization will be stratified by current use of gabapentin and/or pregabalin. Assignment to a treatment arm will be centralized, using an independent predetermined randomization scheme in a double-blinded fashion. Blinding will be achieved by having the study medication (VM202 and placebo [VM202 vehicle]) prepared by the study pharmacist. Reconstituted VM202 is indistinguishable from the VM202 vehicle.

First Treatment. Prior to the first injection, vital signs, concomitant medications, VAS, BPI-DPN, Semmes-Weinstein monofilament testing, and nerve conduction (only at select sites), testing will be conducted. In addition, blood will be drawn for determination of serum chemistry and hematology, HbA1c, serum HGF, and copies of VM202.

Subjects will receive VM202 or placebo (VM202 vehicle) by intramuscular injections in both legs (in the calf) on Day 0, and Day 14 as follows:

Table 2. First Treatment: Day 0 and 14

TREATMENT GROUP	DOSE VM202 (mg) / VISIT / LEG		FINAL DOSE VM202 / LEG (mg)	FINAL DOSE VM202 / SUBJECT / TREATMENT (mg)
	DAY 0	DAY 14		
VM202	4	4	8	16
Placebo	0	0	0	0

0 = injections of VM202 vehicle

All subjects will receive sixteen (16) 0.5 mL injections evenly distributed over each calf at each visit of VM202 or placebo.

Subjects randomized to the VM202 treatment arm will receive the following intramuscular injections in each calf:

- Day 0 – 16 injections of 0.5mL of VM202 / calf
- Day 14 – 16 injections of 0.5mL of VM202 / calf

Subjects randomized to the placebo control group will receive the following intramuscular injections in each calf:

- Day 0 – 16 injections of 0.5mL of VM202 vehicle / calf
- Day 14 – 16 injections of 0.5mL of VM202 vehicle / calf

Note: Visually, VM202 vehicle is indistinguishable from reconstituted VM202. The subject and clinician will not be able to distinguish placebo from VM202 injections.

1 to 3 hours post injection on Day 0 and Day 14, vital signs, and blood draw for determination of copies of VM202 will be performed, and the occurrence of injection site reactions and adverse events will be assessed.

Subjects will be assessed at Day 21 and Day 60; at both visits, vital signs, and concomitant medications will be determined. Blood will be drawn for determination of serum HGF, and copies of VM202. The occurrence of injection site reactions and adverse events will be assessed.

Within 14 days of the Day 90 visit, the Daily Pain and Sleep Interference Diary will be completed.

Second Treatment. Prior to the second treatment on Day 90, vital signs, concomitant medications, VAS, BPI-DPN, PGIC, and Semmes-Weinstein monofilament testing will be conducted. Blood will be drawn for determination of serum chemistry and hematology, HbA1c, serum HGF, and copies of VM202. The occurrence of injection site reactions and adverse events will be assessed.

Subjects will receive the prior randomly assigned treatment (VM202 or placebo/VM202 vehicle) by intramuscular injections in both calves on Day 90, and Day 104 as follows:

Table 3. Second Treatment: Day 90 and 104

TREATMENT GROUP	DOSE VM202 (mg) / VISIT / LEG		FINAL DOSE VM202 / LEG (mg)	FINAL DOSE VM202 / SUBJECT / TREATMENT (mg)
	DAY 90	DAY 104		
VM202	4	4	8	16
Placebo	0	0	0	0

0 = injections of VM202 vehicle

Note, the Day 104 visit will be scheduled 14 days ± 1 day following the Day 90 visit.

All subjects will receive sixteen (16) 0.5 mL injections evenly distributed over each calf at each visit of VM202 or placebo.

Subjects randomized to the VM202 treatment arm will receive the following intramuscular injections in each calf:

- Day 90 – 16 injections of 0.5mL of VM202 / calf
- Day 104 – 16 injections of 0.5mL of VM202 / calf

Subjects in the placebo control group will receive the following intramuscular injections in each calf:

- Day 90 – 16 injections of 0.5mL of VM202 vehicle / calf

- Day 104 – 16 injections of 0.5mL of VM202 vehicle / calf

1 to 3 hours post injection on Day 90 and Day 104, vital signs, and blood draw for determination of copies of VM202 will be performed, and the occurrence of injection site reactions and adverse events will be assessed.

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 21, Day 60, immediately pre-treatment on Day 90, immediately pre-treatment on Day 104, Day 111, Day 150, Day 180 and Day 270.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 21, Day 60, at Day 90 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 104 (pre-injection, and 2 hours [± 1 hour] post injection), Day 111, Day 150, Day 180 and Day 270.

Serum chemistry, hematology and HbA1c will be determined on Day 0, Day 90, Day 180, and Day 270.

VAS, BPI-DPN, and Semmes Weinstein monofilament testing will be recorded at Day 0, Day 90, Day 180, and Day 270. Patients' Global Impression of Change (PGIC) will be recorded at Day 90, Day 180 and Day 270. MNSI will be conducted at Day 180 and Day 270 to track disease progression.

The Daily Pain and Sleep Interference Diary will be completed by subjects before the Day 90, Day 180, and Day 270 visits.

Nerve conduction will be conducted on Day 0, Day 180 and Day 270 at select sites. Retinal fundoscopy will be conducted at Day 180 and Day 270. Rescue medication (i.e., Acetaminophen [Tylenol]) taken for DPN pain will be dispensed on Day 0 and use will be documented throughout the 9-month follow-up visit.

Adverse events, concomitant medications and vital signs will be recorded throughout the 9-month follow-up period, while injection site reactions will be assessed through Day 150.

A summary of the schedule of evaluations and visits can be found in Appendix 1.

3.3. SUBJECT POPULATION

A total of 477 evaluable subjects with DPN meeting the following study entry criteria will be enrolled.

3.3.1. INCLUSION CRITERIA

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

1. Age ≥ 18 years to ≤ 75 years;
2. Documented history of Type I or II diabetes with current treatment control (glycosylated hemoglobin A_{1c} of ≤ 10.0% at Screening) and currently on medication for diabetes (oral, injectable and / or insulin);
3. No significant changes anticipated in diabetes medication regimen;
4. No new symptoms associated with diabetes within the last 3 months prior to study entry†;
5. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities;
6. Lower extremity pain for at least 6 months;
7. Visual analog scale (VAS) score of ≥ 40 mm at Initial Screening (0 mm = no pain – 100 mm very severe pain);
8. Symptoms from the Brief Peripheral Neuropathy Screening (BPNS) is ≤ 5-point difference between legs at Initial Screening;
9. The average daily pain intensity score of the Daily Pain and Sleep Interference Diary completed after medication wash-out is ≥ 4 with a standard deviation ≤ 2;
10. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Screening;
11. Subjects on gabapentin (Neurontin), pregabalin (Lyrica), duloxetine (Cymbalta) for painful DPN at study entry† must be on stable regimen of these treatments for at least 3 months prior to study entry†; and
12. If female of childbearing potential, negative urine pregnancy test at screening and using acceptable method of birth control during the study.

3.3.2. EXCLUSION CRITERIA

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

1. Peripheral neuropathy caused by condition other than diabetes;
2. Other pain more severe than neuropathic pain that would prevent assessment of DPN;
3. Progressive or degenerative neurological disorder;
4. Myopathy;
5. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
6. Active infection;
7. Chronic inflammatory disease (e.g., Crohn's disease, rheumatoid arthritis);
8. Positive HIV or HTLV at Screening;
9. Active Hepatitis B or C as determined by Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening;

† Study entry is defined as the date of signing informed consent.

10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy;
11. Stroke or myocardial infarction within last 3 months;
12. Clinically significant laboratory values at Screening (e.g., Hemoglobin < 8.0 g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm^3, Creatinine > 2.0 mg/dL; AST and/or ALT > 3 times the upper limit of normal or any other clinically significant lab abnormality) which, in the opinion of the investigator should be exclusionary;
13. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination
14. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at Screening;
15. Subjects with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence for one year); subjects with medical history and/or family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
16. Use of the following drugs / therapeutics is **PROHIBITED**. Subjects may participate in the study if they are willing to discontinue use of these drugs / therapeutics ***7 days prior to starting the Daily Pain and Sleep Interference Diary***. Subjects must refrain from taking these drugs or undergoing these therapies for the duration of the study:

    - skeletal muscle relaxants, opioids, benzodiazepines (except for stable bedtime dose),
    - capsaicin, local anesthetic creams (except for Lidocaine cream prior to IM injection) and patches, isosorbide dinitrate (ISDN) spray,
    - transcutaneous electrical nerve stimulation (TENS), acupuncture

17. If not using gabapentin (Neurontin) or pregabalin (Lyrica), subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on these medications at study entry† must maintain a stable dose until Day 180 visit of the study;
18. If not using duloxetine (Cymbalta), any antidepressants (e.g. amitriptyline and venlafaxine), any other antiepileptics (e.g., valproic acid, carbamazepine, vigabatrin), subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on these medications at study entry† must maintain a stable dose until Day 180 visit of the study;
19. Subjects requiring > 81 mg daily of acetylsalicylic acid; subjects may be enrolled if willing/able to switch to ≤ 81 mg daily of acetylsalicylic acid or to another medication;
20. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or steroids (except inhaled steroids or ocular steroids); subjects may be enrolled if willing/able to undergo medication wash-

out prior to the first dosing and to refrain from taking these drugs until Day 180 visit of the study;

21. Major psychiatric disorder in within last 6 months that would interfere with study participation;
22. Body mass index (BMI) > 45 kg/m^2 at Screening;
23. Any lower extremity amputation due to diabetic complications;
24. Use of an investigational drug or treatment in past 6 months or prior participation in any study of VM202; and
25. 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 and IBC (if applicable).

3.4.1. INFORMED CONSENT

The investigator 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 2). The subject will sign and date the informed consent form. The investigator 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.

Following is a detailed list of study visits from screening to final follow-up and the required procedures/tests. Methodologies for specific tests/ procedures are described in Section 4.

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 a unique identifier in the following format: XX-YYY-ZZZ. XX is the 2 digit assigned site number, YYY is the sequential subject ID number, and ZZZ are the subject initials (initials of first name/middle name (if applicable)/last name). For example, the first subject named John Simon Doe at site 11 will be assigned 11-001-JSD. Subject ID numbers will not be re-used (e.g., if the subject is determined to be a screen failure).

3.4.3. SCREENING (DAY -90 TO DAY 0)

Prior to screening, subjects will give informed consent and then be initially screened using the VAS, the symptoms portion of the BPNS and the MNSI. Only subjects with a VAS score of ≥ 40 mm, a ≤ 5-point difference in symptom of BPNS between legs and MNSI physical assessment score of ≥ 3 will be allowed to proceed with the full screening procedures.

If the VAS, BPNS and MNSI criteria are met, the rest of screening will proceed. If applicable, the subject will be washed-out of prohibited medications. During medication wash-out and prior to randomization, subject eligibility will be assessed as follows:

- Evaluation of Eligibility Criteria
- Medical History
- Concomitant Medications
- Vital Signs
- Physical Exam, including height
- EKG
- Retinal Fundoscopy
- Serum Chemistry and Hematology
- HbA1c
- Urine pregnancy test (for women of childbearing potential only)
- Cancer screening should be conducted per the current American Cancer Society Guidelines for the Early Detection of Cancer. Testing should also include: pap smear and mammogram if not performed within past 12 months (females only); chest X-ray or chest CT scan (if the subject has a previous history of tobacco use, a CT scan will be performed instead of X-ray) within 3 months prior to study entry†; for subjects ≥ 50 years old, fecal occult blood test. Note, subjects with medical history and/or family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy within past 12 months with negative findings.
- Viral screening – HIV, Anti-Human T-Cell Lymphotropic Virus (HTLV), Positive Hepatitis B or C as determined by Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV), at Screening
- ***Following medication washout (if applicable) and within 14 days prior to Day 0 (first injections).*** Subjects will keep a Daily Pain and Sleep Interference Diary for 7 days. They will be asked to rate their 24-hour average daily pain intensity score using an 11-point numerical scale with 0 mm = no pain – 100 mm worst possible pain, and to evaluate how much their pain interferes with sleep (also using an 11-point numerical rating scale from 0 (did not interfere with sleep) to 10 (completely interfered with sleep; subject was not able to sleep due to pain). The subject must record *at least five assessments* of the 24-hour average daily pain intensity score during the seven-day period. The mean 24-hour scores at Screening will represent the baseline reference value. In case less than five assessments are recorded, a new Daily Pain and Sleep Interference Diary will be provided and the Day 0 visit will be rescheduled to allow completion of the Diary. The average pain score of the Daily Pain and Sleep Interference Diary must be ≥ 4 with a standard deviation ≤ 2 in order to be eligible for study participation.

