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

Protocol VMDN-002 / C

August 1, 2012

Sponsor

[redacted]

[redacted]

DISCLOSURE STATEMENT

[redacted]

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

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	A Phase II, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects with Painful Diabetic Peripheral Neuropathy
STUDY PHASE	II
INVESTIGATIONAL AGENT	VM202
DOSE	Two doses will be tested: 16 mg and 32 mg VM202.
POPULATION	Subjects aged ≥ 18 years to ≤ 75 years diagnosed with painful diabetic neuropathy in both lower extremities.
STUDY DESIGN	A phase II, 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 calf of subjects with painful diabetic peripheral neuropathy (DPN). One-hundred (100) subjects will be randomized in a 2:2:1 ratio to one of three treatment groups: Low Dose: 16 mg VM202 - 40 subjects High Dose: 32 mg VM202 - 40 subjects Control – Placebo (normal saline) - 20 subjects Up to twenty (20) sites will participate in the study. Safety will be monitored throughout the study and assessed by an independent Data Safety Monitoring Board (DSMB).
STUDY OBJECTIVES	• To evaluate the safety of IM administration of VM202 in subjects with painful DPN in lower extremities. • To evaluate the potential bioactivity of IM administration of VM202 in subjects with painful DPN, when compared with placebo, on pain.
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 oral medication and / or insulin
3. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities;
4. Lower extremity pain for at least 6 months
5. Visual analog scale (VAS) score of ≥ 40 mm at Initial Screening (0 mm = no pain – 100 nm very severe pain);
6. Symptoms from the Brief Pain Neuropathy Screening (BPNS) is ≤ 5 point difference between legs at Initial Screening;
7. 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;
8. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Screening;
9. Stable treatment of diabetes for at least 3 months with no anticipated changes in medication regimen, and no new symptoms associated with diabetes; and
10. 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 (HBcAb), antibody to Hepatitis B surface antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening;
10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy;
11. Stroke or myocardial infarction within last 3 months;
12. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
13. Specific laboratory values at Screening including: 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;

14. Uncontrolled hypertension as defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at Screening;
15. Patients 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); patients with 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 any opioids; subjects may be enrolled if willing and able to discontinue use of these drugs 14 days prior to starting the 7 Day Daily Pain and Sleep Interference Diary and refrain from taking these drugs for the duration of the study;
17. 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;
18. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or high dose steroids (excepting inhaled 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 for the duration of the study;
19. Major psychiatric disorder within last 6 months that would interfere with study participation;
20. Body mass index (BMI) > 45 kg/m^2 at Screening;
21. Any lower extremity amputation;
22. Use of an investigational drug or treatment in past 6 months; and
23. Unable or unwilling to give informed consent.

STUDY PROCEDURES

Screening should occur within the 60 days prior to Day 0 (day of injection) and assessments other than the completion of the Diary may be scheduled during medication washout. Screening will include assessment of study eligibility, a complete medical history, vital signs, physical exam, concomitant medications, cancer screening tests, viral screening, MNSI, VAS, 12 lead EKG, retinal fundoscopy, serum chemistry and hematology, and pregnancy test (women of childbearing potential only).

Prior to full 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 score of ≥ 3 will be allowed to proceed with the full screening procedures. The remaining screening activities will include assessment of the other study eligibility criteria, a complete medical history, vital signs, physical exam, concomitant medications, cancer screening tests, viral screening, 12 lead EKG, retinal fundoscopy, serum chemistry and hematology including HbA1c, urinalysis, and pregnancy test (women of childbearing potential only).

If applicable, the subject will be washed out of prohibited medications prior to initiation of the 7 day Daily Pain and Sleep Interference Diary; completion of the Diary should occur within 14 days prior to the first round of injections. 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 2:2:1 ratio to the low dose, high dose or placebo group.

Prior to injections, subjects will undergo a skin biopsy (one 3 mm diameter round sample from the left ankle, the left calf and the left upper thigh, for a total of 3 samples / subject). Subjects will receive VM202 or placebo (normal saline) by intramuscular injections in both legs (in the calf) on Day 0, and Day 14 as follows:

Treatment Group	Dose VM202 (mg) / Visit / Leg		Final Dose VM202 / Leg (mg)	Final Dose VM202 / Patient (mg)
	Day 0	Day 14		
Low Dose	4	4	8	16
High Dose	8	8	16	32
Placebo	0	0	0	0

0 indicates injections of normal saline

VM202 will be delivered in a solution of 0.5mg VM202 / mL. All subjects will receive thirty-two (32) 0.5 mL injections evenly distributed over each calf at each visit of VM202 or placebo as follows:

Subjects in the Low Dose Group (8mg VM202 / leg) will receive the following intramuscular injections in each calf:

- Day 0 – 32 injections / calf:

    - 16 injections of 0.5mL of VM202 / calf – (4 mg of VM202 / calf)
    - 16 injections of 0.5mL of normal saline / calf
- Day 14 – 32 injections / calf:
    - 16 injections of 0.5mL of VM202 / calf – (4 mg of VM202 / calf)
    - 16 injections of 0.5mL of normal saline / calf

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

Subjects in the High Dose Group (16 mg VM202 / leg) will receive the following intramuscular injections in each calf:

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

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

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 30, Day 60 and Day 90.

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 30, Day 60 and Day 90.

VAS, and Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), will be recorded at Day 0, Day 30, Day 60, Day 90, at 6 months and 9 months. Patients' Global Impression of Change (PGIC) will be recorded at Day 30, Day 60, Day 90, at 6 months and 9 months. MNSI will be conducted at 6 months and 9 months to track disease progression. Skin biopsy will be repeated at 6 months and symptoms of the Brief Peripheral Neuropathy Screening (BPNS) will be recorded at 6 months.

The Daily Pain and Sleep Interference Diary will be filled out by patients before Day 90, the 6 Month and 9 Month visits.

Retinal fundoscopy will be conducted at 9 months.

	Adverse events will be recorded throughout the 9 month follow-up period.
SCHEDULE OF EXAMINATIONS	Screening (Day -60 to Day 0) Day 0 Day 14 ± 1 days Day 21 ± 3 days Day 30 ± 3 days Day 60 ± 3 days Day 90 ± 7 days Month 6 ± 1 month Month 9 ± 1 month
STUDY ENDPOINTS	The primary study endpoint is the change in the average 24 hour pain score (change from baseline to the 6-month follow-up). The difference in the mean of the change in the average 24-hour pain score will be compared between the treatment groups and the placebo arm to determine the treatment effect. The average pain scores will be obtained from the Daily Pain and Sleep Interference Diary (recorded daily by the patient for 7 days during Screening prior to the first round of injections and again, before the 6 month follow-up).
SAFETY	Any subject who receives study drug (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 months 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 safety parameters. All subjects will all undergo testing as presented in the American Cancer Society Cancer Screening Guidelines as part of their baseline testing to rule out cancer.
PHARMACOKINETICS	Determination of HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 30, Day 60, and Day 90. 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 30, Day 60 and Day 90.
OTHER EFFICACY MEASURES	The 24 hour average pain score obtained from the Daily Pain and Sleep Interference Diary will be compared at all other study visits,

as will the Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), the VAS score obtained during follow-up visits, symptoms of the Brief Peripheral Neuropathy Screening (BPNS), the Patients' Global Impression of Change (PGIC), MNSI, and histological findings on skin biopsy.

