A PHASE I/II OPEN LABEL, DOSE-ESCALATION STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF VM202 IN PATIENTS WITH PAINFUL DIABETIC PERIPHERAL NEUROPATHY

Protocol VMDN-001/G

September 23, 2010

Sponsor:

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- I have read and understand fully the Investigator Brochure.
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Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	A Phase I/II, Open Label, Dose-Escalation Study to Assess the Safety and Tolerability of VM202 in Patients with Painful Diabetic Peripheral Neuropathy
STUDY PHASE	I/II
INVESTIGATIONAL AGENT	VM202
DOSE	Three doses will be tested: 4 mg, 8 mg and 16 mg VM202.
POPULATION	Patients aged ≥ 18 years to ≤ 75 years diagnosed with painful diabetic neuropathy in both lower extremities.
STUDY DESIGN	A phase I/II, open label, dose-escalation, multicenter, 12-month study designed to assess the safety and tolerability of unilateral intramuscular injection in the calf of VM202 in patients with painful diabetic peripheral neuropathy (DPN). The study will consist of three (3) cohorts with a total of 4 patients enrolled in each cohort. A Data Safety Monitoring Board (DSMB) will monitor patient safety throughout the study. After the first patient in a dose cohort completes the Day 30 follow-up evaluation and the other three patients enrolled in the same cohort complete at least the Day 14 follow-up (second dosing), an interim safety evaluation will be performed by the DSMB. If the DSMB recommends proceeding, the next dose cohort will be treated. This process will be repeated between the second and third dose cohort. All three dose cohorts will be followed for one year from the time of the first dose of study drug administration. If a dose limiting toxicity (DLT) is observed in one patient in any dose group, two additional patients will be added to the dose cohort in which the toxicity was observed. If no additional DLTs are observed in the 6 patients at this dose level, it will be considered the Maximum Tolerated Dose (MTD). If a DLT occurs in 2 patients at any dose level, then the preceding dose level will be considered the MTD. The study will be stopped in the event that 2 DLTs occur at any point in the study.
NUMBER OF PATIENTS	12 to a maximum of 14

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%);
3. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities;
4. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Screening;
5. Visual analog scale (VAS) score of ≥ 4 cm at Screening (0 cm = no pain – 10 cm worst imaginable pain);
6. Stable treatment of diabetes for at least 3 months with no anticipated changes in medication regimen, and no new symptoms associated with diabetes;
7. Lower extremity pain for at least 6 months; and
8. If female of childbearing potential, negative 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;
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, Rheumatoid Arthritis)
8. Positive HIV or HTLV at Screening
9. 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 or known immunosuppression or on chronic treatment with immunosuppressive drugs, chemotherapy or radiation therapy;
10. Stroke or myocardial infarction within last 6 months;
11. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination:

    - Cataract surgery within 6 months of trial;
    - Vascular lesions of the anterior segment of the eye (infection or ulceration of the cornea, rubeotic glaucoma, etc);
    - Vascular lesions of the posterior segment of the eye or proliferative retinopathy, macular edema, s/p

photocoagulation for macular edema or proliferative retinopathy; sickle cell retinopathy, ischemic retinopathy due to retinal venous stasis or carotid artery disease;
- Choroidal angiogenesis; and
- Large elevated choroidal nevi, choroidal vascular tumors (choroidal hemangioma), or melanomas.

12. Specific laboratory values at Screening including: Hemoglobin < 9.0 g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm^3, Creatinine > 2.0 mg/dL; GFR < 50, AST and/or ALT > 2 times the upper limit of normal or any other clinically significant lab abnormality which in the opinion of the investigator should be exclusionary;
13. Use of gamma-linolenic acid (GLA), alpha lipoic acid or any other high dose dietary antioxidant supplement for symptomatic relief of DPN;
14. Uncontrolled hypertension as defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
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);
16. Malignant tumors or abnormal screening test suspicious for cancer, or patients in whom screening exams indicate possible occult malignancy unless malignancy has been ruled out. 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;
17. Elevated PSA unless prostate cancer has been excluded;
18. Subjects requiring > 81 mg daily of acetylsalicylic acid; If > 81 mg are taken at screening, subjects may be enrolled if willing/able to switch to another medication;
19. Major psychiatric disorder in past 6 months;
20. History of drug or alcohol abuse / dependence in the past 2 years;
21. History of recent tobacco abuse (within past 5 years);
22. BMI > 45 kg/m^2;
23. Use of an investigational drug or treatment in past 12 months; and
24. Unable or unwilling to give informed consent.

STUDY PROCEDURES

Patients will be screened for study eligibility after giving informed consent. Screening should occur within the 60 days prior to Day 0 (day of injection). Screening will include assessment of study eligibility, a complete medical history, vital signs, physical exam,

photograph and measurement of ulcers (if any), cancer screening tests, viral screening, MNSI, VAS, 12 lead EKG, retinal fundoscopy, clinical chemistry, hematology, urinalysis, and pregnancy test (women of childbearing potential only), and documentation of any ulcers or gangrenous areas.