† Study entry is defined as the date of signing informed consent.

3.4.4. RESCUE MEDICATION

The only allowed rescue medication is Tylenol. On Day 0, the site will dispense extra strength Tylenol (500 mg) provided by the Sponsor. The subject will be instructed to take 2 tabs every 6 hours as needed for DPN pain for a maximum of 6 tabs (3 grams) / day. The study-issued Tylenol is only to be used for DPN pain, and the subject is not to use any other source of acetaminophen or Tylenol for DPN pain. The subject will be provided with a diary to record their pain level (VAS, 0 mm = no pain – 100 mm very severe pain) before use, the date and time of use, and the amount of Tylenol used. The subject will be asked to return the diary and the bottle of rescue medication at each visit. At each visit, the site will count how many tabs were taking between visits and will dispense additional bottles as needed.

3.4.5. (PROHIBITED) CONCOMITANT MEDICATIONS

3.4.5.1. MEDICATION THAT MAY INTERFERE WITH VM202 BIOACTIVITY

COX-1 and COX-2 inhibiting drugs, and steroids (except inhaled steroids or ocular steroids) may interfere with the bioactivity of VM202, and are therefore prohibited from use during the study. Other than the maximal 81 mg daily dose of aspirin (acetylsalicylic acid), subjects must agree to not take any of these drugs until Day 180 visit of the study. The subject needs to be advised that common over the counter medications excluded include: Bayer (> 81mg), Excedrin, Aleve, Advil (Motrin, ibuprofen). A full list of the excluded medications, including the washout period, can be found in Appendix 3.

Subjects taken gabapentin (Neurontin) and / or pregabalin (Lyrica) at study entry† must be on stable dosing regimen for at least 3 months prior to study entry. † It is not allowed to increase the dosage of either of these medications until Day 180 visit of the study. If a subject is not taking gabapentin and / or pregabalin at study entry†, the subject must agree not to start these drugs until Day 180 visit of the study.

3.4.5.2. MEDICATIONS THAT MAY INTERFERE WITH ASSESSMENT OF VM202 EFFECT ON PAIN

Subjects must discontinue use of the following drugs / therapeutics listed below. Subjects may participate in the study if they are willing to discontinue use of these drugs / therapeutics ***7 days prior to starting the Daily Pain and Sleep Interference Diary***. Subjects must refrain from taking these drugs or undergoing these therapies for the duration of the study:

- skeletal muscle relaxants, opioids, benzodiazepines (except for stable bedtime dose),
- capsaicin, local anesthetic creams (except for Lidocaine cream prior to IM injection) and patches, isosorbide dinitrate (ISDN) spray,
- transcutaneous electrical nerve stimulation (TENS), acupuncture

† Study entry is defined as the date of signing informed consent.

If not using duloxetine (Cymbalta), any antidepressants (e.g. amitriptyline and venlafaxine), any other antiepileptics (e.g., valproic acid, carbamazepine, vigabatrin) at screening, subjects must agree not to start these drugs until Day 180 visit of the study. Subjects on these medications at study entry† must maintain a stable dose until Day 180 visit of the study.

3.4.5.3. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as screen failures. End of study procedures will not be performed for these subjects, but their reason for discontinuation will be recorded on Screening Log. Screen failures will be replaced.

3.4.6. TREATMENT ASSIGNMENT

After providing written informed consent, potential study participants will undergo Screening assessments. The site will log in into the electronic data capturing (EDC) system and enter the screening assessments. If the site selects that the subject meets all inclusion and exclusion criteria, the EDC will indicate whether the subject can be treated, and will send a **separate** notification to the Pharmacist, the drug depot and the unblinded Pharmacy Monitor with the subject ID, randomly assigned kit number, and randomly assigned study treatment. The Investigator or designee will coordinate with the Pharmacist and schedule the Day 0 visit.

3.4.7. RANDOMIZATION AND BLINDING

A randomization schedule with subjects allocated to VM202 (treatment) or placebo (control) in a 2:1 ratio will be used. Randomization will be stratified by current use of gabapentin and/or pregabalin.

The drug depot will prepare and send the appropriate kit with associated dose preparation worksheets and treatment assignment notification to the Pharmacy. The Pharmacist or designee will keep the notification and dose preparation worksheets in a secure location with access limited to Pharmacy personnel responsible for preparing the syringes with assigned study treatment.

After study initiation, randomly assigned VM202 and VM202 vehicle (placebo) will be provided to the site's pharmacy by the drug depot for each eligible subject. Depending on the assigned study treatment, syringes of VM202 or placebo will be prepared **after** the clinic notifies the Pharmacy that the subject has arrived in the clinic to undergo study treatment.

Blinding will be achieved by having the study medication (VM202) prepared by the study pharmacist or designee. Reconstituted VM202 is indistinguishable from VM202 vehicle (placebo). The site pharmacist prepares the vials according to the instructions (which vials to reconstitute with water for injection [WFI]. The site pharmacist and select individuals (but excluding study monitors and study director) will be unblinded to the treatment assignments. The subject and study personnel, including core lab, principal investigator, co-investigators, study coordinators, study

monitors and study director will remain blinded until all data has been entered into the database and the database is locked.

IN CASE OF EMERGENCY ONLY, i.e. SERIOUS ADVERSE EVENT (SAE) AND ONLY WHEN THIS INFORMATION INFLUENCES THE SUBJECT'S MANAGEMENT, the Investigator may contact the Pharmacist or unblinded Pharmacy Monitor to unblind the study medication assignment. The date and reason for unblinding will be documented by the Investigator on the Unblinding Form, and a copy of this form will be provided to the unblinded Pharmacy Monitor.

3.4.8. DAY -7 (-7 DAYS)

- Daily Pain and Sleep Interference Diary

3.4.9. DAY 0 – 1ST INJECTIONS

3.4.9.1. PRE-INJECTION (WITHIN 4 HRS PRIOR TO INJECTIONS)

- Concomitant Medications
- Changes in medical history
- Vital Signs
- VAS
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Semmes-Weinstein Monofilament Testing
- Nerve Conduction (testing may be performed anytime between randomization and/ or on Day 0)
- Serum Chemistry and Hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood

3.4.9.2. 1ST DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in each calf for a total of 32 injections will be administered.

3.4.9.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.10. DAY 14 ± 1 DAY – 2ND INJECTIONS

3.4.10.1. PRE-INJECTION (WITHIN 4 HOURS PRIOR TO THE INJECTIONS)

- Concomitant Medications
- Vital Signs

- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.10.2. 2ND DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in each calf for a total of 32 injections will be administered.

3.4.10.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.11. DAY 21 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- Copies of VM202 in whole blood
- Serum HGF
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.12. DAY 60 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- Copies of VM202 in whole blood
- Serum HGF
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.13. DAY 90 ± 7 DAYS – 3RD INJECTIONS

- *Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to the visit*

3.4.13.1. PRE-INJECTION (WITHIN 4 HRS PRIOR TO INJECTIONS)

- VAS
- Semmes-Weinstein monofilament testing
- BPI-DPN
- PGIC
- Vital Signs

- Concomitant Medications
- Serum Chemistry and Hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.13.2. 3RD DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in each calf for a total of 32 injections will be administered.

3.4.13.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.14. DAY 104 (13-15 DAYS AFTER DAY 90 VISIT) – 4TH INJECTIONS

3.4.14.1. PRE-INJECTION (WITHIN 4 HOURS PRIOR TO THE INJECTIONS)

- Concomitant Medications
- Vital Signs
- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.14.2. 4TH DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in each calf for a total of 32 injections will be administered.

3.4.14.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

- Vital Signs
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.15. DAY 111 (4-10 DAYS AFTER DAY 104 VISITS)

- Concomitant Medications
- Vital Signs

- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.16. DAY 150 (5 MONTHS) ± 7 DAYS

- Concomitant Medications
- Vital Signs
- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Injection site assessment
- Adverse event assessment

3.4.17. DAY 180 (6 MONTHS) ± 7 DAYS

- *Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to the visit*
- Retinal Fundoscopy (testing may be performed anytime within the visit window)
- Concomitant Medications
- Vital Signs
- VAS
- MNSI
- Semmes-Weinstein monofilament testing
- BPI-DPN
- PGIC
- Nerve Conduction (testing may be performed anytime within the visit window)
- Serum Chemistry and Hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Adverse event assessment

3.4.18. DAY 270 (9 MONTHS) ± 14 DAYS

- *Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to visit*
- Retinal Fundoscopy (testing may be performed anytime within the visit window)
- Concomitant Medications
- Vital Signs
- VAS
- MNSI
- Semmes-Weinstein monofilament testing
- BPI-DPN

- PGIC
- Nerve Conduction (testing may be performed anytime within the visit window)
- Serum Chemistry and Hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood
- Tylenol Usage
- Adverse event assessment

3.5. STUDY COMPLETION

3.5.1. COMPLETED SUBJECTS

Each subject in the study will be considered completed when all assessments through 9 months have been performed in accordance with the study protocol.

3.5.2. DISCONTINUED SUBJECTS

Any subject may voluntarily discontinue the study at any time without prejudice. The investigator may discontinue a subject from the study at any time if (s)he considers that remaining in the study compromises the subject's health or the subject is not sufficiently cooperative. In either event, reason(s) for discontinuation should be recorded on the study worksheets.

Possible reasons for study discontinuation include the following:

- Adverse events (AEs) necessitating discontinuation from the study (pre-treatment).
- The subject is lost to follow-up.
- Subject decision (specify).
- Investigator decision (specify).
- Other reason (specify).

The reasons for any subject discontinuation will be recorded on the study completion form of the study worksheets.

Additional subjects may be enrolled if subjects discontinue (investigational treatment) prior to the 90-day visit in order to achieve a 477 subject dataset with 90 day data (primary efficacy endpoint).

Subjects discontinued for AE(s) will be followed-up after subject's discontinuation until the event is resolved or considered medically stable by the investigator.

Subjects who withdraw prior to study completion will undergo the following if possible:

- Retinal Fundoscopy
- Concomitant Medications
- Serum Chemistry and Hematology
- Vital Signs
- Serum HGF
- Copies of VM202
- Injection site reaction assessment if discontinued prior to Day 150
- Adverse Events

In case of a subject lost-to-follow-up, the investigator must do his/her best to contact the subject (by phone or letter) at least twice. If no response is obtained from the subject, the investigator is encouraged to contact one of the subject's relatives or his/her general practitioner. Documentation of these contacts must be recorded in the subject medical chart. It can be, for instance, the acknowledgement of receipt of a letter sent to the subject.

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.

3.6. INVESTIGATIONAL DRUG PRODUCT AND ACCOUNTABILITY

3.6.1. INVESTIGATIONAL DRUG PRODUCT

VM202 is a DNA plasmid containing a novel genomic cDNA hybrid human hepatocyte growth factor (HGF) coding sequence [redacted] expressing two isoforms of HGF, HGF [redacted] and HGF [redacted] The key feature of HGF-X7 is that it was designed [redacted] so that both isoforms of HGF protein are expressed simultaneously and efficiently as in the human genome. Because there is no change in the coding region of the HGF gene, HGF proteins generated from VM202 are identical to the wild-type human HGF proteins.

The plasmid has [redacted] base pairs, a [redacted] enhancer / promoter, a growth hormone [redacted] terminator sequence, [redacted] originator, and the [redacted] on a [redacted] backbone.

VM202 is supplied in a sterile glass vial containing [redacted] mg of [redacted] study product. VM202 should be stored in a refrigerator at temperatures between 2°C and 8°C in an appropriately locked room accessible only to the pharmacist, or a duly designated person. Since VM202 does not contain preservatives, opened vials of VM202 and VM202 reconstituted with water for injection (WFI) must be used

within 12 hours when stored at room temperature. VM202 should never be frozen. A complete description of test article administration can be found in Appendix 7.

3.6.2. PLACEBO

The placebo will be sterile VM202 vehicle. Components of VM202 vehicle are provided in Table 4. VM202 excipients are supplied in a sterile glass vial in liquid form. Each vial is only to be used for one subject. Visually, VM202 vehicle is indistinguishable from reconstituted VM202.

Table 4. Components of VM202 Vehicle

COMPONENT	FUNCTION	COMPOSITION
[redacted]	[redacted]	[redacted]

3.6.3. PRODUCT ACCOUNTABILITY

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

Investigational drugs are to be used only in accordance with this protocol and under supervision of the Study Pharmacist or a duly designated person. The Study Pharmacist or his/her designee will maintain an accurate record of the receipt of the VM202 and placebo as shipped by the Sponsor/Designee, including the date received. In addition, an accurate study drug disposition record will be kept, specifying the date and amount dispensed to each subject. This inventory record must be available for inspection at any time by the unblinded Pharmacy Monitor. Copies of this record will be provided to the Sponsor by the Study Pharmacist at the conclusion of the study.