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ABBREVIATIONS

AE / SAE	Adverse Event / Serious Adverse Event
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
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulation
CLI	Critical Limb Ischemia
cm	Centimeter(s)
CRF	Case Report Form
CRO	Clinical Research Organization
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicities
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
FDA	Food and Drug Administration
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core antibody
HBsAb	Antibody to Hepatitis B surface antigen (IgG and IgM)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IND	Investigational New Drug
LLOQ	Lower limit of quantitation
MNSI	Michigan Neuropathy Screening Instrument
PGIC	Patients' Global Impression of Change
PSA	Prostate Specific Antigen
RNA	Ribonucleic Acid
SBP	Systolic Blood Pressure
SGPT	Serum Glutamic Pyruvic Transaminase (same as ALT)
SOP	Standard Operating Procedure
VAS	Visual Analog Scale
WBC	White Blood Cell Count
WFI	Water for Injection

PERSONNEL AND FACILITIES

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1. BACKGROUND

1.1. DIABETES

Approximately 23.6 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 2007 was $174 billion, including $116 billion in excess medical expenditures and $58 billion in reduced national productivity.[1]

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.[2] 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.[3,4]

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, 3.9 million diabetics over the age of 40 already have symptomatic DPN.[5] The total annual cost of DPN and its complications in the U.S. is estimated to be between $4.6 and $13.7 billion.[6,7] 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

† CDC. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. Available at http://www.cdc.gov/diabetes/pubs/factsheet07.htm#contents.

stress.[8] Vascular dysfunction, driven by metabolic change, is thought to play a crucial role in the progression of diabetic neuropathy.[9-12] Figure 1 portrays the relationship of hyperglycemia to oxidative stress, metabolic alterations, vascular dysfunction and neural damage.

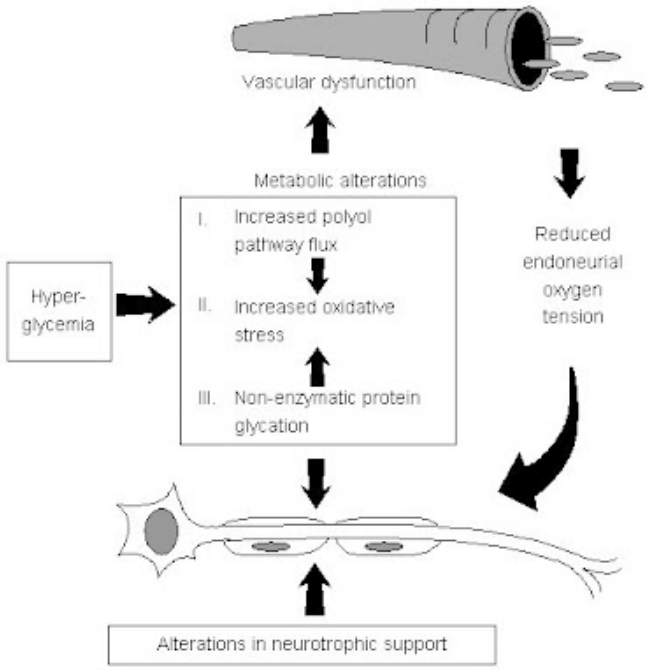


Figure 1. The neurodestructive effects of hyperglycemia

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.[13]

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. Hyperglycemia induces an increased presence of markers of oxidative stress, such as superoxide and peroxynitrite ions, and decreases antioxidant defense moieties in patients with DPN. It is associated with the development of apoptosis in neurons and supporting glial cells [14]

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.[15]

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.[16-18]

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, smoking, and hypertension.[19]

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.[20]

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.[2]

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 once a 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.[21]

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 patients had mixed results.[22]

Pancreatic transplantation. Pancreatic transplantation in patients with diabetes can stabilize neuropathy and in some instances improve motor, sensory, and autonomic function.[23]

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. There is currently no effective treatment for diabetic neuropathy, and good glycemic control is the only way to minimize the risk of occurrence. 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.[24,25] It is a multi-functional mesenchyme-derived cytokine with potent angiogenic and anti-apoptotic effects [24-27] HGF stimulates DNA, RNA and protein synthesis by endothelial cells in a dose-dependent manner and attenuates high D-glucose-induced endothelial cell death. 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*.[28,29] Recently, HGF gene transfer has been shown to produce significant augmentation of collateral formation in the rabbit hind limb ischemia model.[25] Furthermore, a significant increase in blood flow was achieved by HGF gene transfer both in rat diabetic and non-diabetic hind limb ischemia models.[27,30]

Recent research also indicates that HGF can function as a neurotrophic factor.[31] 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.[32-36] 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,[37] 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.[38-41]

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.[42,43]

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 (HGF-X7) expressing two isoforms of HGF, HGF 728 and HGF 723.

The key feature of HGF-X7 is that it was designed by inserting a series of intron sequences into certain sites of HGF cDNA so that both isoforms of HGF protein are expressed simultaneously and efficiently as in the human genome. Because there is

[redacted]
VM202 are identical to the wild-type human HGF proteins.

[redacted]

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.[44-46] This local effect of conventionally injected naked plasmid DNA is well known.[47,48]

Potential Efficacy of VM202. VM202 has demonstrated potential for stimulating angiogenesis in animal models. The development of new blood vessels may improve blood flow to peripheral nerves and potentially replace damaged capillary bed. As there is some overlap in the pathology of critical limb ischemia and diabetic neuropathy,[49] VM202 may have the ability to decrease neuropathic pain, and improve quality of life and exercise capacity.

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 three clinical trials.

1.6.1. PHASE I STUDY IN CRITICAL LIMB ISCHEMIA

VM202was 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 2 mg, 4 mg, 8 mg, or 16 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 to be 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 ABI and 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. $TCPO_2$ showed an improvement trend (increase). A significant reduction in pain was reported by nine of eleven subjects, with median 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 (4 mg VM202) than in any other cohort. Cohort I (2 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 16 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 have been published in *Gene Therapy* in 2011.[50]

1.6.2. PHASE II STUDY IN CRITICAL LIMB ISCHEMIA

VM202 is being evaluated for treatment of CLI in a prospective, double-blind, placebo-controlled, multicenter Phase II study. Eligible subjects are randomized to a low dose of VM202 (8mg, n=20), high dose of VM202 (16mg, n=20) or placebo (n=10). Subjects are receiving a final dose of 8 mg VM202, 16 mg VM202 or placebo by IM injections in the affected, unilateral calf on Days 0, 14, 28, and 42. As of July 29, 2011, 33 thirty-three (33) subjects have been enrolled into the study. All 33 received at least one round of injections; 31 subjects have completed all four rounds of injections. Twenty-four (24) completed the 90 day follow-up evaluation; 14 completed the six months follow-up; 8 completed the 9 month follow-up, and 3 subjects have completed the 12 month follow-up and have been exited from the study. To date, two patients have been discontinued or withdrawn early from the study. One patient withdrew after completing all rounds of injections but prior to the 90-day follow- prior to clinical hold.