Patients will be treated with 4 mg, 8 mg or 16 mg of VM202 by intramuscular injections in the right calf on Day 0 and again on Day 14. VM202 will be delivered in a solution of 0.5 mg VM202 / mL in 0.5 mL injections. Patients in Cohort I will receive a final dose of 4 mg of VM202; Cohort II will receive a final dose of 8 mg VM202; and Cohort III will receive a final dose of 16 mg VM202.

Cohort	Final Dose VM202	Number of Injections		Total Volume Injected
		Day 0	Day 14	
I	4 mg	8	8	8 mL
II	8 mg	16	16	16 mL
III	16 mg	32	32	32 mL

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

The number of 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.

VAS score, the SF-MPQ and BPI-DPN will be recorded at Day 30, Day 60, Day 90, at 6 months and 12 months. Retinal fundoscopy will be conducted at 12 months. Adverse events will be recorded throughout the one year 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 ± 7 days
Day 90 ± 7 days
Month 6 ± 1 month
Month 12 ± 1 month

STUDY ENDPOINTS	The primary study endpoint is to evaluate safety and tolerability of intramuscular injection in the calf of VM202 in patients with painful DPN. Secondary endpoints include the assessment of the potential of VM202 to reduce the pain associated with DPN.
SAFETY	Any patient who receives VM202 will be included in the safety analysis population. Adverse events (including serious adverse events, and adverse events leading to treatment discontinuation) throughout the 12 month follow-up will be described according to severity and to their relationship with the study drug and / or device and procedure. Descriptive statistics (N, mean, median, SD, minimum and maximum values, where applicable) will be used to characterize safety parameters. All patients 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, Day 30, and Day 60. The number of 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.
EFFICACY	This is a phase I /II study, not powered to assess efficacy. However, descriptive statistics (N, mean, median, SD, minimum and maximum values, where applicable) of clinically meaningful endpoints will be tabulated. Change in pain level, as measured by the VAS, SF-MPQ and BPI-DPN will be recorded. The status of preexisting ulcers will also be reported.

TABLE OF CONTENTS

FIGURES & TABLES

TABLE OF APPENDICES

GLOSSARY

ABI	Ankle-Brachial Index
AE / SAE	Adverse Event / Serious Adverse Event
ALT	Alanine Transaminase (SGPT)
Anti-HCV	Hepatitis C antibodies
AST	Aspartate Transaminase (SGOT)
BP	Blood Pressure
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Nephropathy
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulation
cm	Centimeter(s)
CRF	Case Report Form
CRO	Clinical Research Organization
DCF	Data Clarification Form
DLT	Dose Limiting Toxicities
DNA	Deoxyribonucleic Acid
DPN	Diabetic Peripheral Neuropathy
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
FDA	Food and Drug Administration
FOBT	Fecal occult blood test
GCP	Good Clinical Practices
HBV	Hepatitis B Virus
HBcAB	Hepatitis B core antibody
HBsAb	Antibody to Hepatitis B antigen (IgG and IgM)
HBsAg	Hepatitis B surface antigenHCV Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
PSA	Prostate Specific Antigen
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
SF-MPQ	Short Form version of the McGill Questionnaire
SGPT	Serum Glutamic Pyruvic Transaminase (same as ALT)
SOP	Standard Operating Procedure
TBI	Toe-Brachial Index

TCA	Tricyclic Antidepressants
$TCPO_2$	Transcutaneous pressure of oxygen
VAS	Visual Analog Scale (Pain Scores)
VEGF	Vascular Endothelial Growth Factor
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 (NIDDK), 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.