After the study is completed, the Study Pharmacist must account for all study drug used, unused and partially used. Unused study medication from the study site will be returned to the Sponsor/Designee as directed in writing by the Sponsor or designee for gross reconciliation.

3.6.4. DOSE AND ADMINISTRATION

VM202 is supplied in a sterile glass vial containing [redacted] mg of [redacted] study product. Before administration, it will be reconstituted with 5 mL of water for injection (WFI) by the study pharmacist for a final VM202 concentration of [redacted] mg / mL. Each reconstituted vial is only to be used for one subject. The VM202 arm will receive only VM202 injections. The placebo group will receive only VM202 vehicle injections. All subjects will receive 16 injections per calf per visit. A complete description of test article administration can be found in Appendix 7.

3.7. PRIOR AND CONCOMITANT MEDICATION

All concomitant medications (taken within 60 days of the first injection) 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. EXAMINATIONS AND EVALUATIONS

4.1. EVALUATIONS CONDUCTED AT BASELINE ONLY

4.1.1. MEDICAL HISTORY

A complete medical history will be obtained at Baseline. All positive and negative findings will be carefully documented on the study worksheets. Any new finding discovered during the Screening/Baseline evaluation and prior to the first study drug administration (Day 0) will be considered to be part of the medical history and will not be recorded as an adverse event.

The Investigator will perform an especially detailed assessment of past diabetes history to include all events and interventions prior to study enrollment. Other potential causes of peripheral neuropathy will be excluded (e.g., alcohol consumption, renal failure, liver disease, hypothyroidism, collagen vascular diseases, vasculitis, osteoarthritis of the ankle or foot, gout, bursitis, fasciitis, and B-12 or folate deficiency).

4.1.2. PHYSICAL EXAM

A physical exam will be performed at Screening. The exam will include the following: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and gastrointestinal systems. Any abnormalities should be categorized as clinically significant (CS) or not clinically significant (NCS), and the abnormalities should be recorded in the subject's study worksheets. Actual height will be measured.

4.1.3. CANCER SCREENING

All subjects participating in this trial must undergo routine cancer screening. The history and diagnosis of potential or apparent malignant and non-malignant diseases and neoplasms will be assessed through several diagnostic tests and procedures. Some diagnostic tests and procedures performed prior to study consent and documented in the subject's medical history may be acceptable where noted. Routine cancer screening includes the following:

1. For subjects ≥ 50 years old, fecal occult blood test. A positive fecal occult blood test (current or reported within the past 12 month) requires follow-up testing which is beyond the scope of this study. If follow-up testing rules out cancer, the subject will be able to participate in the study if the subject is still interested. For subjects with medical history and/or family history of colon cancer in any first degree relative, must have documentation of a negative colonoscopy performed within past 12 months.
2. Chest X-ray or chest CT scan within 3 months prior to study entry†: (if the subject is currently using tobacco or has a previous history [within 15 years] of tobacco use, a CT scan will be performed instead of X-ray).
3. Mammogram within 1 year prior to study entry† (females ≥ 40 years only)
4. Papanicolaou (Pap) smear within 1 year prior to study entry† – (females ≥ 21 years only except for women who had a complete hysterectomy [removal of uterus and cervix] and females ≥ 70 years with 3 normal pap smears and no abnormal pap smear during the last 10 years).

4.1.4. VIRAL SCREENING

The local laboratory will be responsible for Screening viral testing and assays to include: HIV-1, HIV-2, HTLV, and HBV and HCV as determined by Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV).

4.1.5. 12-LEAD EKG

A 12 lead electrocardiogram (EKG) will be conducted at Screening. The EKG recording will be printed out, and a copy will be placed with subject records. Any (clinically significant) abnormalities will be reported.

4.1.6. BRIEF PERIPHERAL NEUROPATHY SCREENING (BPNS)

Symptoms of BPNS will be assessed at initial screening in order to evaluate the bilateral extent of DPN (see Appendix 11).

4.1.7. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

For women of childbearing potential, a urine beta human chorionic gonadotropin (β-HCG) test will be performed at Screening. Results of the test must be negative and effective contraception documented. Acceptable methods of contraception include:

- Barrier type devices (e.g., female condom, diaphragm and contraceptive sponge) used only in combination with a spermicide;
- Intrauterine device;
- Oral contraceptive agents;
- Depo-provera (medroxyprogesterone acetate);
- Levonorgestrel implants;

† Study entry is defined as the date of signing informed consent.

Abstention, the rhythm method or contraception by a partner are not considered acceptable methods of contraception.

4.2. EVALUATIONS CONDUCTED THROUGHOUT THE STUDY

4.2.1. RETINAL FUNDOSCOPY

Proliferative retinopathy, defined as the presence of new proliferating blood vessels (neovascularization) arising from the retina or optic disc and growing on the retinal surface or into the vitreous cavity, will be assessed by retinal fundoscopy at Screening for eligibility and repeated at Day 180 and Day 270. Retinal fundoscopy must be performed by an ophthalmologist within 3 months of Screening.

In cases where fundoscopy alone is deemed insufficient to determine eligibility, fluorescein angiography may be conducted at Screening.

4.2.2. CONCOMITANT MEDICATIONS

Concomitant medications will be recorded at each visit using the trade name or generic name as described in Section 3.7.

4.2.3. VITAL SIGNS

Vital signs consisting of blood pressure (while subject is sitting), temperature, weight, heart rate, and respiratory rate will be measured and recorded at Screening and at every visit through the 9-month follow-up.

4.2.4. SERUM CHEMISTRY, HEMATOLOGY AND HBA1C

Evaluation of serum chemistry and hematology will be conducted at Screening, Day 0, Day 90, Day 180 (6 months) and Day 270 (9 months). Evaluations will be conducted by a local laboratory at each site.

Serum chemistry evaluations will include: calcium, glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, albumin, and total protein.

Hematology evaluations will include: complete blood count (CBC): red blood cells (RBC); hemoglobin (Hgb), hematocrit (HCT), platelets and white blood cells (WBC) with differential. Abnormal readings do not necessarily constitute an adverse event; the results need to be reviewed in the context of the subject's health.

HbA1c will be determined at Screening, Day 0, Day 90, Day 180 (6 months) and Day 270 (9 months) at a local laboratory at each site. Laboratory testing by visit is provided in Appendix 1.

4.2.5. SERUM HGF

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 21, Day 60, immediately pre-treatment on Day 90, immediately pre-treatment on Day 104, Day 111, Day 150, Day 180 and Day 270.

A minimum 6 cc blood draw will be taken at each time point. Allow blood to clot for 30 – 60 minutes at room temperature then centrifuge for 10 minutes at 1000 x g. Divide the isolated serum into six (6) equal aliquots of ~0.3 mL each. (0.5mL plastic storage tubes provided). Samples should be labeled with study number, subject ID, draw date, and visit interval (i.e., Day 0, 14, 21, 60, 90, 104, 111, 150, 180 or 270). Samples will be maintained in a cooler containing dry ice and then placed in a ≤ -65°C freezer until shipped for analysis.

Serum HGF samples will be batched with VM202 samples and shipped bimonthly (i.e., odd months: January, March, May, July, September, November) in a special container with temperature tracking recorder to [redacted] for analysis. Please see the [redacted] for detailed instructions.

[redacted]

Note, [redacted] will provide collection tubes, plastic vials, labels, shipment materials including temperature tracking devices to each participating site for use during the study.

4.2.6. COPIES OF VM202 IN WHOLE BLOOD

The number of copies of VM202 in whole blood will be determined by PCR at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 21, Day 60, at Day 90 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 104 (pre-injection, and 2 hours [± 1 hour] post injection), Day 111, Day 150, Day 180 and Day 270.

Six (6) cc of whole blood will be collected in EDTA-coated tubes, inverted >5 times and transferred to plastic sterile and or RNase and DNase free vials of ~0.6 – 1 cc aliquots each for a total of 5 aliquots per time point. These will be maintained in a ≤ -65°C freezer until shipped for analysis. Samples should be labeled with study number, subject ID, draw date and time, and visit interval (i.e., Day 0 pre, Day 0 post, Day 14 pre, Day 14 post, Day 21, Day 60, Day 90 pre, Day 90 post, Day 104 pre, Day 104 post, Day 111, Day 150, Day 180 or Day 270).

VM202 samples will be batched with serum HGF samples and shipped bimonthly (i.e., odd months: January, March, May, July, September, November) in a special

container with temperature tracking recorder to [redacted] for analysis. Please see the [redacted] for detailed instructions.

[redacted]

Note, [redacted] will provide collection tubes, plastic vials, labels, shipment materials including temperature tracking devices to each participating site for use during the study.

4.2.7. VISUAL ANALOG SCALE (VAS) SCORE

Pain will be recorded during site visits at Screening, Day 0 before the treatment (injection), on Day 90 before treatment (injection), at Days 180 and 270 using the visual analog scale (VAS). The VAS scoring instrument is a 100mm line, oriented horizontally, with the left end indicating "no pain" and the right end representing "very severe pain". The subject is asked to mark a place on the line corresponding to the current pain intensity. The distance along the scale is then converted into a numeric reading by measuring the distance of the subject's mark in millimeters from the beginning of the scale (the 0 mark). The VAS is illustrated in Appendix 9. Upon completion of the VAS, the study coordinator will check the VAS for completeness. Note, the subject will be required to initial and date the VAS.

4.2.8. DAILY PAIN AND SLEEP INTERFERENCE DIARY

Subjects will be asked to keep a Daily Pain and Sleep Interference Diary (see Appendix 10). 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 at Screening following wash-out of prohibited medications (if applicable), and within 14 days prior to the Day 90, Day 180 (6 months) and Day 270 (9 months) visits. 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 90, Day 180 (6 months) or Day 270 (9 months), 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 study coordinator at each site 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.

Optionally at the Day 90, Day 180 (Month 6) and Day 270 (Months 9) visits only (not at Screening): if the subject states that the Diary was completed and it is a hardship for the subject to reschedule the visit (e.g., distance or transportation issues), the site may provide a completed FedEx shipping bill to the subject so the subject can send the completed Diary to the site using FedEx.

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.

4.2.9. MICHIGAN NEUROPATHY SCREENING INSTRUMENT

The Michigan Neuropathy Screening Instrument (MNSI) will be conducted at Screening in order to confirm the diagnosis of diabetic peripheral neuropathy and at Day 180 (6 months) and Day 270 (9 months) to track disease progression.[52-54] The MNSI is comprised of a subject questionnaire (15 questions) and of a physical evaluation which includes a foot inspection, vibration sensation testing, muscle stretch reflexes, and monofilament testing. The MNSI forms and instructions can be found in Appendix 5. Upon completion of the MNSI questionnaire, the study coordinator will check the questionnaire for completeness. Any omissions or ambiguous answers will be clarified by the subject prior to leaving the clinic. Note, the subject will be required to initial and date the MNSI questionnaire.

4.2.10. SEMMES WEINSTEIN MONOFILAMENT TEST

The Semmes-Weinstein monofilament test will be conducted at Day 0, 90 Days, Day 180 (6 months) and Day 270 (9 months). Testing will be performed on the plantar aspect of great toe, first, third and fifth metatarsal heads of each foot. The Semmes Weinstein monofilament test instructions can be found in Appendix 6.

4.2.11. BRIEF PAIN INVENTORY FOR SUBJECTS WITH DIABETIC PERIPHERAL NEUROPATHY (BPI-DPN)

The brief pain inventory (BPI-DPN) [55,56] will be self-administered during site visits on Day 0 before the treatment (injection), on Day 90 before the treatment (injection), and at 180 and 270 days. The Questionnaire includes numeric rating scale that assesses the severity of pain, its impact on daily functioning, and other aspects of pain (e.g. location of pain, relief from medications). The questionnaire was modified to distinguish between pain due to DPN and pain due to other causes. 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 full Questionnaire can be found in Appendix 8. Note, the subject will be required to initial and date the BPI-DPN.

4.2.12. 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.[65] 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 90, Day 180 and Day 270.

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 12. Note, the subject will be required to initial and date the PGIC.

4.2.13. NERVE CONDUCTION TESTING

Nerve conduction testing will be conducted pre-treatment on Day 0, Day 180 and Day 270 at select sites. Unilateral testing will be performed on the sural sensory nerve and peroneal motor nerve of the left leg. The nerve conduction testing instructions can be found in Appendix 13.

4.2.14. INJECTION SITE REACTION ASSESSMENT

Local injection sites reactions will be assessed on Day 0 post injection, Day 14 pre and post injection, Day 21, Day 60, Day 90 pre and post injection, Day 104 pre and post injection, and at Day 111 and Day 150 Injection site reactions will be completed using the Injection Site Adverse Event form. The location (calf area) and temporal relationship to the most recent injections will determine whether the event is an injection site reaction or adverse event.