As of July 29, 2011, fourteen (14) subjects experienced 20 serious adverse events, none of which were considered related to the study medication. Ten (10) patients experienced one SAE to date, three (3) patients have experienced 2 SAEs, and one (1) patient has experienced 4 SAEs. There were eleven (11) incidents of 'worsening of peripheral arterial disease (PAD)', which included increased pain, acute-on-chronic critical limb ischemia, increased ulceration requiring skin grafting, or the development of gangrene/infection requiring amputation. There were two (2) incidents of femoral artery thrombosis, two (2) gastrointestinal bleeds, and one each of arrhythmia resulting in pacemaker implantation, acute renal failure, chest pain, , worsening of COPD, and pancreatitis.

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

VM202 was evaluated for treatment of DPN in an ongoing prospective, dose-escalation Phase I study. The study consisted of three (3) cohorts of four (4) subjects. Subjects received 4 mg, 8 mg, or 16 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 patient each in Cohort I and Cohort II did not experience a reduction in pain. At 6 month, mean change in VAS was -8.2 in Cohort I, -31.6 in Cohort II and -25 in Cohort III.

At 12 month, 9 out of 12 subjects (9/12, 75%) experienced a reduction in pain. The same 2 patients, one each in Cohort I and Cohort II did not experience a reduction in pain, and one patient in Cohort III returned to baseline levels at 12 month. At 12 month, 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 (BPI-DPN).
Intramuscular injections of VM202 appear to be well tolerated at doses as high as 16 mg in patients 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.

Preliminary Conclusions. These early 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

DPN, 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 seen thus far in the phase I CLI study, the ongoing phase II CLI study and the safety and preliminary efficacy data from the phase I/II study of VM202 injections in patients with DPN, we propose bilateral treatment in this phase II study.

Two doses of VM202 will be tested against placebo (normal saline). The dose of VM202 per leg will remain within the dosing scheme of the phase I/II study (8 mg / leg and 16 mg /leg), and the same dosing schedule used in the DPN phase I study will be followed in this study (namely, intramuscular injections in the calf will be

given on Day 0, and Day 14). As in all three prior studies, VM202 will be delivered in a solution of 0.5 mg VM202 / mL. Subjects will be treated with an overall final dose of 16 mg VM202, 32 mg VM202 or placebo, dosages well within those supported by the body of pharmacology and toxicology safety studies of VM202. Safety studies in rabbit, rat and mouse models demonstrate that doses approximately 2½ (80mg/70kg) to 30 (960mg/70kg) times the maximum clinical dose (32 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 II study is to evaluate the safety of IM administration of VM202 in subjects with painful DPN in lower extremities. In addition, the potential bioactivity of IM administration of VM202 in subjects with painful DPN, when compared with placebo, on pain will be assessed.

3.2. STUDY DESIGN

This is a phase II, 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 full 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 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

and hematology including HbA1c, urinalysis, and pregnancy test (women of childbearing potential only).

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 shall be completed with 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; patient 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.

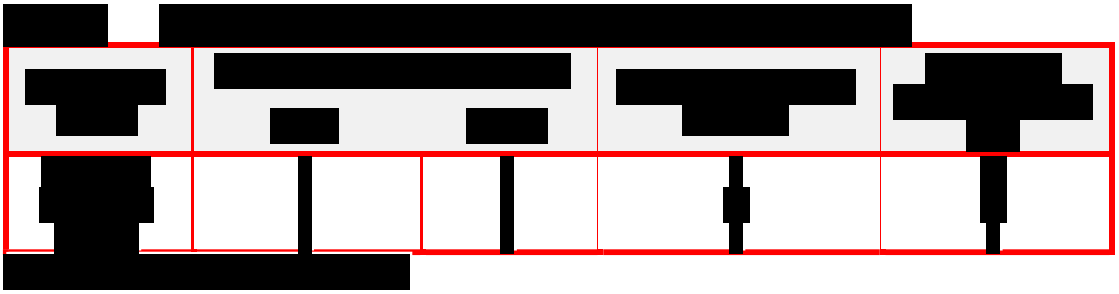
Data from the Daily Pain and Sleep Interference Diary at screening and BPI-DPN on Day 0 will represent the baseline reference values.

All screening assessments should occur within the 60 days prior to Day 0 (day of first injections).

Randomization. Subjects who meet the eligibility criteria will be randomly assigned in a 2:2:1 fashion to one of the three treatment arms: Low Dose (16 mg VM202 total dose, 8 mg / leg), High Dose (32 mg VM202 total dose, 16 mg / leg), or placebo, respectively. 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 (test and control products) prepared by the study pharmacist. Reconstituted VM202 is indistinguishable from saline solution.

Injection. Prior to the first injection, vital signs, concomitant medications, VAS, and BPI-DPN will be conducted. Blood will be drawn for determination of serum HGF, serum chemistry and hematology, and copies of VM202. Subjects will also undergo a skin biopsy (one 3 mm diameter round sample from left calf and one 3 mm diameter round sample from left upper thigh and ankle for a total of 3 samples / subject).

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



- VM202 will be delivered in a solution of 0.5mg VM202 / mL. All subjects will receive thirty-two (32) 0.5 mL injections evenly distributed over each calf at each visit of VM202 or placebo as follows:

  Subjects in the Low Dose Group (8mg VM202 / leg) will receive the following intramuscular injections in each calf:

  - Day 0 – 32 injections / calf:
    - 16 injections of 0.5mL of VM202 / calf – (4 mg of VM202 / calf)
    - 16 injections of 0.5mL of normal saline / calf

  - Day 14– 32 injections / calf:
    - 16 injections of 0.5mL of VM202 / calf – (4 mg of VM202 / calf)
    - 16 injections of 0.5mL of normal saline / calf

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

  Subjects in the High Dose Group (16 mg VM202 / leg) will receive the following intramuscular injections in each calf:

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

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

  HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 30, Day 60, and Day 90.

  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 30, Day 60 and Day 90.

  Serum chemistry and hematology will be determined on Day 0, Day 30, Day 90 and 9 months. HbA1c will be determined on Day 90, 6 months and 9 months.

VAS and Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) will be recorded at Day 0, Day 30, Day 60, Day 90, at 6 months and 9 months. Patients' Global Impression of Change (PGIC) will be recorded at Day 30, Day 60, Day 90, at 6 months and 9 months. MNSI will be conducted at 6 months and 9 months to track disease progression. Skin biopsy will be repeated at 6 months and the symptoms portion of the Brief Peripheral Neuropathy Screening (BPNS) will be recorded at 6 months.

The Daily Pain and Sleep Interference Diary will be filled out by patients prior to the Day 90, and the 6 Month and 9 Month visits.

Retinal fundoscopy will be conducted at 9 months. 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 60.

A summary of the schedule of evaluations and visits from screening through the end of the study can be found in Appendix 1.