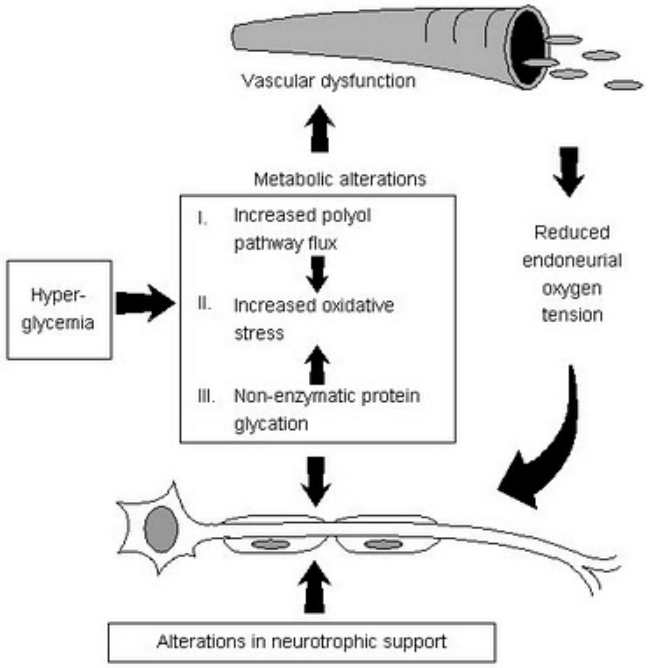

Figure 1. The neurodestructive effects of hyperglycemia

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 patients with type 2 diabetes and symptomatic neuropathy. One hundred eighty one (181) patients 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 patients 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 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 and its cognate receptor, the Met receptor, and localized exogenous HGF has been shown to promote the growth (but not survival) of sympathetic neurons.[32-35] 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,[36] 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.[37-40]

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.[41, 42]

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 no change in the coding region of the HGF gene, HGF proteins generated from

VM202 are identical to the wild-type human HGF proteins. VM202 has been developed using the pCK DNA plasmid that has been safely used in previous ViroMed-sponsored clinical trials with VEGF as the therapeutic gene, known as VMDA-3601.

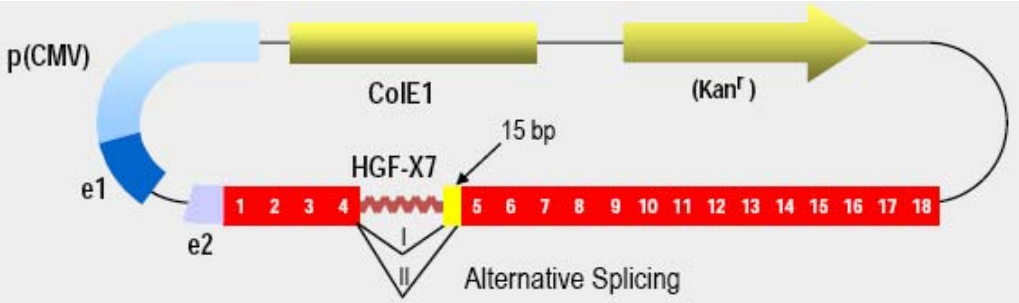

Figure 2. VM202 construct

Safety of VM202. The use of plasmids for targeted delivery of angiogenic factors into muscle tissue is a particularly attractive and a relatively safe therapeutic approach, because plasmids have been shown to effectively transfect postmitotic cells such as skeletal and heart muscle and to successfully express angiogenic genes with very little dissemination and persistence at distant sites. Following intramuscular injection, the plasmid that persists is extrachromosomal and integration into host DNA, if it occurs, is negligible.[43-45] This local effect of conventionally injected naked plasmid DNA is well known.[46, 47]

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,[48] VM202 may have the ability to decrease neuropathic pain, and improve patient 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 (0.11 mg/kg for a 70 kg patient), the maximum dose administered on a single day in the phase I study. 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 patients with painful diabetic peripheral neuropathy.

1.6. CLINICAL DATA

VM202 is being evaluated for treatment of critical limb ischemia in a prospective, dose-escalation Phase I study. The study consists of four (4) cohorts of three (3) patients. Patients 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. All 4 dose cohorts were followed for one year from the time of the first dose of study drug administration.

Enrollment and follow-up are now complete. Between March of 2007 and October of 2008, twelve (12) patients 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 patient underwent a major amputation. Median ankle brachial index (ABI) and toe brachial index (TBI) significantly increased from 0.35 to 0.52 ($p=0.005$) and 0.15 to 0.24 ($p=0.01$) at 12 months follow-up. Transcutaneous pressure of oxygen ($TCPO_2$) showed a trend of increase. A significant reduction in pain was reported by nine of eleven patients, 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.

To date, data indicate that VM202 treatment is safe and well-tolerated. HGF levels remained unchanged and there was no HGF plasmid detectable via biodistribution studies after 59 days even at the highest dose cohort (16 mg). 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 patients in each of these cohorts (Pt ID 001102, 001103, 001104, and 001109) all 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.

Preliminary Conclusions. These early data support the feasibility of intramuscular injections of VM202 in patients with critical limb ischemia. 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, while high, did not appear to be significantly different between treatment cohorts. Continued study of VM202 in patients with CLI and / or diabetes is warranted.

1.7. STUDY AND DOSE RATIONALE

This is a dose escalating study. For each cohort, VM202 will be administered as unilateral intramuscular injections in the calf of 4 mg, 8 mg, or 16 mg of VM202. Only the right leg will be treated in this study, unless medically contraindicated. VM202 will be delivered 2 divided doses with a 2-week interval between injections. Each injection will contain 0.25mg VM202. Individual injections will be of 0.5 mL.