Table 5. Injection Reaction Assessment

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Injection site reaction	Pain, itching, erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated		
Ulceration		Superficial ulceration < 2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g. hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting	Death
Allergic reaction / hypersensitivity	Transient flushing or rash; drug	Rash; flushing; urticaria; dyspnea; drug	Symptomatic bronchospasm, with or without urticaria;	Anaphylaxis	Death

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
	fever < 38°C (<100.4°F)	fever ≥38°C (≥100.4°F)	parenteral medications(s) indicated; allergy-related edema/ angioedema; hypotension		

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 worsens 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 the first study drug administration on Day 0 and the 9-month follow-up visit of the study 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 9 month follow-up 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 9-month 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.

6. STATISTICAL CONSIDERATIONS

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

6.1. SAMPLE SIZE CALCULATION

The sample size for the primary efficacy endpoints is calculated based on the hypothesis for the primary efficacy endpoints. The primary efficacy endpoints are as follows:

1. The change in the average pain score from baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary.
2. The outcome of at least a 50% reduction (i.e. $\geq 50\%$) in the average pain score from baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary.

The statistical hypotheses for the first primary efficacy endpoint are:

$H_0: \mu_t = \mu_p$ versus $H_a: \mu_t \neq \mu_p$, (I)

where μ_t and μ_p are the mean pain change from baseline to 3-month follow-up for the VM202 and Placebo groups, respectively. A negative mean value means a

reduction in the pain score, and a positive mean value means an increase in the pain score.

If the null hypothesis for the first primary efficacy endpoint above is rejected, then the formal statistical test will be performed for the second primary efficacy endpoint. The statistical hypotheses for the second primary efficacy endpoint are:

H_0: $p_t = p_p$ versus H_a: $p_t \neq p_p$, (II)

where p_t and p_p are the percentage of subjects with a change in the average pain score from the Daily Pain and Sleep Interference Diary from baseline to the 3-month follow-up of $\leq$ -50% (or a reduction of $\geq$ 50%, the 3-month responder) for the VM202 and Placebo groups, respectively.

The intent-to-treat population and efficacy group in the Phase II study (Protocol VMDN-002, injection at Day 0 and Day 14 only) showed the following mean pain change from baseline and standard deviation for the low dose and placebo groups:

Table 6. Mean and Standard Deviation of Pain Change from Baseline and Percentage of Subjects with a $\geq$ 50% Reduction in Pain (Low Dose vs Placebo in Phase II Study)

	ITT		Efficacy	
	VM202	Placebo	VM202	Placebo
Mean (SD)				
Month 3	-2.89 (2.47)	-1.70 (1.72)	-3.03 (2.53)	-1.53 (1.76)
Month 6	-2.58 (2.18)	-1.63 (1.75)	-2.78 (2.23)	-1.59 (1.89)
Percentage of Subjects with a $\geq$ 50% Reduction				
Month 3	45.9%	23.8%	48.4%	17.6%
Month 6	34.3%	15.0%	38.7%	17.6%

Based on the Phase II findings, it is assumed that the standard deviation of the pain change from baseline is 3.0. The true percentages of subjects with a pain reduction of $\geq$ 50% are assumed to be 35% and 18% for the VM202 group and placebo group, respectively.

- The statistical power is 90% for a detectable mean difference of –1.0 (i.e., mean pain reduction for the VM202 group is higher than that for the Placebo group) for the first statistical hypotheses using a t-test. The statistical power is also 90% for the second statistical hypotheses provided the assumptions of p_t = 35% and p_c = 18% using a chi-square test.
- The two-sided significance level is 0.05. Since the formal statistical test for the

second primary efficacy endpoint will not be performed unless the null hypothesis of the first primary efficacy endpoint is rejected, no adjustment on the significance level is performed.

- The randomization ratio for the VM202 group and the placebo group is 2:1.

Based on the items above, the sample sizes calculated for the VM202 group and placebo group are 286 and 143 subjects, respectively, for first statistical hypotheses; those for second statistical hypotheses are 212 VM202 subjects and 106 placebo subjects. Therefore, 286 VM202 subjects and 143 placebo subjects are needed for data analyses. With a dropout rate of 10%, at least 477 subjects should be randomized in order to have 318 VM202 subjects and 159 placebo subjects.

In order to control the type I error, the statistical hypotheses for the two secondary efficacy endpoints will be formally evaluated only if the statistical tests for the two primary efficacy endpoints are statistically significant (i.e. p-value < 0.05).

6.2. ANALYSIS POPULATION

6.2.1. INTENT-TO-TREAT POPULATION (ITT)

This subset includes all subjects who were randomized on the VMDN-003 study.[2] All baseline characteristics will be summarized based on ITT. Subjects in the ITT will be analyzed according to original treatment assignment, regardless of actual treatment received. The primary analyses of the primary and secondary efficacy endpoints will be based on this ITT population.

6.2.2. SAFETY POPULATION

The safety analysis population will contain all subjects who are randomized and receive at least one study injection. Subjects will be grouped according to their actual treatment received, not according to their randomization assignment (as randomized). Subjects treated with any VM202 dose will be grouped in the VM202 group; subjects treated without any VM202 will be grouped in the placebo group.

6.2.3. MODIFIED ITT (MITT) POPULATION

The mITT population includes all subjects randomized that meet the following:

[2] Per FDA/ICH E9 Statistical Guidance, pg. 29:

"In some situations, it may be reasonable to eliminate from the set of all randomized subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment. In other situations it may be necessary to eliminate from the set of all randomized subjects any subject without data post randomization. No analysis should be considered complete unless the potential biases arising from these specific exclusions, or any others, are addressed."

Helixmith is aware of 7 subjects in VMDN-003 who were randomized in error (did not meet Inclusion / Exclusion criteria or who were randomized without PI oversight). These 7 subjects were subsequently withdrawn before receiving study medication and without knowledge of treatment assignment. Details are summarized in a Note-to-File, July 12, 2019, which was prepared according to Helixmith SOP QA-002.

- Received at least one dose of study medication;
- Correctly completed the Daily Pain and Sleep Interference Diary at the 3-month follow-up;
- Satisfies inclusion/exclusion criteria

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

6.2.4. PER PROTOCOL (PP) POPULATION

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

- Subject absent of any major protocol deviations
- Additional criteria, if any, will be established before unblinding the randomization code by the independent CDRC that is masked to the treatment information of each study subject.

6.3. STUDY ENDPOINTS

6.3.1. PRIMARY ENDPOINTS

There are two primary efficacy endpoints that will be evaluated in sequential order. The primary efficacy endpoints are:

1. The change in the average 24-hour pain score from baseline to the 3-month follow-up [Day 90] obtained from the Daily Pain and Sleep Interference Diary.
2. The outcome of at least a 50% reduction (i.e. ≥ 50%) in the average 24-hour pain score from baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary.

6.3.2. SECONDARY EFFICACY ENDPOINTS

The key secondary efficacy endpoints are:

1. The change in the average 24-hour pain score from baseline to the 6-month follow-up [Day 180](3 months after the Day 90 injection) obtained from the Daily Pain and Sleep Interference Diary.

2. The outcome of at least a 50% reduction (i.e. ≥ 50%) in the 24-hour average pain score from baseline to the 6-month follow-up [Day 180] (3 months after the Day 90 injection) obtained from the Daily Pain and Sleep Interference Diary.

6.3.3. EXPLORATORY EFFICACY ENDPOINTS

- The outcome of at least a 20%, 30%, 40%, or 60% reduction in the average pain score from baseline to the 3-month follow-up obtained from the Daily Pain and Sleep Interference Diary.
- The outcome of at least a 20%, 30%, 40%, or 60% reduction in the average pain score from baseline to the 6-month follow-up obtained from the Daily Pain and Sleep Interference Diary.
- Change in the average pain score from baseline to the 9-month follow-up (Day 270) obtained from the Daily Pain and Sleep Interference Diary.
- The outcome of at least a 20%, 30%, 40%, or 60% reduction in the average pain score from baseline to the 9-month follow-up obtained from the Daily Pain and Sleep Interference Diary.
- Change in VAS for Pain from baseline to the 3-month, 6-month and 9-month follow-up visits.
- Michigan Neuropathy Screening Instrument (MNSI) physical assessment and history changes from baseline to the 6-month and 9-month follow-up.
- Average sleep interference score change from baseline to the 3-month, 6-month, and 9-month follow-up obtained from the Daily Pain and Sleep Interference Diary.
- BPI-DPN pain interference and severity changes from baseline to the 3-month, 6-month, and 9-month follow-up.
- Patient's Global Impression of Change (PGIC) at the 3-month, 6-month, 9-month follow-up.
- Semmes-Weinstein monofilament testing changes from baseline to the 3-month, 6-month, and 9-month follow-up.

6.3.4. SAFETY

Safety analyses in this study will evaluate the safety profile of VM202, as compared with control. No formal statistical testing will be conducted for the safety analyses. All subjects in the safety subset will be included in these analyses. Subjects will be grouped by treatment received. All safety summaries will be derived based on available data. No imputation will be performed for missing values.

6.3.5. PHARMACOKINETICS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 21, Day 60, immediately pre-treatment on Day 90, immediately pre-treatment on Day 104, Day 111, Day 150, Day 180, and Day 270.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 21, Day 60, at Day 90 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 104 (pre-injection, and 2 hours [± 1 hour] post injection), Day 111, Day 150, Day 180 and Day 270.

6.3.6. DATA SAFETY MONITORING BOARD (DSMB) AND INTERIM ANALYSES

An independent data safety monitoring board (DSMB) will periodically review a limited set of un-blinded tables and/or listings, including all reported AEs. The objectives of the DSMB meetings are to review the safety outcomes of the study and provide guidance to study sponsor regarding the safety of the VM202. The data analyses for the DSMB meetings will be directly provided to the DSMB members and no data will be released to the study sponsor and blinded designees. There will be no adjustment for multiple testing due to the DSMB data review. Further details of DSMB responsibilities are included in the DSMB Charter.

No interim efficacy analyses are planned.

6.4. SUBJECT CATEGORIZATION

Screen Failure - Any subject who was consented and entered into the Screening process appropriately, but subsequently did not meet the entry criteria in order to be treated. Subjects who fail screening will not be followed for safety or efficacy assessment, and no other study procedures will be performed. Screen failures will be replaced.

Evaluable Subject - Any subject who received the study drug.

Lost to follow-up - A subject deemed to be lost to follow-up is any subject who received treatment, but who does not complete scheduled study visits. This includes those subjects who withdraw consent and refuse further study participation and all attempts to contact the subject are deemed unsuccessful.

7. 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.

8. 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.

9. 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.

10. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

The sites at which this trial is being conducted will ensure that an Institutional Biosafety Committee (IBC) is in place. The IBC will ensure that the site conforms to the requirements set forth in the Section IV-B-2 of the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules, promulgated by the National Institutes of Health/Office of Biotechnology Activities (NIH/OBA).

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

If a potential clinical site does not receive any NIH funding (either directly or indirectly) and does not have an institutional IBC, they can participate in the study if they issue a certification statement to that effect. The certification statement will be submitted to the OBA.

11. INFORMED CONSENT PROCESS

It is the responsibility of the investigator 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 2. 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.

12. 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.

13. 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.

14. 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.

15. 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).
- A copy of the original approval for conducting the study by the IBC, if applicable. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IBC policy.
- 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).
- All IBC correspondence.
- 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.

16. 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.

17. 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.

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APPENDICES

TABLE OF APPENDICES

Appendix 1. Schedule of Evaluations and Visits & Laboratory Tests by Visit

SCHEDULE OF EVALUATIONS AND VISITS

PROCEDURE	Screening / Baseline (-90 – 0 D)	First Treatment: D0, D14				Day 21 ± 3 D	2M Day 60 ± 3 D	Second Treatment: D90, D104				Day 111 7 ± 3 Days after 4th Injection
		1st Injection Day 0		2nd Injection Day 14 ± 1 D				3rd Injection Day 90 ± 7 D		4th Injection 13-15 Days after D 90		
		Pre-dose	Post-dose*	Pre-dose	Post-dose*			Pre-dose	Post-dose*	Pre-dose	Post-dose*	
Visit Number	1	2		3		4	5	6		7		8
Baseline Evaluation												
Informed Consent	✓											
Medical History	✓	✓										
Physical Exam	✓											
Symptoms of BPNS	✓											
Cancer Screening†	✓											
Viral Screening – HIV, HTLV, HBV, HCV	✓											
ECG	✓											
Urine Pregnancy Test	✓											
Retinal Fundoscopy	✓											
Safety and Efficacy Parameters												
MNSI	✓											
VAS	✓	✓						✓				
Daily Pain and Sleep Interference Diary	✓							✓				
HbA1c	✓	✓						✓				
Serum Chemistry and Hematology	✓	✓						✓				
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓		✓		✓	✓	✓		✓		✓
BPI-DPN		✓						✓				
Semmes-Weinstein Filament Test		✓						✓				
PGIC								✓				
Study Injections		✓		✓				✓		✓		
Copies of VM202 in whole blood		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum HGF		✓		✓		✓	✓	✓		✓		✓
Nerve Conduction (only at select sites)		✓										
Tylenol Usage				✓		✓	✓	✓		✓		✓
Treatment												
Injection Site Reaction Assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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); for subjects ≥ 50 years old, fecal occult blood test.