3.3. SUBJECT POPULATION

One-hundred (100) 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 oral medication and / or insulin;
3. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities;
4. Lower extremity pain for at least 6 months;
5. Visual analog scale (VAS) score of ≥ 40 mm at Pre-Screening (0 mm = no pain – 100 mm very severe pain);
6. Symptoms from the Brief Pain Neuropathy Screening (BPNS) is ≤ 5 point difference between legs at Initial Screening;
7. 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;
8. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Screening;
9. Stable treatment of diabetes for at least 3 month with no anticipated changes in medication regimen, and no new symptoms associated with diabetes; and

10. 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 (HBcAb), antibody to Hepatitis B antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV) at Screening;
10. Subjects with known immunosuppression or currently receiving immunosuppressive drugs, chemotherapy or radiation therapy;
11. Stroke or myocardial infarction within last 3 months;
12. Ophthalmologic conditions pertinent to proliferative retinopathy;
13. Specific laboratory values at Screening including: 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;
14. Uncontrolled hypertension as defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at Screening;
15. Patients 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); patients with 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 any opioids; subjects may be enrolled if willing and able to discontinue use of these drugs 14 days prior to starting the Daily Pain and Sleep Interference Diary and refrain from taking these drugs for the duration of the study;
17. 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;
18. Subjects requiring regular COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting drugs, or high dose steroids (excepting inhaled 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 for the duration of the study;

19. Major psychiatric disorder in within last 6 months that would interfere with study participation;
20. Body mass index (BMI) > 45 kg/m^2 at Screening;
21. Any lower extremity amputation;
22. Use of an investigational drug or treatment in past 6 months; and
23. 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-YY-ZZZ. XX is the 2 digit assigned site number, YY 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 11-01-JSD.

3.4.3. SCREENING (DAY -60 TO DAY 0)

Prior to full 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 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
- Complete Medical History
- Concomitant Medications
- Vital Signs, including height
- Complete Physical Exam,
- EKG
- HbA1c
- Serum chemistry and hematology
- Urinalysis
- 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; PSA within past 3 months (males only);[†] for subjects ≥ 50 years old, colonoscopy within past 10 years; for subjects with family history of colon cancer in any first degree relative, colonoscopy within past 12 months.
- Viral screening – HIV, Anti-Human T-Cell Lymphotropic Virus (HTLV), Positive Hepatitis B or C as determined by Hepatitis B core antibody (HBcAb), antibody to Hepatitis B antigen (IgG and IgM; HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV), at Screening
- Retinal Fundoscopy – in cases where fundoscopy alone is deemed insufficient to rule out exclusionary conditions (see exclusion criterion # 12), fluorescein angiography may be conducted
- ***Following medication washout (if applicable) and within 14 days prior to injection.*** 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 – 10 0 mmworst 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; patient 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.

[†] subjects can participate in the study if PSA is elevated, but cancer can be excluded

3.4.4. PROHIBITED CONCOMITANT MEDICATIONS

3.4.4.1. MEDICATION THAT MAY INTERFERE WITH VM202 BIOACTIVITY

COX-1 and COX-2 inhibiting drugs will 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 completion of the 9 month follow-up visit. The patient 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.

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

Subjects may not take new drugs for DPN symptoms during the study and must be on the same medication for at least one month prior to screening. However, subjects are allowed to stop the existing medication during the study.

Subjects must discontinue use of all opioid drugs fourteen days prior to the completion of the Daily Pain and Sleep Interference Diary and agree to remain off of these medications until completion of the 9 month follow-up visit.

3.4.4.3. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as a 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.

3.4.5. TREATMENT AUTHORIZATION

After providing written informed consent, potential study participants will undergo Screening assessments. The site will complete a Treatment Authorization Form (TAF) for subjects determined to be eligible for study participation. The TAF includes the subject identification number, demographic information (gender, date of birth) and indication that the subject meets all inclusion and exclusion criteria. The completed TAF and completed Daily Pain and Sleep Interference Diary will be faxed to the Sponsor or its designee. The Sponsor or its designee will confirm whether the subject can be treated, and return the TAF to the investigational site and a copy to the drug depot. Upon receipt, the Investigator will schedule the subject to undergo the study treatment. Note: adherence to this process is mandatory to track enrollment and to assure proper randomization.

3.4.6. RANDOMIZATION AND BLINDING

A randomization schedule with subjects allocated to high dose, low dose or control in a 2:2:1 ratio will be sent to a centralized drug depot, which will prepare individual kits that contain the appropriate treatment based on the randomization schedule. When a site identifies a subject and treatment authorization is granted, the Sponsor or its designee will notify the drug depot.

The drug depot will:

1. Ship the next kit in sequence to the study pharmacist at the site, labeled with the subject identification number.
2. Record which kit was assigned to which site/subject and the date.
3. Include in the kit, a sealed envelope that identifies the subject identification number on the outside and the assigned treatment inside, to be opened by the Investigator or designee only in the case of a medical emergency.
4. Send another sealed envelope to the Sponsor with the subject identification number on the outside and the assigned treatment inside, to be opened by the Sponsor or designee only in the case of a medical emergency.

Blinding will be achieved by having the study medication (VM202) prepared by the study pharmacist. Reconstituted VM202 is indistinguishable from saline solution. The site pharmacist prepares the vials according to the instructions in the kit (which vials to reconstitute with water for injection [WFI]. The drug depot, site pharmacist and select individuals at [redacted] (but not including study monitors and study manager) will be unblinded to the treatment assignments. The subject and study personnel, including core lab, principal investigator, co-investigators and study coordinators, 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 open the sealed envelope to unblind the study medication assignment.

For each opened envelope, the Investigator will provide the name of the person who opened the envelope, reason, date, and signature on the envelope. At the end of the study, all (opened and unopened) envelopes will be returned to the Sponsor.

3.4.7. DAY -7 (-7 DAYS)

- Daily Pain and Sleep Interference Diary

3.4.8. DAY 0 – 1ST INJECTIONS

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

- Concomitant Medications
- Vital Signs
- VAS
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Serum Chemistry and Hematology
- Serum HGF
- Copies of VM202 in whole blood
- Skin biopsy

3.4.8.2. 1ST DOSE OF VM202 OR PLACEBO

Thirty-two (32) IM injections of randomly assigned study medication in each calf for a total of 64 injections will be administered per patient.

3.4.8.3. POST-INJECTION

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post injection)
- Injection site assessment
- Adverse event assessment

3.4.9. DAY 14 ± 1 DAY – 2ND INJECTIONS

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

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

3.4.9.2. 2ND DOSE OF VM202 OR PLACEBO

Thirty-two (32) IM injections of randomly assigned study medication in each calf for a total of 64 injections will be administered per patient.