The first cohort of patients will receive a total dose of 4 mg of study product in 8 mL of solution (eight injections on Day 0, and eight injections on Day 14). The second cohort of patients will receive a total dose of 8 mg of study product in 16 mL of solution (sixteen injections on Day 0, and sixteen injections on Day 14). The third cohort of patients will receive a total dose of 16 mg of study product in 32 mL of solution (thirty-two injections on Day 0, and thirty-two injections on Day 14).

These doses were chosen because no toxicity was detected in rabbit, rat and mouse toxicity studies and safety was demonstrated at doses that were approximately 5 (80mg/70kg) to 60 (960mg/70kg) times the maximum cumulative clinical dose (16 mg in Cohort III) proposed in this study:

1. Single intramuscular or intravenous doses in rat: 1.2mg/kg that is approximately 5 times the maximum cumulative clinical dose.
2. Repeated dose toxicity in rabbit (IM): 6mg/kg that is approximately 26 times the maximum cumulative clinical dose.
3. Repeated dose toxicity in rat (IM): 13.68mg/kg that is approximately 60 times the maximum cumulative clinical dose.
4. Single dose toxicity in rat (IM): 6.84mg/kg that is approximately 30 times the maximum cumulative clinical dose.
5. Immunotoxicity in mice (IM): 1.14mg/kg that is approximately 5 times the maximum cumulative clinical dose.
6. Genomic integration / reproductive tissue distribution in rat (IM): 6.84 mg/kg that is approximately 30 times of the maximum cumulative clinical dose.

2. GOOD CLINICAL PRACTICES 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 Good Clinical Practice 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 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 I/II study is to evaluate the safety and tolerability of intramuscular injection in the calf of VM202 in patients with diabetic peripheral neuropathy. Secondarily, the potential role of VM202 to reduce pain in patients with diabetic peripheral neuropathy will be explored. Efficacy parameters include changes in the sensory portion of the Short Form McGill Pain Questionnaire (SF-MPQ), the Brief Pain Inventory (BPI-DPN), and the VAS Pain score.

3.2. STUDY DESIGN

This is a phase I/II, open label, dose-escalation, multicenter, 12 month study. Patients with painful DPN will be screened for study eligibility after giving informed consent. Patients will be treated with 4 mg, 8 mg or 16 mg of VM202 by intramuscular injections in the right calf on Day 0 and again on Day 14. Study drug will only be administered unilaterally. If injection in the right leg is medically contraindicated, the left leg may be treated and noted on the appropriate case report form.

VM202 will be delivered in a solution of 0.5 mg VM202 / mL. Individual injections will be 0.5 mL. Patients in Cohort I will receive 2 mg of VM202 on Day 0 and Day 14 for a final dose of 4 mg; Cohort II will receive 4 mg of VM202 on Day 0 and Day 14 for a final dose of 8 mg; and Cohort III will receive 8 mg of VM202 on Day 0 and Day 14 for a final dose of 16 mg VM202. Table 2 lists the final dose and number of injections to be administered by study cohort. Patients will be followed for a period of 12 months.

Table 2. VM202 administration for each cohort

Cohort	Final Dose VM202	Number of Injections		Total Volume Injected
		Day 0	Day 14	
I	4 mg	8	8	8 mL
II	8 mg	16	16	16 mL
III	16 mg	32	32	32 mL

This is a dose escalation study. Cohorts of increasing dose will be enrolled sequentially. Dose escalation decisions (permission to treat at higher doses) will be made by the Data Safety Monitoring Board (DSMB) based on review of adverse events and on the occurrence of dose limiting toxicities (DLT) in each cohort. The decision to proceed to the next higher dose cohort will be made according to the following scheme.

After the first patient in a dose cohort completes the Day 30 follow-up evaluation and the other three patients enrolled in the same cohort complete at least the Day 14 follow-up (second dosing), an interim safety evaluation will be performed by the DSMB.

- If no DLT is observed at the current dose cohort, then the dose may be escalated as planned for the next cohort.
- If a DLT is observed in one patient in a dose group, then 2 additional patients will be treated at the same dose level. If no further DLTs are observed in the additional patients at Day 30, then that Dose will be considered the Maximum Tolerated Dose (MTD).
- If a DLT occurs in 2 patients, then the preceding dose level will be considered the MTD.

If a DLT is observed in a patient in a dose cohort with complete enrollment, but after a dose escalation has occurred, further dose escalation may be delayed pending review of the data. If 2 patients in a dose cohort experience a DLT, then the study will be stopped.

A DLT is defined as any of the following SAEs:

- acute anaphylaxis (including erythema, hives, wheezing, stridor or respiratory distress) attributable to VM202 injection;
- temperature >102ºF with negative blood cultures and in absence of viral syndrome within 24 hours of study drug administration; or
- evidence of active tissue necrosis of grade 3 or greater at the injection site within two weeks of study drug administration.