* 2 hours after injection (± 1 hour)

SCHEDULE OF EVALUATIONS AND VISITS (CONTINUED)

PROCEDURE	5M Day 150 ± 7 D	6M Day 180 ± 7 D	9M Day 270 ± 14 D	Early Withdrawal
Visit Number	**9**	**10**	**11**	
Safety and Efficacy Parameters				
Vital Signs	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓	✓
Retinal Fundoscopy		✓	✓	✓
VAS		✓	✓	
MNSI		✓	✓	
Daily Pain and Sleep Interference Diary		✓	✓	
BPI-DPN		✓	✓	
PGIC		✓	✓	
Semmes-Weinstein Filament Test		✓	✓	
Nerve Conduction (only at select sites)		✓	✓	
HbA1c		✓	✓	
Serum Chemistry and Hematology		✓	✓	✓
Study Injections				
Copies of VM202 in whole blood	✓	✓	✓	✓
Serum HGF	✓	✓	✓	✓
Tylenol Usage	✓	✓	✓	✓
Treatment				
Injection Site Reaction Assessment	✓			✓[1]
Adverse Events	✓	✓	✓	✓

1 If withdrawal occurs before Day 150 Visit

SCHEDULE OF LABORATORY EVALUATIONS

Parameters	Screen	Day 0	Day 14	Day 21	Day 60	Day 90	Day 104	Day 111	Day 150	Day 180	Day 270	Early Withdrawal
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
HbA1c	✓	✓				✓				✓	✓	
Serum HGF		✓ pre-injection	✓ pre-injection	✓	✓	✓ pre-injection	✓ pre-injection	✓	✓	✓	✓	✓
VM202		✓ pre & post injection	✓ pre & post injection	✓	✓	✓ pre & post injection	✓ pre & post injection	✓	✓	✓	✓	✓
HTLV, HIV-1, HIV-2	✓											
Hepatitis B, Hepatitis C†	✓											
Hematocrit	✓	✓				✓				✓	✓	✓
Hemoglobin	✓	✓				✓				✓	✓	✓
RBC	✓	✓				✓				✓	✓	✓
WBC with differential	✓	✓				✓				✓	✓	✓
Platelets	✓	✓				✓				✓	✓	✓
Albumin	✓	✓				✓				✓	✓	✓
Alkaline Phosphatase	✓	✓				✓				✓	✓	✓
ALT	✓	✓				✓				✓	✓	✓
AST	✓	✓				✓				✓	✓	✓
Bicarbonate	✓	✓				✓				✓	✓	✓
BUN	✓	✓				✓				✓	✓	✓
Calcium	✓	✓				✓				✓	✓	✓
Chloride	✓	✓				✓				✓	✓	✓
Creatinine	✓	✓				✓				✓	✓	✓
Glucose	✓	✓				✓				✓	✓	✓
Potassium	✓	✓				✓				✓	✓	✓
Sodium	✓	✓				✓				✓	✓	✓
Total Protein	✓	✓				✓				✓	✓	✓
Total Bilirubin	✓	✓				✓				✓	✓	✓

† Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B surface antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV)

Appendix 2. Sample Informed Consent

TITLE: 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-003)

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 if you meet the criteria, based on the results of your medical tests, which must be done before you are asked to continue your participation in the 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 have type I or II diabetes with current treatment control and, you are experiencing painful diabetic peripheral neuropathy (DPN) in both lower extremities [legs].

The specific events that result in painful diabetic peripheral neuropathy are not well understood, but high blood sugar, reduced blood flow in the limbs, and changes in the blood vessels are thought to result in damage to the nerves in the affected areas. Stimulating the growth of new blood vessels may stimulate growth or regeneration of nerves and may reduce pain. Researchers have discovered that a protein called hepatocyte growth factor (HGF) that your body naturally produces in small amounts can cause the growth of new blood vessels and protect nerves. Unfortunately, your body only makes a small amount of this protein and not always in the areas where you need it. Researchers have found a way to increase the amount of HGF in your legs. They have isolated the genes responsible for directing the production of HGF, and have designed a product that can be injected into your leg.

In the research study, the HGF gene will be injected into your calf muscle cells to evaluate if it changes your pain related to diabetic neuropathy. The product being used in this study is called VM202. VM202 is an experimental drug that is not yet approved by regulatory authorities (the US Food and Drug Administration [FDA]). VM202 is a plasmid (a small piece of DNA), which includes the HGF genes.

VM202 has been used in two studies (a small feasibility study and a larger study) in the United States in subjects with painful diabetic neuropathy; in a study in Korea in subjects with coronary artery disease and in two other studies in the United States in subjects with critical limb ischemia (decreased blood flow to the legs). VM202 is currently tested in the United States in subjects with Lou Gehrig's disease. VM202 has also been tested in people undergoing coronary bypass surgery. It is hoped that VM202 injected into your calf muscle will reduce pain related to diabetic neuropathy.

This study is intended to help determine the safety and efficacy of VM202 in subjects with painful diabetic neuropathy. VM202 will be injected into both your calf muscles using a syringe with a fine needle.

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?
A total of 477 patients will take part in this study at up to 30 hospitals in the United States and Korea.

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 need to undergo some tests done to see if you qualify for the study. If you do not meet all of the study entry criteria, you will not be able to participate in the study and your doctor will discuss with you other options that you may have for treatment of your medical condition. The study doctor will tell you whether you are able to participate in this study after the initial test results are received and reviewed.

This study is a double-blind, placebo-controlled, randomized clinical study. If you agree and are eligible to participate you will be "randomly" assigned (like flipping a coin) to one of two groups as listed below. "Double-blind" means that you and your doctor will not know the treatment you are getting during the study. However, your doctor can find out if needed for safety reasons. "Placebo controlled" means that not all participants will be assigned to a treatment group that will receive the study drug. Some participants may only receive saline injections. What group you are assigned to is done by a computer and is not known by you and your doctor until the study is completed.

You will be randomly assigned to one of two possible study groups. In each study group, you will receive 16 injections in each calf at the Day 0, Day 14, Day 90 and Day 104 visits. The contents of the injections depend on your study group:

- **VM202 Treatment Group** – if you are selected for this group, you will receive 32 mg of VM202 over the course of the four injection visits (8 mg of VM202 at the Day 0 visit, 8 mg of VM202 at the Day 14 visit, 8 mg of VM202 at the Day 90 visit, and 8 mg of VM202 at the Day 104 visit). At all 4 injection visits, you will receive 16 injections of 0.5 mL of VM202 in each calf. The total volume of all of the injections is about 2 teaspoons of fluid. Approximately sixty-five percent (65%) of patients will be assigned to this group.

- **Placebo Control Group** – if you are selected for this group, you will not receive VM202. You will only receive injections of VM202 vehicle (ingredients of VM202 without the genetic material which mainly contains sterile salt solution). At all 4

injection visits, you will receive 16 injections of 0.5 mL of saline in each calf. The total volume of all of the injections is about 2 teaspoons of fluid. Approximately thirty-five percent (35%) of patients will be assigned to this group.

Before your first treatment, you will be asked to fill out a daily questionnaire for a week (7 days). You will be asked to rate your pain 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 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 not be able to receive injections if you do not complete this diary.

What tests, procedures, and diagnostic studies will be done during this study?
There are 11 visits which span 9 months total time from visit #2 to visit #11. Depending on the visit, different tests will be done. Visit #1 may actually take more than one visit to accomplish depending on how many tests can be scheduled on that first day, but is usually completed within a few weeks before the first injection procedure (Visit #2). Below is a detailed description of each of the required visits and the laboratory tests, procedures, and evaluations that will be done during the visits.

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

Medical history – Discussion with your doctor of your medical history, including diabetes history and any changes that have happened.

Physical exam – Your doctor will examine you. This exam includes taking your sitting blood pressure, temperature, heart rate and weight (**vital signs**).

Medication review – Discussion with your doctor of what medications and dietary supplements you have taken and are currently taking. Please note, some medications may not be taken during the study since they may interfere with the potential effect of the study medication or ability to assess the response to the study medication. The doctor will talk to you about these medications; if you are currently taking any of these medications, you will be asked to stop taking these medications for the duration of the study.

Rescue Medication – You will be given extra strength Tylenol (500mg) for DPN pain and a Tylenol diary for use during the study. It is important to only use this bottle of Tylenol for DPN pain and no other (pain) indications. You are allowed to take 2 tabs every 6 hours as needed for DPN pain for a maximum of 6 tabs (3 grams) / day. Every time you take Tylenol, please record your pain level before use, the date and time of use, and the amount of Tylenol used on the Tylenol diary provided to you. At each visit, please return the diary and the bottle of Tylenol even if you have not taken any Tylenol. At each visit, the site will count how many tabs you have taken between visits and will dispense additional bottles of Tylenol and/or diary pages as needed.

Assessment of neuropathy – Assessment by your doctor of the condition of your feet and legs, your reflexes, and sensitivity to touch.

Injection site reaction assessment – Assessment by your doctor of any pain or other reaction at the locations where VM202 or placebo was injected.

Assessment of side effects – Assessment by your doctor of any unpleasant medical experiences, side effects, or discomforts that may have happened to you.

Questionnaires – You will be asked to complete short questionnaires about feeling/pain in your legs and feet.

Nerve Conduction Studies (Select Sites Only – Omit section if not applicable) - You will be asked to lie on a table or bed so your muscles are relaxed. The skin over the areas to be tested is cleaned. Several flat metal disc electrodes are attached to your skin with tape or a paste. A shock-emitting electrode is placed directly over the nerve, and a recording electrode is placed over the muscles controlled by that nerve. Several quick electrical pulses are given to the nerve, and the time it takes for the muscle to contract in response to the electrical pulse is recorded. The speed of the response is called the conduction velocity. When the test is done, the electrodes are removed. You will be able to feel the electrical pulses; note, a very low-voltage electrical current is used, and each pulse is very quick (less than a split-second).

Pain and Sleep Interference Diary - You will be asked to assess your average pain in your feet and lower legs for 7 days. You will also be asked to assess to what degree your pain in your feet and lower legs interferes with your sleep.

Cancer screening – Cancer screening includes pap smear and mammogram if not performed within past 12 months (females only); if you are 50 years of age or older, fecal occult blood test [stool samples will be tested for the presence of blood] - if you have a medical history and/or family history of colon cancer in any first degree relative, you must have undergone a colonoscopy in the past 12 month with negative findings; and X-ray or CT scan of chest.

Retinal Fundoscopy (specific Eye Exam) – An ophthalmologist (eye doctor) will dilate your pupils and perform a retinal examination with retinal photographs at Screening. If your ophthalmologist determines that a more detailed image of the blood vessels in your eye is necessary to determine if you are eligible for study participation, he / she may conduct another test called fluorescein angiography. This involves injecting a dye into a vein in your arm; the dye then circulates through the bloodstream and to the blood vessels of your eye. Retinal photographs of the back of your eye will be taken again at 6 month and 9 months, but the fluorescein angiography will not be repeated. If dilating eye drops are used, they may impair focusing of the eyes for several hours. Therefore, arrangements should be made for someone else to drive after the examination. Wearing sunglasses or tinted lenses may make dilated pupils more

comfortable. You should tell the examiner if you are allergic to any medications, are taking any medications, or have glaucoma or a family history of glaucoma.

Pregnancy test – If you are a female of child bearing age, you will have a urine pregnancy test to confirm that you are not pregnant. You cannot participate if you are pregnant or plan to become pregnant during the course of the trial.

12 Lead EKG – An electrocardiogram (EKG) is a measurement of your heart's electrical activity that is traced and sent to a machine, which can be read by your doctor. This procedure is not painful and involves lying as still as possible for a few minutes with sticky pads (electrodes) on your chest, arms and legs which are connected through wires to the EKG machine. This test typically takes approximately 15 to 20 minutes.