3.4.9.3. POST-INJECTION

- Vital Signs
- Copies of VM202 in whole blood (2 hours ± 1 hour post injection)
- Injection site assessment
- Adverse event assessment

3.4.10. DAY 21 ± 3 DAYS

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

3.4.11. DAY 30 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- VAS
- Patient's Global Impression of Change (PGIC)

- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Serum Chemistry and Hematology
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.12. DAY 60 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- VAS
- Patient's Global Impression of Change (PGIC)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

3.4.13. DAY 90 ± 7 DAYS

- Concomitant Medications
- Vital Signs
- VAS
- Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to the visit
- Patient's Global Impression of Change (PGIC)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Serum Chemistry and Hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood
- Adverse event assessment

3.4.14. 6 MONTHS ± 1 MONTH

- Concomitant Medications
- Vital Signs
- VAS
- Michigan Neuropathy Screening Instrument (MNSI)
- Daily Pain and Sleep Interference Diary – to be completed within 14 days prior to the visit
- Patient's Global Impression of Change (PGIC)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Brief Peripheral Neuropathy Screening (BPNS)
- HbA1c
- Skin biopsy

- Adverse event assessment

3.4.15. 9 MONTHS ± 1 MONTH

- Retinal fundoscopy
- Concomitant Medications
- Vital Signs
- VAS
- Michigan Neuropathy Screening Instrument (MNSI)
- Daily Pain and Sleep Interference Diary – completed within 14 days prior to visit
- Patient's Global Impression of Change (PGIC)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Serum Chemistry and Hematology
- HbA1c
- 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 CRF.

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 CRF.

Additional subjects may be enrolled if subjects discontinue prior to the 90 day visit in order to achieve a 100 patient dataset with 90 day data.

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

- Retinal Fundoscopy
- Concomitant Medications
- Serum Chemistry and Hematology
- HbA1c
- Vital Signs
- Serum HGF if discontinued prior to Day 90
- Copies of VM202 in whole blood if discontinued prior to Day 90
- Injection site reaction assessment if discontinued prior to Day 60
- 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 [redacted]

3.6.2. PLACEBO

The placebo will be sterile normal saline. Sodium Chloride Injection, USP is a sterile, nonpyrogenic solution for fluid and electrolyte replenishment. It contains no antimicrobial agents. The nominal pH is 5.5 (4.5 to 7.0) and it contains 9.0 g/L Sodium Chloride, USP (NaCl) with an osmolarity of 308 mOsmol/L (calc). Visually, normal saline is indistinguishable from reconstituted VM202.

3.6.3. PRODUCT ACCOUNTABILITY

In accordance with federal regulations (21CFR 312.62), all Investigators 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 test drug as shipped by the Sponsor/Designee, including the date received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This inventory record must be available for inspection at any time. 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 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 for gross reconciliation.

3.6.4. DOSE AND ADMINISTRATION

VM202 is supplied in a sterile glass vial containing 2.5 mg of lyophilized 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 0.5 mg / mL. Each reconstituted vial is only to be used for one subject. . The placebo group will receive only normal saline injections. All subjects will receive 32 injections per calf per visit. The Low Dose arm will receive VM202 and normal saline injections. The High Dose arm will receive only VM202 injections. A complete description of test article administration can be found in Appendix 5.

3.7. PRIOR AND CONCOMITANT MEDICATION

All concomitant medications (taken within 60 days of the first injection) will be recorded on the CRF 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. COMPLETE MEDICAL HISTORY

A complete medical history will be obtained at Baseline. All positive and negative findings will be carefully documented on the CRF. 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. COMPLETE PHYSICAL EXAM

A complete 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, gastrointestinal, and dermatological systems. Any clinically significant abnormalities should be recorded in the subject's CRF.

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, colonoscopy within past 10 years; for subjects with family history of colon cancer in any first degree relative, colonoscopy within past 12 months.
2. 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

3. Mammogram (females only)-within 1 year prior to study entry
4. Papanicolaou (Pap) testing - women within 1 year prior to study entry
5. Prostate specific antigen (PSA) – men within 3 months prior to study entry. †

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 (HBcAb), antibody to Hepatitis B antigen (IgG and IgM; 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. URINALYSIS

Specific gravity, pH, color, protein, sugar, and byproducts will be evaluated at baseline.

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;

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

† – subjects can participate in the study if PSA is elevated, but cancer can be excluded

4.2. EVALUATIONS CONDUCTED THROUGHOUT THE STUDY

4.2.1. RETINAL FUNDOSCOPY

Proliferative retinopathy is 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 9 months. Retinal fundoscopy must be performed by an ophthalmologist within 3 months of Screening.

In cases where fundoscopy alone is deemed insufficient to rule out exclusionary conditions (see exclusion criterion # 12), 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, body weight, heart rate, and respiratory rate will be measured and recorded at Screening and at every visit through the 9 month follow-up and recorded in the subjects CRF.

4.2.4. SERUM CHEMISTRY, HEMATOLOGY AND HBA1C

Evaluation of serum chemistry and hematology will be conducted at Screening, Day 0, Day 30, Day 90 and 9 months. Evaluations will be conducted at 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), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), 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 90, 6 months and 9 months at a local laboratory at each site. Laboratory testing by visit is provided in Appendix 1.

4.2.5. SERUM HGF

Serum HGF will be determined by ELISA at the following follow-up visits: immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day

30, Day 60, and Day 90. 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 subject ID, draw date, study number and visit interval (i.e., Day 0, 14, 30, 60 or 90). Samples will be maintained in a cooler containing dry ice and then placed in a ≤ -65°C freezer until shipped for analysis. At the request of the Sponsor or its designee, serum HGF samples will be batched with VM202 samples, and shipped in a special container with temperature tracking recorder to [redacted] for analysis.

[redacted]

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 1 to 3 hours post injection), Day 14 (pre-injection, and 1 to 3 hours post injection), Day 21, Day 30, Day 60 and Day 90. 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 6 aliquots per time point. These will be maintained in a ≤ -65°C freezer until shipped for analysis. Samples should be labeled with subject ID, draw date and time, study number, and visit interval (i.e., Day 0 pre, Day 0 post, Day 14 pre, Day 14 post, Day 21, Day 30, Day 60 or Day 90). At the request of the Sponsor or its designee, VM202 samples will be batched with serum HGF samples, and shipped in a special container with temperature tracking recorder to [redacted] for analysis.

[redacted]

Note, [redacted] will provide collection tubes, plastic vials, labels, shipment materials including temperature tracking recorder 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 30, Day 60, Day 90, at 6 months and 9 months 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 patient 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 patients mark in centimeters from the beginning of the scale (the 0 mark). The VAS is illustrated in Appendix 8.

4.2.8. DAILY PAIN AND SLEEP INTERFERENCE DIARY

Subjects will be asked to keep a Daily Pain and Sleep Interference Diary (see Appendix 9). Subjects will be asked to rate their 24-hour average daily pain intensity score11 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; patient was not able to sleep due to pain).

The diary will be completed at Screening following washout of prohibited medications and within 14 days prior to the Day 90, 6 months and 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 at each site will call the subjects to remind them of their upcoming visit at Day 90, 6 months or 9 months, and the requirement to complete the diary pages 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, Month 6 and 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 Dairy for completeness. Any omissions or ambiguous answers will be clarified by the subject prior to leaving the clinic.

4.2.9. 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.[54] This questionnaire takes measures a patients 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 30, Day 60, Day 90, at 6 months and 9 months.