The DSMB will make a formal recommendation to proceed (or not proceed) to the next dose cohort between the first and second dose cohort, and again between the

second and third dose cohort (if applicable). The DSMB will monitor patient safety throughout the 12 month follow-up period.

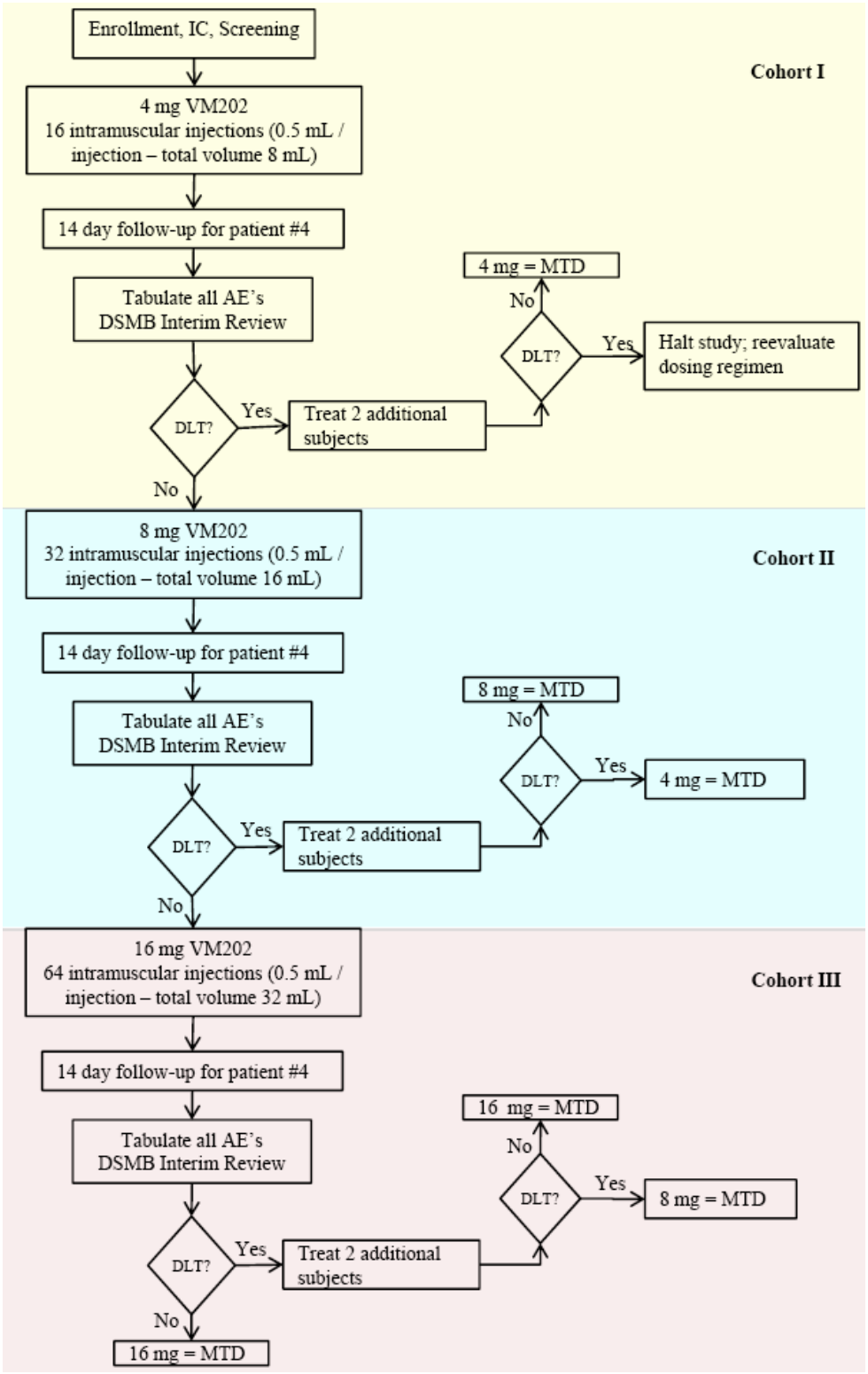

Figure 3. Study flowchart

Screening/Baseline assessments should occur within the 60 days prior to Day 0 (day of injection). Baseline assessments include assessment of study eligibility, a complete medical history, vital signs, complete physical exam, photograph and measurement of ulcers (if any), cancer screening tests, viral screening, MNSI Score, VAS, 12 lead EKG, retinal fundoscopy, clinical chemistry, hematology, urinalysis, and pregnancy test (women of childbearing potential only), and documentation of any ulcers or gangrenous areas.