Blood tests – Routine blood tests will be done at certain visits. Laboratory tests will also include testing for **VM202** and **HGF** levels in the blood at certain visits. The screening evaluation laboratory tests will include viral tests for various diseases including **HIV** (the AIDS virus), **HTLV** (human T-cell lymphotropic virus), hepatitis B (**HBV**), and hepatitis C (**HCV**).

Below is a list of each visit and the specific tests that will be done:

Visit # 1: Screening/Baseline Evaluations
Screening is a process of evaluating your initial health status and assessing the status of your pain related to diabetic neuropathy. Screening is usually completed within 2-3 months before the first study injections if you qualify for this study. If you agree to take part in this research study, you will first sign this consent form, and then undergo screening. Screening will involve the following procedures: medical history, physical exam, vital signs, medication review, completion of questionnaires, assessment of neuropathy, cancer screening, retinal fundoscopy; blood tests including a viral screen; urine pregnancy test (if you are a female of childbearing age), 12 lead EKG, and completion of a pain and sleep interference diary.

Please note: If any of your viral test results are positive you may need to have a second test done to make sure the results are the same. The doctor or his/her nurse will tell you how to find medical help and counseling as needed, and you will not be able to take part in this study. The study sponsor will not pay for the cost of the repeat tests, or any other follow-up medical care, or counseling for a positive or abnormal test result.

It takes approximately one to two weeks to get all of the initial test results. After your doctor has reviewed the results of these tests he/she will determine whether you are eligible for participation in the study. If you are eligible for the study and you do wish to continue, you will be assigned by chance (randomly) to receive VM202 or the placebo control group. You will then be scheduled for the first set of injections which will be done at your next visit (Visit #2).

Visit # 2 – First Injection Procedure (injections of VM202 or placebo into both calf muscles)

Before Injection Procedure:
The following tests will be performed before you have your injection procedure done: update of any changes in your medical history, medication review, completion of questionnaires, nerve conduction (select sites), vital signs, and blood tests including HGF, and VM202.

Injection Procedure:
The injection procedure will be done in your doctor's office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 or saline solution at sites evenly distributed over your calf muscles. You will receive 16 injections in each calf. Each injection will take 3 - 5 seconds. Each site will be marked with an indelible marker. The entire injection procedure is expected to take 15-30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home discharge instructions about what you need to do to take care of yourself, what medications you should take, and who to call if you have a problem after you leave the clinic, will be reviewed with you by the nurse and/or doctor. Research personnel will be on call anytime to answer any questions that you may have and respond to reports you may have of any symptoms.

Visit # 3 – Second Injection Procedure (injections of VM202 or placebo into both calf muscles; 14 Days after the First Injection Procedure)

Before Injection Procedure:
The following tests will be performed before you have your injection procedure done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor's office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 or saline solution at sites evenly distributed over your calf muscles. You will receive 16 injections in each calf. Each injection will take 3 - 5 seconds. Each site will be marked with an indelible marker. The entire injection procedure is expected to take 15-30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, blood tests for VM202, injection site reaction assessment, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 4 – 21 Days after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment and assessment of side effects.

Visit # 5 – 60 Days after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment and assessment of side effects.

Visit # 6 –Third Injection Procedure (injections of VM202 or placebo into both calf muscles; 90 Days after the First Injection Procedure)
You will be asked to fill out the 7-day Pain and Sleep Interference Diary **before** this visit and to bring the diary with you for this visit.

Before Injection Procedure:
The following tests will be performed before you have your injection procedure done: medication review, completion of questionnaires, assessment of neuropathy, review of your completed diary entries, vital signs, blood tests including HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor's office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 or saline solution at sites evenly distributed over your calf muscles. You will receive 16 injections in each calf. Each injection will take 3 - 5 seconds. Each site will be marked with an indelible marker. The entire injection procedure is expected to take 15-30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, injection site reaction assessment, blood tests for VM202, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 7 – Fourth and Final Injection Procedure (injections of VM202 or placebo into both calf muscles; 13 to 15 Days after the Third Injection Procedure)

Before Injection Procedure:
The following tests will be performed before you have your injection procedure done: medication review, vital signs, blood tests including for HGF and VM202, injection site reaction assessment, and assessment of side effects.

Injection Procedure:
The injection procedure will be done in your doctor's office. The doctor will use a syringe with a fine needle to inject 0.5 ml of VM202 or saline solution at sites evenly distributed over your calf muscles. You will receive 16 injections in each calf. Each injection will take 3 - 5 seconds. Each site will be marked with an indelible marker. The entire injection procedure is expected to take 15-30 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, blood tests for VM202, injection site reaction assessment, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 8 – 4-10 Days after the Fourth Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment and assessment of side effects.

Visit # 9 – 5 Months after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment and assessment of side effects.

Visit # 10 – 6 Months after the First Injection Procedure
You will be asked to fill out the 7-day Pain and Sleep Interference Diary **before** this visit and to bring the diary with you for this visit. At this visit, the following tests or evaluations will be done: retinal fundoscopy, medication review, vital signs, nerve conduction (select sites), blood tests including for HGF, VM202, completion of questionnaires, assessment of neuropathy, and assessment of side effects.

Visit # 11 – 9 Months after the First Injection Procedure
You will be asked to fill out the 7-day Pain and Sleep Interference Diary **before** this visit and to bring the diary with you for this visit. At this visit, the following tests or evaluations will be done: retinal fundoscopy, medication review, vital signs, nerve conduction (select sites), blood tests including for HGF, VM202, completion of questionnaires, assessment of neuropathy, and assessment of side effects.

After you have completed your 9-month follow-up visit, you do not have to return for any more visits.

Medication Use during the Study

The study doctor will review your medications with you using the following directions:

- You are allowed to continue taking Lyrica (pregabalin) and/or gabapentin (Neurontin), and/or Cymbalta (duloxetine) during the study if you have been taking these medications for more than 3 months prior to Screening, but you are not allowed to start these medications or increase the dosage of either these medications until Day 180 visit of the study.

- Some medications have pain reduction as a side effect. If you are using any antidepressants (e.g. amitriptyline and venlafaxine), or any other antiepileptics (e.g., valproic acid, carbamazepine, vigabatrin) at Screening, you must maintain a stable dose of these medications until Day 180 visit of the study and you are not allowed to start these drugs until Day 180 visit of the study.

- The following therapies are not allowed during the study:
  - skeletal muscle relaxants
  - opioids
  - benzodiazepines (except for stable bedtime dose)
  - capsaicin
  - local anesthetic creams and patches (except for Lidocaine cream prior to study drug injections)
  - isosorbide dinitrate (ISDN) spray
  - transcutaneous electrical nerve stimulation (TENS)
  - acupuncture

  Your doctor will review these medications and treatments with you to make sure that you understand what is prohibited during the study.

- You are not allowed to use COX-2 inhibitor drug(s), non-specific COX-1/COX-2 inhibiting drugs, steroids, and more than 81 mg/day of aspirin during the study because these medications may interfere with VM202. For example, this includes medications such as Bayer aspirin (> 81 mg), Motrin and Advil (ibuprofen), Aleve (naproxen), and Excedrin (aspirin/acetaminophen/caffeine). Your doctor will review these medications with you to make sure you understand which medications are prohibited during the study.

  If the study doctor or you feel that you cannot adhere to these directions, please do not sign up for study participation.

How long will I be in this research study?
Your last follow up visit will be approximately 9 months after your first injection procedure. After this visit, you will have completed this study.

What do I have to do as a participant in this study?
Participation in this study requires you to make sure that you are available to attend all your scheduled visits.

During your participation in the study you will be asked to report any unpleasant medical experiences that you may have.

You must not use any additional prescription medication during the treatment period without first checking with your study doctor. Please note, some medications (prescription and non-prescription medications) may not be taken during the study since they may interfere with the potential effect of the study medication or ability to assess the response to the study medication. If you use any non-prescription medication you should inform your doctor of the details (medication, dose, etc.) at each study visit.

You also must not participate in any other clinical trial while participating in this study.

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 are known risks and discomforts involved in some of the tests and evaluations. There are also unknown risks. Below is a description of these risks. Your doctor will discuss the risks and procedures with you before you start in the study.

Risks from Injection Procedures
VM202 or placebo will be injected into the calf muscles using a fine needle. There may be some pain at the injection site at the time of injection. There may be swelling, bruising or

inflammation near the injection site. You may experience an increase in the level of pain in the treated leg. There may be a risk of an allergic reaction (anaphylaxis), fever or tissue damage from the injection (ulceration, necrosis). Because HGF (if you receive VM202) has the potential to create new blood vessels (angiogenesis), there may be risk of promoting tumor growth (cancer).

Risks to women who can get pregnant or are breastfeeding

Being a part of this study while pregnant may expose the unborn child to significant risks. Therefore, pregnant women cannot take part in this study. If you are a woman who can get pregnant, a urine pregnancy test will be done and it must show that you are not pregnant before you can participate in this study. You must also agree not to become pregnant during this study. You may not take part in this study if you are breastfeeding. If you are sexually active and with childbearing potential, you must agree to use an acceptable method of birth control during the whole study.

The following birth control measures are acceptable:

- Barrier type devices (examples are condom, diaphragm, and contraceptive sponge) used only in combination with a spermicide;
- Intrauterine device (IUD);
- Birth control pills
- Depo-provera (medroxyprogesterone acetate);
- Levonorgestrel implants;

Abstention, the rhythm method, and/or contraception by the partner are not acceptable methods of contraception.

If you do become pregnant during this study or think that you might be pregnant, you must inform your study doctor immediately. If this happens, the study doctor will discuss with you what you should do. If you get pregnant, you will be asked to stop taking part in the study and you will be asked for information about the pregnancy and the baby.

Risks from taking a blood sample

You will have routine blood samples taken from a vein in your arm by a needle stick. Risks associated with drawing blood from your arm include slight discomfort and/or bruising. Infection, bleeding, clotting, or fainting are also possible, although unlikely. The number of times that you will have a blood sample drawn for this study totals about 14 times over approximately 11 months. Each time your blood is drawn roughly 1 to 2 tablespoons of blood will be taken.

Risks from cancer screening

Cancer screening includes pap smear and mammogram if not performed within past 12 months (females only); for subjects 50 years of age or older, fecal occult blood test; and X-ray or CT scan of chest within the past 3 months.

Possible risks include a small amount of radiation exposure from a chest X-ray (or chest CT scan, if you have a history of smoking) and mammogram (if you are female), discomfort associated with pap smear and mammography (if you are female).

Risks from Nerve Conduction Studies (Select Sites Only – Omit if not applicable)
There is no chance of problems with nerve conduction studies. Nothing is put into your skin, so there is no chance of infection. The voltage of electrical pulses is not high enough to cause an injury. You may experience some discomfort or pain for a few seconds during nerve stimulation. The discomfort will end as soon as the stimulation is over.

Risks from Retinal Fundoscopy
The test itself involves no risk. If dilating eye drops are used, the drops may produce a brief stinging sensation when put in the eyes and a medicinal taste in the mouth caused by the medication draining from the tear ducts into the throat. Dilating eye drops rarely produce nausea, vomiting, dryness of the mouth, flushing, dizziness, or an attack of narrow-angle glaucoma. If glaucoma is suspected, drops generally are not used.

Risks from Fluorescein Angiography (if deemed necessary by the ophthalmologist at Screening). Side effects associated with injection of fluorescein dye into a vein in the arm include nausea and/or vomiting (approximately 5% of subjects) hives and itching (approximately 0.5% of subjects) and, rarely a life threatening allergic reaction, consisting of possible seizures and difficulty in breathing (less than 0.01%). There may be a local temporary discomfort at the site of injection.

Risks from EKG
In rare circumstances, a rash or irritation at the location of the electrocardiogram electrode placement can occur due to the adhesive. If this should occur, it will be assessed and treated using clinical standards of care with appropriate medication(s) and/or compresses.

Unknown risks
In addition to the risks already described, there may be other discomforts or risks from this study drug and/or procedures that we do not know about. You will be watched for signs and symptoms of any side effects and you should tell your doctor if you do not feel well or experience any unusual symptoms.

Are there benefits to taking part in this research study?
There may be no direct benefit to you by participating in this study. However, it is possible that the pain related to your diabetic neuropathy will improve.

Knowledge from this study may help us better understand how to treat people with 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, urine and blood tests, and study evaluations and procedures that are required for this research study are provided to you at no cost to you. You will also not need to pay for the VM202/placebo injections. 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 although you would not be able to get the VM202 product.

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 [redacted].), 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), representatives of the central laboratory facilities appointed by the Sponsor responsible for analyzing the blood tests, 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?

Currently, there are no approved drugs or treatment strategies known to stop or reverse the progression of diabetic peripheral neuropathy. Treatments goals are to reduce pain, improve physical function, reduce psychological distress, and improve quality of life. Good glycemic control is the only factor shown to slow the progress of neuropathy symptoms. Lowering your triglyceride level, losing weight (if you are overweight), stopping smoking (smokers only) and reducing blood pressure have also shown to reduce diabetic neuropathy symptoms.