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 6.

4.2.10. 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 6 months and 9 months to track disease progression.[51-53] 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 4.

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 30, Day 60, Day 90, at 6 months and 9 months. The Questionnaire is a patient - completed 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 also 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 7.

4.2.12. BRIEF PERIPHERAL NEUROPATHY SCREENING (BPNS)

Symptoms of BPNS will be assesses at pre-screening and Month 6 in order to evaluate the bilateral extent of DPN (see Appendix 10).

4.2.13. 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 30 and Day 60 by the National Cancer Institute's Common Terminology for Adverse Events v3.0. The grading categories are as follows and will be recorded on the CRF as described in Table 3.

Table 3. 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 fever < 38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medications(s) indicated; allergy-related edema/ angioedema; hypotension	Anaphylaxis	Death

4.2.14. SKIN BIOPSY

Prior to the first round of injection, subjects will undergo a skin biopsy (one 3 mm diameter round sample from the left ankle, the left calf and the left upper thigh, for a total of 3 samples / subject). Skin biopsies will be performed again at the 6 month follow-up visit. Skin biopsies will be conducted under local anesthesia with the aid of a sterile 3mm skin punch. Samples will be sent to a central laboratory (TBD) to characterize change in peripheral innervation.

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).

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 and the 9 month follow-up visit of the study by a subject must be recorded on the AE form provided with the CRF. 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 CRF page(s).

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 that occurs during this investigation, whether or not related to the study medication, must be reported immediately (within 72 hours) to the Sponsor and MedTech Consultants, Inc., the designated CRO.

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 concerning each SAE to the CRO and Sponsor within 5 calendar days of the event. This information must be recorded in the subject's medical record and then transcribed onto the SAE Form. The completed SAE Form (including the Investigator's opinion of the relationship of the SAE to the study medication), copies of related results/reports, consultant report(s), and other relevant information will be faxed and mailed to the CRO.

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. Any follow-up information obtained must be recorded on an SAE follow-up report form.

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 METHODS

The objective of this Phase II study is to evaluate the safety of IM administration of VM202 in subjects with painful DPN in lower extremities; and, to evaluate the potential bioactivity of IM administration of VM202 in subjects with painful DPN, when compared to placebo, on rest pain (as assessed by frequency of pain, pain medication use history, sleeping history, and intensity of pain) and sensory perception.

6.1. GENERAL METHODS

Means, standard deviations (SD), medians and minimum and maximums will be presented for continuous variables, the number and percentage of patients in each category will be presented for nominal and ordered categorical variables. Statistical tests with a p value <0.05 will be considered statistically significant, unless otherwise stated.

6.2. ANALYSIS POPULATION

Efficacy Analysis Population – Subjects that received all injections of the correct dose of study drug medication based on randomization schedule and have completed the 6-month assessment; subjects must not have any protocol violation or major deviation which will be determined in a blinded review before database lock for data analyses.

Safety Analysis Population – Subjects that have received any injections

Intent to Treat (ITT) Population – All randomized patients

6.3. STUDY ENDPOINTS

The objectives of this study are o evaluate the safety of IM administration of VM202 in subjects with painful DPN in lower extremities; and to evaluate the potential bioactivity of IM administration of VM202 in subjects with painful DPN, when compared with placebo, on pain.

6.3.1. PRIMARY ENDPOINT

The primary study endpoint is the change in average 24-hour pain score from baseline to the 6-month follow-up. The average pain scores will be obtained from the Daily Pain and Sleep Interference Diary (recorded daily by the patient for 7 days prior to the first round of injections and again, for 7 days before the 6 month follow-up). The difference in the mean change in average 24 hour pain score between the two treatment groups and the placebo arm will be evaluated to determine the treatment effect.

The primary analysis will be conducted in the Efficacy Analysis Group. A secondary analysis will be conducted in the ITT group, and further analyses conducted as necessary to explore any inconsistency between the two results.

6.3.2. SECONDARY EFFICACY ENDPOINTS

Other secondary endpoints and evaluations will include:

- Difference in all clinical parameters measured (VAS, BPI DPN, MNSI,PGIC, average pain score and sleep interference score from the Daily Pain and Sleep Interference Diary) and histological findings on skin biopsy between the low dose and high dose groups at all time points
- Change between treatment arms and placebo in VAS score from baseline to Day 30, Day 60, Day 90, 6 months, and 9 months.
- Change in mean pain score from the Daily Pain and Sleep Interference Diary between treatment arms and placebo from baseline to Day 90, 6 months and 9 months.
- Change between treatment arms and placebo in mean MNSI score from baseline to 6 months and 9 months.
- Change between treatment arms and placebo in BPI-DPN from baseline to Day 30, Day 60, Day 90, 6 months, and 9 months.

- Change in PGIC between treatment arms and placebo at Day 30, Day 60, Day 90, 6 months, and 9 months.
- Change between treatment arms and placebo in histological findings on skin biopsy from baseline to 6 months

6.3.3. SAFETY

Any patient who receives injections (study drug 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 safety parameters.

6.3.4. PHARMACODYNAMICS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 30, Day 60, and Day 90. Copies of VM202 in whole blood will be determined at Day 0 (pre-injection and 2 hours post injection), at Day 14 (pre-injection and 2 hours post injection), Day 21, Day 30, Day 60 and Day 90.

6.3.5. DATA SAFETY MONITORING AND INTERIM ANALYSES

For ethical reasons, and to ensure study integrity, an interim examination of key safety data will be performed when approximately 50% of the patients (n=50) have Day 90 data. The primary objective of this analysis will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either active treatment arm. An independent data safety monitoring board (DSMB) will perform the review.

The DSMB Chair will review a limited set of unblinded tables and listings, including all reported AEs and SAEs, every three months through to the full DSMB interim analysis and continue the review every six months thereafter. The DSMB chair may request additional data for review and/or additional meetings of the committee as he / she sees fit.

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 MedTech 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. In addition to conducting a site visit prior to initiation of enrollment, 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 source documents used in the preparation of the CRFs to verify the accuracy and completeness of the information contained in those reports in preparation for retrieval. All source documents must contain all information required by the CRF. All data generated during this study and the source documents from which they originated are subject to inspection by the Sponsor or its representative, 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 (SOP) 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 CRFs, 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. A copy of the notification must be forwarded to the Sponsor and to MedTech Consultants.

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 that is composed of at least 5 appropriately-qualified members. 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. Subjects will be asked to initial each page of the informed consent form to acknowledge awareness of its contents. 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

All data relating to study procedures will be entered into CRFs provided by the Sponsor or its designee. All requested information must be entered on the CRF. If an item is not available or not applicable this fact should be indicated.

Obvious errors (self-evident corrections) will be corrected and documented by the Sponsor or its designee. Other errors or omissions will result in queries which will be sent to the investigational site on Data Clarification Forms (DCF)/Query for resolution. A copy of the signed DCF is to be kept by the site with the CRFs. Once the original is received by the Sponsor or its designee, the resolutions will be reviewed and entered into the database.