Patients will be treated with 8, 16 or 32 – 0.5 mL intramuscular injections in the right calf of VM202 on Day 0 and again on Day 14. Each injection will contain 0.25 mg VM202. The first cohort of patients will receive a total dose of 4 mg of study product in 8 mL of solution (eight injections on Day 0, and eight injections on Day 14). The second cohort of patients will receive a total dose of 8 mg of study product in 16 mL of solution (sixteen injections on Day 0, and sixteen injections on Day 14). The third cohort of patients will receive a total dose of 16 mg of study product in 32 mL of solution (thirty-two injections on Day 0, and thirty-two injections on Day 14).

Adverse events will be recorded throughout the one year follow-up period. HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 14, on Day 30, and Day 60. The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours post injection), Day 14 (pre-injection, and 2 hours post injection), Day 21, Day 30, Day 60 and Day 90. VAS score, the SF-MPQ and BPI-DPN will be recorded on Day 0, Day 30, Day 60, Day 90, at 6 months and 12 months. Retinal fundoscopy will be conducted at screening and at 12 months.

3.3. PATIENT POPULATION

Up to 14 evaluable patients with DPN meeting the following study entry criteria will be enrolled.

3.3.1. INCLUSION CRITERIA

1. Age ≥ 18 years to ≤ 75 years;
2. Documented history of Type I or II diabetes with current treatment control (glycosylated hemoglobin A1c of ≤ 10.0%);
3. Diagnosis of painful diabetic peripheral neuropathy in both lower extremities;
4. The physical examination component of the Michigan Neuropathy Screening Instrument Score (MNSI) is ≥ 3 at Screening;
5. Visual analog scale (VAS) score of ≥ 4 cm at screening (0 cm = no pain – 10cm worst imaginable pain);
6. Stable treatment of diabetes for at least 3 months with no anticipated changes in medication regimen, and no new symptoms associated with diabetes;
7. Lower extremity pain for at least 6 months; and
8. If female of childbearing potential, negative pregnancy test at screening and using acceptable method of birth control during the study.

3.3.2. EXCLUSION CRITERIA

1. Peripheral neuropathy caused by condition other than diabetes;
2. Other pain more severe than neuropathic pain;
3. Progressive or degenerative neurological disorder;
4. Myopathy;
5. Have an inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
6. Active infection;
7. Chronic inflammatory disease (e.g. Crohn's, Rheumatoid Arthritis)
8. Positive HIV or HTLV
9. 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 or known immunosuppression or on chronic treatment with immunosuppressive drugs, chemotherapy or radiation therapy;
10. Stroke or myocardial infarction within last 6 months;
11. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination:

    - Cataract surgery within 6 months of trial;
    - Vascular lesions of the anterior segment of the eye (infection or ulceration of the cornea, rubeotic glaucoma, etc);
    - Vascular lesions of the posterior segment of the eye or proliferative retinopathy, macular edema, s/p photocoagulation for macular edema or proliferative retinopathy; sickle cell retinopathy, ischemic retinopathy due to retinal venous stasis or carotid artery disease;
    - Choroidal angiogenesis; and
    - Large elevated choroidal nevi, choroidal vascular tumors (choroidal hemangioma), or melanomas.

12. Specific laboratory values at Screening including: Hemoglobin < 9.0, g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm3, Creatinine > 2.0 mg/dL; GFR < 50, AST and/or ALT > 2 times the upper limit of normal or any other clinically significant lab abnormality which in the opinion of the investigator should be exclusionary;
13. Use of gamma-linolenic acid (GLA), alpha lipoic acid or any other high dose dietary antioxidant supplement for symptomatic relief of DPN;
14. Uncontrolled hypertension as defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
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);

16. Malignant tumors or abnormal screening test suspicious for cancer, or patients in whom screening exams indicate possible occult malignancy unless malignancy has been ruled out. 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;
17. Elevated PSA unless prostate cancer has been excluded;
18. Subjects requiring > 81 mg daily of acetylsalicylic acid; If > 81 mg are taken at screening, subjects may be enrolled if willing/able to switch to another analgesic;
19. Major psychiatric disorder in past 6 months;
20. History of drug or alcohol abuse / dependence in the past 2 years;
21. History of recent tobacco abuse (within past 5 years);
22. BMI > 45 kg/m2;
23. Use of an investigational drug or treatment in past 12 months; and
24. Unable or unwilling to give informed consent.

3.4. STUDY PROCEDURES

Prior to recruitment of any patients into the study, written approval of the protocol and informed consent must be obtained from the Institutional Review Board (IRB).

3.4.1. INFORMED CONSENT

The investigator will explain the study purpose, procedures, and patient's responsibilities to the potential participant. The patient's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained (Appendix 2). The patient 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 patient records; a copy will be provided to the patient.

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. PATIENT IDENTIFICATION

To maintain confidentiality, the patient's name should not be recorded on any study document other than the informed consent form. All patients that give informed consent (sign the informed consent form) will be assigned a unique identifier.