If you choose not to take part in this study, other commonly prescribed medicines may be available for treatment of your diabetic neuropathy. 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. Medications Excluded from Use During the Study

WASHOUT TABLE FOR COX-2 INHIBITORS & STEROIDS

Drug	Example of Common Name(s)	Maximum Dose Allowed During Study	Washout Period
Cox-2 specific Inhibitors			
celecoxib	Celebrex	none	2 weeks
Non-Steroidal Anti-inflammatory Drugs (NSAIDs: nonspecific inhibitors of both Cox-1 and Cox-2)			
acetylsalicylic acid	Aspirin Arthritis Foundation Safety Coated Aspirin, Bayer Aspirin, Bayer Children's Aspirin, Ecotrin	81 mg daily	2 weeks for doses over 81 mg daily
diclofenac	Voltaren Arthrotec, Cambia, Cataflam, Flector, Pennsaid, Solaraze, Zipsor	none	2 weeks
diflunisal	Dolobid	none	2 weeks
etodolac	Lodine	none	1 week
fenoprofen	Nalfon	none	1 week
flurbiprofen	Ansaid	none	1 week
ibuprofen	Motrin, Advil, Caldolor, Profen	none	1 week
indomethacin	Indocin	none	1 week
ketoprofen	Nexcede, Orudis	none	None for topical formulation, 1 week for all others
ketorolac	Sprix, Acuvail, Acular, Toradol	none	1 week
mefenamic acid	Ponstel	none	1 week
meloxicam	Mobic	none	1 week
nabumetone	Relafen, Relifex and Gambaran	none	1 week
naproxen sodium	Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inza, Midol Extended Relief, Miranax, Naposin, Naprelan, Naprogesic, Naprosyn, Narocin, Proxen, Synflex, Xenobid	none	2 weeks
oxaprozin	Daypro	none	1 week
piroxicam	Feldene	none	1 week
sulindac	Clinoril	none	1 week
tolmetin	Tolectin	none	1 week
Corticosteroids (injected, oral, topical)	Prednisone, betamethasone, dexamethasone, cortisone, triamcinolone	none†	1 week

Please note, some of these medications are provided in combination with other drugs in new formulations (e.g. AGGRENOX® (aspirin/extended-release dipyridamole); Excedrin (acetaminophen; aspirin; caffeine))

† inhaled steroids and ocular steroids are allowed.

WASHOUT OF OPIOIDS AND OTHER THERAPIES

Subjects must refrain from taking these drugs or undergoing these therapies for the duration of the study since these therapies may interfere with assessment of VM202 effect on pain:

- skeletal muscle relaxants
- opioids (e.g., morphine, oxycodone, tramadol [Ultram], methadone, fentanyl etc.)
- benzodiazepines (except for stable bedtime dose),
- capsaicin
- local anesthetic creams (except for Lidocaine cream prior to IM injection) and patches
- isosorbide dinitrate (ISDN) spray,
- transcutaneous electrical nerve stimulation (TENS)
- acupuncture

Subjects must discontinue use of these therapies seven (7) days prior to starting the Daily Pain and Sleep Interference Diary at Screening.

Subject must agree to remain off of these medications/treatments until completion of the 9-month follow-up visit.

Appendix 4. Continued Stable Use of Specific Medications/Treatments during the Study

During the study, subjects must be on a ***stable regimen*** for painful DPN. If subjects are using any of the following medications at Screening, they must continue the use of these medications at the same regimen for the first 6 months of the study:

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Duloxetine (Cymbalta)
- Any antidepressants (e.g. amitriptyline and venlafaxine)
- Any anti-epileptics (e.g., valproic acid, carbamazepine, vigabatrin)

If the subject is **not using** any of these medications, subjects must agree ***not to start*** any of these medications for the first 6 months of the study.

Moreover, in order to meet inclusion criterion #11, subjects must be on a ***stable regimen*** of the following medications for painful DPN **for at least 3 months prior to study entry** (date of signing the informed consent):

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Duloxetine (Cymbalta)

Appendix 5. Michigan Neuropathy Screening Instrument

Patient Version

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

A. History (To be completed by the person with diabetes)

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

1. Are you legs and/or feet numb?	☐ Yes	☐ No
2. Do you ever have any burning pain in your legs and/or feet?	☐ Yes	☐ No
3. Are your feet too sensitive to touch?	☐ Yes	☐ No
4. Do you get muscle cramps in your legs and/or feet?	☐ Yes	☐ No
5. Do you ever have any prickling feelings in your legs or feet?	☐ Yes	☐ No
6. Does it hurt when the bed covers touch your skin?	☐ Yes	☐ No
7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	☐ Yes	☐ No
8. Have you ever had an open sore on your foot?	☐ Yes	☐ No
9. Has your doctor ever told you that you have diabetic neuropathy?	☐ Yes	☐ No
10. Do you feel weak all over most of the time?	☐ Yes	☐ No
11. Are your symptoms worse at night?	☐ Yes	☐ No
12. Do your legs hurt when you walk?	☐ Yes	☐ No
13. Are you able to sense your feet when you walk?	☐ Yes	☐ No
14. Is the skin on your feet so dry that it cracks open?	☐ Yes	☐ No
15. Have you ever had an amputation?	☐ Yes	☐ No

Total: _____

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

B. Physical Assessment (To be completed by health professional)

1. Appearance of Feet

	Right	Left
a. Normal	☐ 0 Yes ☐ 1 No	Normal ☐ 0 Yes ☐ 1 No
b. If no, check all that apply:		If no, check all that apply:
Deformities	☐	Deformities ☐
Dry skin, callus	☐	Dry skin, callus ☐
Infection	☐	Infection ☐
Fissure	☐	Fissure ☐
Other	☐	Other ☐
specify: _____		specify: _____

	Right		Left	
	Absent	Present	Absent	Present
2. Ulceration	☐ 0	☐ 1	☐ 0	☐ 1

	Right			Left		
	Present	Present/ Reinforcement	Absent	Present	Present/ Reinforcement	Absent
3. Ankle Reflexes	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1

	Right			Left		
	Present	Decreased	Absent	Present	Decreased	Absent
4. Vibration perception at great toe	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1

	Right			Left		
	Normal	Reduced	Absent	Normal	Reduced	Absent
5. Monofilament	☐ 0	☐ 0.5	☐ 1	☐ 0	☐ 0.5	☐ 1

Signature:_____ Total Score _____/10 Points

How to Use the Michigan Neuropathy Screening Instrument

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

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

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

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

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

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

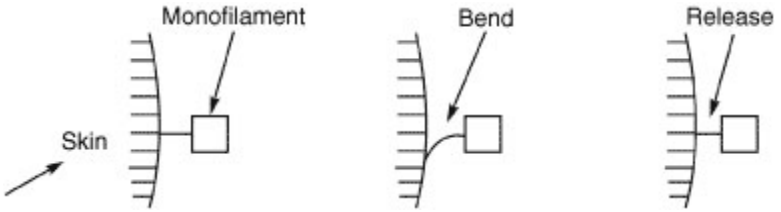
Monofilament Testing: For this examination, it is important that the subject's foot be supported (i.e., allow the sole of the foot to rest on a flat, warm surface). The filament should initially be

prestressed (4-6 perpendicular applications to the dorsum of the examiner's first finger). The filament is then applied to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. The filament is applied perpendicularly and briefly, (<1 second) with an even pressure. When the filament bends, the force of 10 grams has been applied. The subject, whose eyes are closed, is asked to respond yes if he/she feels the filament. Eight correct responses out of 10 applications is considered normal: one to seven correct responses indicates reduced sensation and no correct answers translates into absent sensation.

Appendix 6. Semmes Weinstein Monofilament Testing

Directions for use of Semmes – Weinstein Monofilament Testing[3]

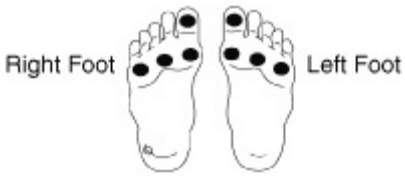
1. Assess integrity of monofilament (no bends/breaks).
2. Show the monofilament to the client. Place the end of the monofilament on his/her hand or arm to show that the testing procedure will not hurt.
3. Ask the client to turn his/her head and close his/her eyes or look at the ceiling.
4. Hold the monofilament perpendicular to the skin.



5. Place the end of the monofilament on the sole of the foot. Ask the subject to say 'yes' when he/she feels you touching his/her foot with the monofilament. DO NOT ASK THE SUBJECT, "did you feel that?" If the subject does not say 'yes' when you touch a given testing site, continue on to another site. When you have completed the sequence RETEST the area(s) where the subject did not feel monofilament.
6. Push the monofilament until it bends, then hold for 1-3 seconds.
7. Lift the monofilament from the skin. Do not brush or slide along the skin.
8. Repeat the sequence randomly at each testing site on the foot (see pictures below).

ALL TESTING IS PERFORMED BILATERALLY (ON BOTH FEET)

Sites on the sole of the foot for monofilament testing



PLANTAR ASPECT OF GREAT TOE, FIRST, THIRD AND FIFTH METATARSAL HEADS OF EACH FOOT

Dorsal aspect of the great toe for monofilament testing

The same location used for the MNSI assessment will be tested, specifically, filaments are applied to the dorsum of the great toe midway between the nail fold and the DIP joint.

Testing with the monofilaments begins with filaments in the normal threshold level and progresses to filaments of increasing pressure until touch is identified by the subject. The smallest monofilament (lowest grams) that can be felt by the subject should be indicated for each

[3] Use of Semmes-Weinstein Monofilament Testing – Nursing Best Practices Guidelines http://pda.rnao.ca/content/use-semmes-weinstein-monofilament (downloaded 14Oct14)

location. Filaments should be applied a minimum of three times, *with one response out of three taken as an affirmative response.*

The following filaments will be used.

Filament	Force (g)	Interpretation
2.83	0.07	Normal
3.61	0.4	Diminished Light Touch
4.31	2.0	Diminished Protective Sensation
4.60	4.0	Mild Loss of Protective Sensation
5.07	10	Moderate Loss of Protective Sensation
6.65	300	Deep Pressure Sensation Only

Notes

- Apply only to intact skin. Avoid calluses, ulcerated or scarred areas.
- DO NOT use a rapid or tapping movement.
- If the monofilament accidentally slides along the skin, retest that area later in the testing sequence.
- Store the monofilament according to the manufacturer's instructions.
- Clean the monofilament according to agency infection control protocols.

Appendix 7. Test Article Administration

1. ***Test article preparation***

VM202 - VM202 is supplied in a sterile glass vial containing 2.5 mg of lyophilized study product. Before administration, it will be reconstituted with 5.0 mL of water for injection (WFI) for a final VM202 concentration of 0.5 mg / mL. Each reconstituted vial is only to be used for one subject. For subjects randomized to the VM202 arm of the study, the final doses of VM202 will be divided evenly between the Day 0, Day 14, Day 90 and Day 104 administration. Each individual injection will be 0.5 mL and the use of Luer lock syringes is recommended. All injections will be administered by intramuscular injections.

Placebo - Subjects assigned to the placebo arm will receive VM202 vehicle injections. The placebo group will receive only VM202 vehicle injections. The VM202 arm will receive 16 injections of VM202 in each leg at all four injection visits. Visually, VM202 vehicle is indistinguishable from reconstituted VM202.

Table 7. Single dose preparation and delivery for Day 0, Day 14, Day 90 and Day 104 Visits

Treatment Arm	Number of Vials at each visit	Number of injections† / leg	Total Volume to be Injected / leg
VM202 4 mg / leg Total Dose: 8 mg VM202	4 Vials VM202, reconstituted with WFI	16 of VM202	8 mL
Placebo – VM202 vehicle	4 Vials of VM202 Vehicle	16 of placebo	8 mL

†Injection volume for each individual injection = 0.5 mL

2. ***Test material administration*** – Subjects will receive injections of VM202 or placebo on Day 0, Day 14, Day 90 and Day 104. A fine needle (e.g. 27 gauge, 1.25") suitable for IM injections will be used. **Both calves will be treated with 16 injections each at each visit.** Distribute injection sites evenly over the calf muscle, carefully avoiding fascia.

3. Inject the entire amount of the drug per each injection in about 3-5 seconds. Immediately after completion of injection, lightly press the injection site with the finger head in order to prevent reflux. Do not massage the injection site. An indelible marker should be used to identify each injection site.

4. ***Subsequent administrations*** – Subsequent administrations should also be distributed evenly over the calf, and, as much as is possible, at different injection sites. If marks made to identify previous injection sites are visible, every effort should be made to inject at alternate locations.