Data will be entered into a computer database developed specifically for this trial. Access to the database will be restricted to personnel responsible for data entry and to data management and statistics personnel who are directly involved in the management or analysis of this trial. During the course of the trial, data queries will be generated for data items that are potentially erroneous and require appropriate clarification or correction. Prior to database lock, statistical verification of the data will be undertaken in order to further assure data quality.

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 Sponsor/CRO for submission to the FDA.
- Current signed curriculum vitae and medical licenses (within 2 years) for the Principal Investigator and all co-investigators listed on the 1572.
- A copy of the original approval for conducting the study by the IRB. Renewals, with continuance of the study, must be submitted at yearly intervals or as required by IRB policy.
- A copy of the IRB approved informed consent form.
- IRB member list and DHHS General Assurance Number (if IRB has an Assurance number).
- Signed Financial Disclosure Form for all personnel listed on the 1572 with a statement of non-voting by study staff.
- The signature page of this protocol signed and dated by the Principal Investigator.

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.
- All original informed consent forms with required signatures
- All IRB correspondence (i.e., informed consent [including any approved revisions], protocol, AE, advertisements, newsletters)
- Copy of the Study Monitoring Log Sheet
- Clinical and non-clinical supply shipment forms
- Copies of all 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 its designee
- Copies of all IND Safety Reports submitted to the site by the Sponsor its designee
- Copies of approved package labeling
- Study personnel signature log

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

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

†† MNSI - Michigan Neuropathy Screening Instrument

1. If withdrawal occurred before Day 90 Visit

2. If withdrawal occurred before Day 60 Visit

* PGIC - Patient's Global Impression of Change

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

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

SCHEDULE OF LABORATORY EVALUATIONS

Parameters	Screen	Day 0	Day 14	Day 21	Day 30	Day 60	Day 90	6 Months	9 Months	Early Withdrawal
HbA1c	✓						✓	✓	✓	✓
Serum HGF		✓ pre-injection	✓ pre-injection		✓	✓	✓			✓ (< Day 90)
VM202		✓ pre & post injection	✓ pre & post injection	✓	✓	✓	✓			✓ (< Day 90)
HTLV, HIV-1, HIV-2	✓									
Hepatitis B and C[†]	✓									
Hematology										
Hematocrit	✓	✓			✓		✓		✓	✓
Hemoglobin	✓	✓			✓		✓		✓	✓
RBC	✓	✓			✓		✓		✓	✓
WBC with differential	✓	✓			✓		✓		✓	✓
Platelets	✓	✓			✓		✓		✓	✓
MCV	✓	✓			✓		✓		✓	✓
MCH	✓	✓			✓		✓		✓	✓
MCHC	✓	✓			✓		✓		✓	✓
Chemistry										
Albumin	✓	✓			✓		✓		✓	✓
Alkaline Phosphatase	✓	✓			✓		✓		✓	✓
ALT	✓	✓			✓		✓		✓	✓
AST	✓	✓			✓		✓		✓	✓
Bicarbonate	✓	✓			✓		✓		✓	✓
BUN	✓	✓			✓		✓		✓	✓
Calcium	✓	✓			✓		✓		✓	✓
Chloride	✓	✓			✓		✓		✓	✓
Creatinine	✓	✓			✓		✓		✓	✓
Glucose	✓	✓			✓		✓		✓	✓
Potassium	✓	✓			✓		✓		✓	✓
Sodium	✓	✓			✓		✓		✓	✓
Total Protein	✓	✓			✓		✓		✓	✓
Total Bilirubin	✓	✓			✓		✓		✓	✓

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

Appendix 2. Sample Informed Consent

TITLE: A Phase II, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects with Painful Diabetic Peripheral Neuropathy (Protocol Number: VMDN-002)

SPONSOR: [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 [redacted]. 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.

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 a small feasibility study in the United States in subjects with painful diabetic neuropathy; in a study in Korea in subjects with coronary artery disease and in another study in the United States in subjects with critical limb ischemia (decreased blood flow to the legs). 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 a low and high dose of VM202.
- If there are any effects of VM202 on your symptoms of 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?

[redacted]

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 100 patients will take part in this study at up to 20 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 drawing numbers out of a hat or flipping a coin) to one of three 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 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 your doctor until the study is completed.

You will be randomly assigned to one of three possible study groups. In each study group, you will receive 32 injections in each calf at the Day 0 and Day 14 visits. The contents of the injections depend on your study group:

- **Low Dose** VM202 Treatment Group – if you are selected for this group, you will receive 16 mg of VM202 over the course of the two injection visits (4 mg of VM202 at the Day 0 visit and 4 mg of VM202 at the Day 14 visit in each leg). At each of these two injection visits, you will receive 16 injections of 0.5 mL of VM202 in each leg and 16 injections of 0.5 mL saline in each leg. The total volume of all of the injections is about 3 teaspoons of fluid. Approximately forty percent of patients will be selected for this group.

- **High Dose** VM202 Treatment Group – if you are selected for this group, you will receive 32 mg of VM202 over the course of the two injection visits (16mg of VM202 at the Day 0 visit and, 16mg of VM202 at the Day14 visit). At both injection visits, you will receive 32 injections of 0.5 mL of VM202 in each leg. The total volume of all of the injections is about 3 teaspoons of fluid. Approximately forty percent of patients will be selected for this group.

- **Placebo** Control Group – if you are selected for this group, you will not receive VM202. You will only receive injections of saline. At both injection visits, you will receive 32 injections of 0.5 mL of saline in each leg. The total volume of all of the injections is about 3 teaspoons of fluid. Approximately twenty percent of patients will be selected for 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. A small skin sample will be taken from your left ankle, calf and left upper thigh, for a total of three samples. . These samples will be very small (about the size of a half of a grain of rice) and will be taken using local anesthetic. These samples will be taken again at the 6 month visit and will used to track the progress of your neuropathy.

What tests, procedures, and diagnostic studies will be done during this study?
There are 9 visits which span 9 months total time from visit #2 to visit #9. 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 or 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 taken any of these medications, you will be asked to stop taking these medications for the duration of the study.

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 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.

Questionnaire – You will be asked to fill in short questionnaires about feeling in your legs and feet before the first injection. You will be asked to complete brief questionnaires about pain in your feet and legs at some visits.

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 interferes with your sleep.

Cancer Screening – Cancer screening includes pap smear and mammogram if not performed within past 12 months (females only); PSA within past 3 months (males ≥ 50 years only); for subjects ≥ 50 years old, colonoscopy within past 10 years; for subjects with family history of colon cancer in any first degree relative, colonoscopy within past 12 months; and X-ray or CT scan of chest.

Retinal Fundoscopy – An ophthalmologist may 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 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 done 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**).

Skin biopsy - A small skin sample will be taken from your left ankle, calf and left upper thigh, for a total of three samples. These samples will be very small (about the size of a half of a grain of rice) and will be taken using local anesthetic. These samples will be taken again at the 6 month visit and will be used to track the progress of your neuropathy.

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 two 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 test, 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 either one of the groups to receive VM202 (low or high dose) 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). Prior to that time, you will be reminded to fill out the daily questionnaire for a week (7 days).