3.4.3. SCREENING (DAY -60 TO DAY 0)

Patient enrollment is subject to the rules established in Section 3.2 for dose escalation, but screening procedures can proceed provided the Investigator waits for enrollment confirmation from ViroMed or its Designee.

The following procedures / evaluations will be conducted at screening:

- Obtain informed consent prior to any study-related procedures
- Evaluation of eligibility
- Complete Medical History
- Vital Signs
- Complete Physical Exam
- Concomitant Medications
- Cancer screening – including cancer markers; pap smear and mammogram if not performed within past 12 months (females only); chest X-ray or CT scan of the chest (if the patient has a previous history of tobacco use, a CT scan will be performed instead of the chest X-ray) within 3 months prior to study entry; PSA (males only); for patients ≥ 50 years old, colonoscopy within past 10 years. Note fecal occult blood test (FOBT) is not required since colonoscopy will be performed to screen for colon cancer.
- Retinal Fundoscopy – in cases where fundoscopy alone is deemed insufficient to rule out exclusionary conditions (see exclusion criterion # 11), fluorescein angiography may be conducted
- 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
- Serum chemistry and hematology
- Urinalysis
- Urine pregnancy test (for women of childbearing potential only)
- Photograph and measurement of ulcer(s) – if present
- EKG
- Michigan Neuropathy Screening Instrument
- Visual Analog Scale (VAS) score

3.4.3.1. SCREEN FAILURES

Patients not meeting all study entry criteria will be designated as a screen failures. End of study procedures will not be performed for these patients, but their reason for discontinuation will be recorded on the CRF. Screen failures will be replaced.

3.4.4. TREATMENT AUTHORIZATION

When Screening has determined that the patient is eligible for study participation, the site will complete a Treatment Authorization Form. The form will include the patient identification number, demographic information (gender, date of birth) and will indicate that the patient meets all in/exclusion criteria. The Treatment Authorization Form will be faxed to ViroMed or its designee. ViroMed or its designee will in turn indicate if the patient can be treated and specify the treatment. The authorization form will be returned to site by fax, and upon receipt the patient will be scheduled to undergo the study injections. Note: adherence to this process is important to track enrollment, and to assure assignment to the proper dose level.

3.4.5. DAY 0 – 1ST INJECTIONS

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

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Photograph and measurement of ulcer(s) – if present
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)

3.4.5.2. 1ST DOSE OF VM202

- Intramuscular injections of VM202 in calf (unilateral, right leg only unless contraindicated)

3.4.5.3. POST-INJECTION

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

3.4.6. DAY 14 ± 1 DAYS – 2ND INJECTIONS

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

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Visual Analog Scale (VAS) score
- Adverse event assessment
- Injection site assessment

3.4.6.2. 2ND DOSE OF VM202

- Intramuscular injections of VM202 in calf (unilateral, right leg only unless contraindicated)

3.4.6.3. POST-INJECTION

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

- Adverse event assessment

3.4.7. DAY 21 ± 3 DAYS

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

3.4.8. DAY 30 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Photograph and measurement of ulcer(s) – if present prior to first dosage administration)
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Injection site assessment
- Adverse event assessment

3.4.9. DAY 60 ± 7 DAYS

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Photograph and measurement of ulcer(s) – if present prior to first dosage administration)
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Injection site assessment
- Adverse event assessment

3.4.10. DAY 90 ± 7 DAYS

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Copies of VM202 in whole blood

- Photograph and measurement of ulcer – if present prior to first dosage administration)
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Adverse event assessment

3.4.11. 6 MONTHS ± 1 MONTH

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Photograph and measurement of ulcer – if present prior to first dosage administration)
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Adverse event assessment

3.4.12. 12 MONTHS ± 1 MONTH

- Retinal fundoscopy
- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Photograph and measurement of ulcer(s) – if present prior to first dosage administration)
- Visual Analog Scale (VAS) score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Brief Pain Inventory for Diabetic Neuropathy (BPI-DPN)
- Adverse event assessment

3.5. STUDY COMPLETION

3.5.1. COMPLETED PATIENTS

Each patient in the study will be considered completed when all assessments through 12 months have been performed in accordance with the study protocol.

3.5.2. DISCONTINUED PATIENTS

Any patient may voluntarily discontinue the study at any time without prejudice. The investigator may discontinue a patient from the study at any time if (s)he considers that remaining in the study compromises the patient's health or the patient 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:

- AEs necessitating discontinuation from the study (pre-treatment).
- The patient is lost to follow-up.
- Patient decision (specify).
- Investigator decision (specify).
- Other reason (specify).

The reasons for any patient discontinuation will be recorded on the study completion form of the CRF.