Appendix 8. Brief Pain Inventory for Subjects with Diabetic Peripheral Neuropathy (BPI-DPN)

Upon completion of the questionnaire, the study coordinator will check the BPI-DPN for completeness. Note, the subject will be required to initial and date the BPI-DPN.

STUDY ID #: VMDN-003 DO NOT WRITE ABOVE THIS LINE Subject # _____

Brief Pain Inventory (Short Form)

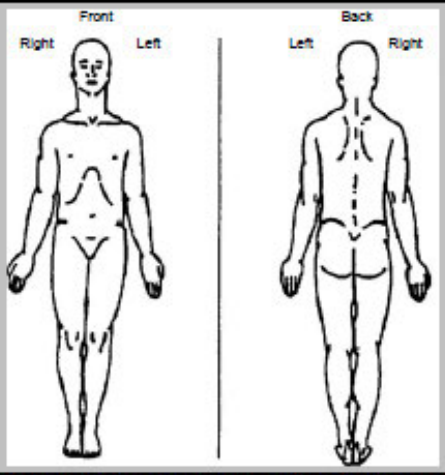
Date: ____/____/____ Time: _____

Visit: ☐2 Day 0 (pre-injection) ☐6 Day 90 (pre-injection) ☐10 Day 180 (Month 6)
☐11 Day 270 (Month 9)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

Page 1 of 2

STUDY ID #: VMDN-003 DO NOT WRITE ABOVE THIS LINE Subject #: _____

Date: ____/____/____ Time: _____

Visit: ☐2 Day 0 (pre-injection) ☐6 Day 90 (pre-injection) ☐10 Day 180 (Month 6)
☐11 Day 270 (Month 9)

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

B. Mood

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

C. Walking Ability

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

E. Relations with other people

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

F. Sleep

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere 1 2 3 4 5 6 7 8 9 10 Completely Interferes

Subject Initials: _____ Date:_____

Appendix 9. Visual Analog Scale

The VAS will be completed by the subject. The subject should be asked: "**How do you currently rate your pain in your legs (below the knee – this includes pain in your feet)**?"

The subject should be instructed to indicate his or her current level of pain in their legs by placing a single vertical line perpendicular to the horizontal line of the scale ensuring that the two lines intersect. Additionally, the subject should be instructed to not use a check mark, "x" or circle that would intersect the horizontal line of the scale multiple times. Ensure the subject understands that the mark must be only one line that is perpendicular to and intersects the scale line. The subject should complete the VAS with a fine or medium point pen; felt tip pens and pencils should not be used.

No pain |_____| Very severe pain

Note, the subject will be required to initial and date the VAS. The VAS should be checked for accuracy and completeness immediately after it is completed by the subject. If the subject's mark does not intersect the line or intersects the line more than once, reinstruct the subject to modify his or her mark so it meets the appropriate criteria. Any corrections should be accompanied by the subject's initial and date.

For Day 0 and Day 90, all corrections MUST be completed prior to injections; do NOT have the subject correct the scale after injections. Instead, use the data collected prior to dosing.

The VAS score (0 to 100mm) will be calculated by measuring the distance from the left end of the line ("No Pain") along the scale to the mark made by the subject. If the mark made by the subject intersects the horizontal line of the scale multiple times and was not corrected, measure to the middle point between the two marks. If the mark made by the subject does not intersect the line of the scale and was not corrected, project the location of the mark vertically to a point on the line of the scale for the measurement.

Appendix 10. 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 11. Symptoms of Brief Peripheral Neuropathy Screening

INSTRUCTIONS FOR RECORDING SUBJECTIVE ELICITED SYMPTOMS:

- Ask the subject to rate the severity of each symptom listed in question 1a-1c on a scale of 01 (mild) to 10 (most severe) for right and left feet, legs.
- Enter the score for each symptom in the column marked Presence/Severity.
- If a symptom has been present in the past, but not since the last visit, enter '00-Currently Absent.'
- If the symptom has never been present, enter '11-Always Been Normal.'

Always Been Normal	Currently Absent	Mild ---------- Severe									
11	**00**	**01**	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**

1. **SYMPTOMS** **PRESENCE/SEVERITY**

	Right	Left
a. Pain, aching, or burning in feet, legs: ……	☐☐	☐☐
b. "Pins and needles" in feet, legs: ……	☐☐	☐☐
c. Numbness (lack of feeling) in feet, legs: ……	☐☐	☐☐
d. Total points (add a + b + c excluding any scores of 11)……	☐☐	☐☐

AT SCREENING, THE DIFFERENCE IN TOTAL SCORE BETWEEN LEGS SHOULD BE ≤ 5 POINTS IN ORDER TO BE ELIGIBLE.

Appendix 12. 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:** _____

Appendix 13. Nerve Conduction Testing (at select sites only)

NERVE CONDUCTION[4] - GENERAL INSTRUCTIONS

Overview: These studies will examine nerve conduction velocity (NCV) and the response amplitude for a distal sensory nerve (i.e., sural nerve) and for a distal motor nerve (i.e., peroneal nerve). These measures will be determined using standard surface electrophysiologic procedures.[5]

The key analysis will be a comparison of mean NCV measures at baseline, and Day 180:

- NCV will be measured in m/sec to the nearest 0.1 m/sec
- Sensory amplitude will be measured in μV to the nearest 0.1 μV
- Motor amplitude in mV to the nearest 0.1 mV.

Recording procedures, distances, electrode placements, limb temperature, instrument calibration, units of measurement and waveform display and will be standardized across sites. All electrophysiologic procedures will be reviewed by a Central Reading site at the Laboratory for Behavioral Neurophysiology – Albert Einstein College of Medicine in NY.

Skin Preparation

The skin where recording, stimulating, and ground electrodes are placed will be cleaned and lightly abraded at each stimulation and recording site.

Temperature Probe

Skin temperature will be measured at a mid-calf site in each patient at each recording session. If necessary, the skin will be gradually warmed using a Hydroculator or warming pads.

Equipment

The equipment used for electrophysiology at each site will need to meet the following criteria: calibration, capacity for data averaging, capacity for appropriate data printing and display with units of measurement. Units that measure motor NCV from a site off the muscle will not be accepted.

[4] Manual of Nerve Conduction Studies – Second Edition. Ralph M. Buschbacher, Nathan D. Prahlow
[5] Electrodiagnosis in Diseases of the Nerves and Muscle: Principles and Practice - J. Kumura, 1981

SURAL NERVE SENSORY NERVE CONDUCTION STUDY

Position:

This study is performed in the side-lying position.

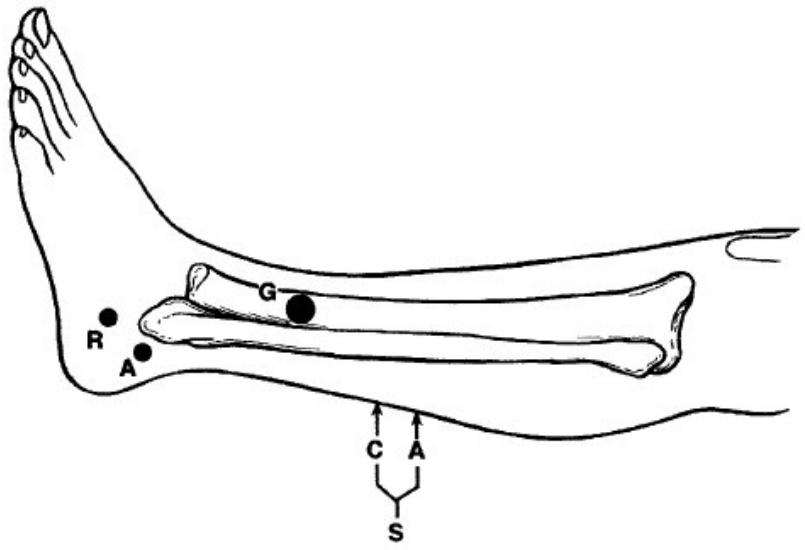
Recording Electrodes

Commercially available disposable electrodes.

- Active electrode (A): Placement immediately behind the lateral malleolus. The electrode should be placed over the sural nerve on a line that goes from the triceps sural tendon to the prominence of the lateral malleolus perpendicular to the sural nerve.
- Reference electrode (R): The reference electrode is placed 4.0 cm distal to the active electrode along the course of the nerve.

Ground Electrode

The ground electrode should be placed on the calf between the active recording electrode and the stimulating electrode.



Electrode Placement

Stimulation Point

The cathode (C) is placed 14.0 cm proximal to the active recording electrode in the midline or slightly lateral to the midline of the posterior lower leg. The anode (A) is proximal. In patients that are short, the distance between the cathode and recording electrode can be reduced, however, in this circumstance the selected distance (e.g., 12 cm) must remain constant across visits for that subject.

Recommended Machine Settings:

- Sensitivity 10 μV/division
- Low frequency filter: 20 Hz
- High frequency filter: 3.0 kHz
- Sweep speed: 1.0 msec/division

Procedure

A. Stimulate the nerve at a point 14.0 cm (or shorter if appropriate) proximal to the active recording electrode.

B. When a supramaximal response is obtained, average at least three but not more than ten responses.

C. Mark the responses with the cursors. If the instrument automatically marks the responses, make sure they are marked correctly. Change the cursors if necessary.

D. Measure and record the distance between the active electrode and the site of the cathode stimulating electrode.

E. Record the skin temperature before and after the nerve conduction is completed.

Print Waveforms

Print a copy of the waveform. Make sure the copy has the following information: name of nerve, side studied, date, patient ID number, and patient initials.

Complete Worksheets

Complete the worksheets. Follow directions carefully and make sure that all information is transcribed correctly.

Left Sural Nerve	Onset Latency msec	Peak Amplitude uV	Distance mm	NCV m/sec	Start Temp (^{0}C)	End Temp (^{0}C)

PERONEAL MOTOR NERVE CONDUCTION STUDY

Position:

This study is performed in the supine position.

Recording Electrodes

- Active electrode (A): Placement is over the center of the palpable portion of the extensor digitorum brevis muscle on the lateral aspect of the dorsum of the foot, 1.0 cm distal to the calcaneous bone (bony prominence from which the muscle takes its origin).
- Reference electrode (R): Placement is over the fifth metatarsal-phalangeal joint on the lateral portion of the foot. It is placed lateral to the long extensor tendons of the small toe.

Ground Electrode (G)

The ground electrode is placed between the active recording electrode and to the cathode stimulating electrode on the dorsum of the ankle.

Stimulation Point 1 (S1)

Distal stimulation site (Ankle)

The cathode (C) is placed on the anterior aspect of the ankle 2-5 cm lateral to the tendon of the tibialis anterior muscle, approximately 5.0 cm proximal to the lateral malleolus, and 8.5 cm from the active electrode. The anode (A) is proximal.

Stimulation Point 2 (S2)
Proximal stimulation site (Fibular head)

The cathode (C) is placed over the nerve where it runs immediately below the fibula and enters the anterior compartment. The anode (A) is proximal.

Stimulation Point 3 (S3)
Proximal stimulation site (Knee)

The cathode (C) is placed over the nerve in the popliteal fossa approximately 10 cm proximal to the head of the fibula. The cathode is placed just medial to the tendon of the long head of the biceps femoris muscle. The anode (A) is proximal.

Recommended Machine Settings:

- Sensitivity 2.0 mV/division; it may be necessary to use a different display sensitivity to ensure the response is a minimum of two divisions high.
- Low frequency filter: 2-3 Hz
- High frequency filter: 10 kHz
- Sweep speed: 5 msec/division

Procedure:

A. Stimulate the nerve at the ankle, fibular head, and the knee.
B. When a supramaximal response is obtained, record the response.
C. Mark the responses with the cursors. If the instrument automatically marks the responses, make sure they are done correctly. Change the cursors if necessary.
D. Measure and record the appropriate distances. Measure the distance between the active recording electrode and the cathode of the stimulator.
(1) Measure the distance between the active electrode at the ankle and the site of the stimulating cathode electrode.
(2) Measure the distance between the ankle and the fibular head.
(3) Measure the distance between the ankle and the knee.
Do not measure the distance between fibular head and knee.
E. Record the temperature before and after the nerve conduction is completed.

Print Waveforms
Print a copy of the waveform. Make sure the copy has the following information: name of nerve, side studied, date, patient ID number, and patient initials.

Complete Worksheets
Complete the worksheets. Follow directions carefully and make sure that all information is transcribed correctly.

Left Peroneal Nerve	Onset Latency (msec)	Peak Amplitude (mV)	Distance mm	NCV m/sec	Start Temp (^{0}C)	End Temp (^{0}C)
Ankle						
Fibular head						