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: medication review, completion of questionnaires, review of your completed diary entries, vital signs, skin biopsy, 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 32 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 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 32 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 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 VM202, injection site reaction assessment, and assessment of side effects.

Visit # 5 – 30 Days after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests including HGF and VM202, completion of questionnaires, and assessment of side effects.

Visit # 6 – 60 Days after the First Injection Procedure
At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests including HGF and VM202, completion of questionnaires, and assessment of side effects.

Visit # 7 – 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 it in with you for this visit. At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests including HGF and VM202, completion of questionnaires, and assessment of side effects.

Visit # 8 – 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 it in with you for this visit. At this visit, the following tests or evaluations will be done: medication review, vital signs, blood tests, completion of questionnaires, skin biopsy, and assessment of side effects.

Visit # 9 – 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 it in with you for this visit. At this visit, the following tests or evaluations will be done: retinal fundoscopy, medication review, vital signs, blood tests, completion of questionnaires, 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.

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. 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 anytime 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 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 has the potential to create new blood vessels (angiogenesis), there may be risk of promoting tumor growth (cancer) or of increasing the number of blood vessels in the back of your eye and damaging your retina (retinopathy).

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 sexually active and with childbearing potential, you must agree to use an acceptable method of birth control for 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 10 times over approximately 11 months. Each time your blood is drawn roughly 1 to 2 tablespoons of blood will be taken.

Risks from taking a skin biopsy
A small skin sample will be taken from the back of each of your calves and from each of your upper thighs (3samples in total) before the first injections and again at 6 months. Risks associated with skin biopsies include bleeding, temporary bruising and infection, although with proper wound care, is not likely.

Risks from cancer screening
Cancer screening includes pap smear and mammogram if not performed within past 12 months (females only); PSA within past 3 months (males≥ 50 years only); for subjects ≥50 years old, colonoscopy within past 10 years; for subjects with family history of colon cancer in any first degree relative, colonoscopy within past 12 months; and X-ray or CT scan of chest. 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), and risks associated with taking a blood sample (as described above). Possible risks from colonoscopy may include: bowel perforation (a hole or tear in the wall of the colon) requiring a repair operation (fewer than 1 out of 1,000 tests), heavy or persistent bleeding from biopsy or polyp-removal sites (1 out of 1,000 tests), adverse reaction to sedative medication causing breathing problems or low blood pressure (4 out of 10,000 tests), infection requiring antibiotic therapy (very rare), and nausea, vomiting, bloating, or rectal irritation caused by medicines taken by mouth to cleanse the bowel.

Risks from Retinal Fundoscopy
The test itself involves no risk. If dilating eye drops are used, they 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)
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 product injections. VM BioPharma 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 (VM BioPharma Co., Ltd.), or its representatives such as members of the Steering Committee, Executive Committee or Data Monitoring Committee, the Contract Research Organization identified as MedTech Consultants, Inc., 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 urine and 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). You are allowed to continue taking these medications during the study if you are taking these medications for more than one month prior to Screening, but you are not allowed to start these medications during the study. You are also not allowed to increase the dosage of either of these medications or begin taking them during the study.

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, VM BioPharma, 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.A. Law. This Web site 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 researcher/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)	Minimum 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, caldorol, profen	none	1 week
idomethacin	Indocin	none	1 week
ketoprofen	Nexcede, Orudis	none	None for topical formulation, 1 week for all others
ketorolac	Sprix, acuvail, acular	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 (topical, injected, oral)	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 for the treatment of respiratory disorders are allowed

WASHOUT OF OPIOIDS

Since opioids may interfere with assessment of VM202 effect on pain, subjects must discontinue use of all opioid drugs fourteen days prior to the completion of the Daily Pain and Sleep Interference Diary at Screening.

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

Appendix 4. 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.

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, halux 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 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 there flex 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 5. 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 Low Dose or High Dose arms of the study, the final doses of VM202 will be divided evenly between the Day 0 administration and the Day 14 administration. Every individual injection will be 0.5 mL. All injections administered by intramuscular injections.

Placebo - Patients assigned to either the placebo arm or the Low Dose arm will receive normal saline injections. The placebo group will receive only normal saline injections; the Low Dose arm will receive 16 injections of VM202 and 16 injections of normal saline in each leg at both injection visits. Visually, normal saline is indistinguishable from reconstituted VM202.

Table 4. Single dose preparation and delivery for Day 0 and Day 14 Visits

Treatment Arm	Number of Vials Reconstituted at each visit	Number of injections† / leg	Total Volume to be Injected / leg
Low Dose 8 mg/ leg Total Dose:16 mg VM202	4 Vials VM202, reconstituted with WFI	16 of VM202 16 of placebo	16 mL
High Dose 16 mg/ leg Total Dose:32 mg VM202	8 Vials VM202, reconstituted with WFI	32 of VM202	16 mL
Placebo – Normal Saline	NA – Normal Saline	32 of placebo	16 mL

†Injection volume for each individual injection = 0.5 mL

2. ***Test material administration*** – Patients will receive injections of VM202 or placebo on Day 0, and Day 14. A fine needle (e.g. 27 gauge, 1") suitable for IM injections will be used. **Both calves will be treated with 32 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 6. Patient's Global Impression of Change

Patient Global Impression of Change (PGIC) Scale

Since the start of the study, my overall status is:
✓ 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 Signature: _____ **Date: _____**

Appendix 7. Brief Pain Inventory for Subjects with Diabetic Peripheral Neuropathy (BPI-DPN)

STUDY ID #: VMDN-002 DO NOT WRITE ABOVE THIS LINE Subject # _____

Brief Pain Inventory (Short Form)

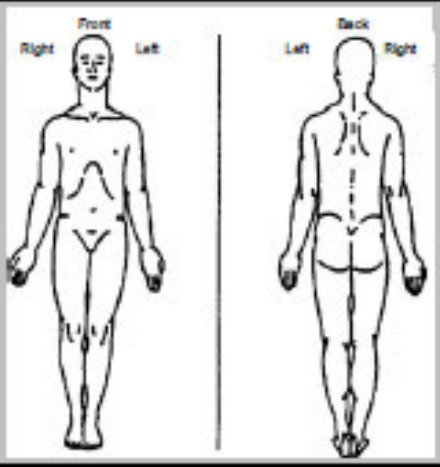
Date: ____/____/____ **Time:** _____

Visit: ☐2 Day 0 (pre-Injection) ☐5 Day 30 ☐6 Day 60 ☐7 Day 90 ☐8 Month 6 ☐9 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-002 DO NOT WRITE ABOVE THIS LINE Subject #: _____

Date: ___/___/____ Time: _____

Visit: ☐2 Day 0 (pre-injection) ☐5 Day 30 ☐6 Day 60 ☐7 Day 90 ☐8 Month 6 ☐9 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%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

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Appendix 8. 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

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 , 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 9. 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. 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 :** ___ ___ / ___ ___ ___ / ___ ___ ___ ___
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	

Appendix 10. 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): ……	☐☐	☐☐

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