Discontinued patient(s) will be replaced in any dose cohort if discontinuation occurs prior to the 60 Day follow-up;

Patients discontinued for AE(s) will be followed-up after patient'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
- Photograph and measurement of ulcer(s) if present at baseline
- Vital Signs
- Serum HGF if discontinued prior to Day 60
- 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 patient lost-to-follow-up, the investigator must do his/her best to contact the patient (by phone or letter) at least twice. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general practitioner. The evidence of these contacts must be recorded in the patient medical chart. It can be, for instance, the acknowledgement of receipt of a letter sent to the patient.

3.5.3. PREMATURE STUDY TERMINATION

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

3.6. INVESTIGATIONAL DRUG PRODUCT AND ACCOUNTABILITY

3.6.1. INVESTIGATIONAL DRUG PRODUCT

VM202 is a DNA plasmid containing a novel genomic cDNA hybrid human hepatocyte growth factor (HGF) coding sequence (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 no change in the coding region of the HGF gene, HGF proteins generated from VM202 are identical to the wild-type human HGF proteins.

The plasmid has 7,377 base pairs, a HCMV enhancer / promoter, a growth hormone polyadenylation terminator sequence, ColEl originator, and the Kanamycin resistance gene, on a pCK backbone.

VM202 is supplied in a sterile glass vial containing 2.2 mg of lyophilized study product. VM202 should be stored in a refrigerator at temperatures between 2^{o}C and 8^{o}C in an appropriately locked room accessible only to the pharmacist, the Principal Investigator, or a duly designated person. Since VM202 does not contain preservatives, opened vials of VM202 and VM202 reconstituted with water for injection (WFI) must be used within 6 hours when stored at room temperature. VM202 should never be frozen. . A complete description of test article administration can be found in Appendix 4.

3.6.2. 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 Principal Investigator. The Principal Investigator or his 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 patient 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 Principal Investigator at the conclusion of the study.

After the study is completed, the Principal Investigator 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.

3.6.3. DOSE AND ADMINISTRATION

VM202 is supplied in a sterile glass vial containing 2.2 mg of lyophilized study product. Before administration, it will be reconstituted with 4.4 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. A complete description of test article administration can be found in Appendix 4.

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).

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 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 Baseline. 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 patient's CRF.

4.1.3. CANCER SCREENING

All patients 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 patient's medical history may be acceptable where noted. Routine cancer screening includes the following:

1. For patients ≥ 50 years old, colonoscopy within past 10 years. Note: FOBT is not required since colonoscopy will be performed to screen for colon cancer.
2. Chest X-ray or CT scan of the chest (if the patient has a previous history of tobacco use, a CT scan will be performed instead of the chest 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

The cancer screening tests performed at baseline for this protocol are consistent with the American Cancer Society "Guidelines for the Early Detection of Cancer" dated: 3/28/07 (see Appendix 7).

4.1.4. VIRAL SCREENING

A Contract Research Laboratory (Lab to be determined) 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),. The results of the viral profile will be sent to the investigational site.

4.1.5. URINALYSIS

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

4.1.6. 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.[49-51] The MNSI is comprised of a patient 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 3.

4.1.7. 12-LEAD EKG

A 12 lead electrocardiogram (EKG) will be conducted at screening. The EKG recording will be printed out in duplicate, and one copy will be placed with patient records. Any clinically meaningful changes from baseline will be recorded as adverse events.

4.1.8. 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 acceptable methods of contraception.

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/Baseline patients for eligibility and repeated at 12 months. Retinal fundoscopy must be performed by an ophthalmologist within 3 months of Screening/Baseline.

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

The vital signs of blood pressure (while patient is sitting), temperature , body weight, heart rate, and respiratory rate will be measured and recorded at screening and at every visit through the 12 month follow-up and recorded in the patients CRF.

4.2.4. SERUM CHEMISTRY AND HEMATOLOGY

Evaluation of serum chemistry and hematology will be conducted at Baseline and at every study visit though the 12 month follow-up. Evaluations will be conducted locally at each site.

Serum chemistry evaluations will include: calcium, phosphorus, glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, alkaline

phosphatase, gamma glutamyl transpeptidase (GGT), lactic dehydrogenase (LDH), uric acid, albumin, and globulin.

Hematology evaluations will include: complete blood count (CBC): red blood cells (RBC); hemoglobin (HgB), HCT, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets and white blood cells (WBC) with differential; and, neutrophils or polymorphonuclear cells (polys), lymphocytes (lymphs), monocytes or macrophages (monos), eosinophils (eos) and basophils (bas). Abnormal readings do not necessarily constitute an adverse event; the reading needs to be reviewed in the context of the patient's health. HbA1c will be conducted at Baseline, 30 days, 90 days, 6 months and 12 months. Laboratory testing by visit is provided in Appendix 9.

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, and Day 60. A minimum 2 cc blood draw will be taken at each time point. Allow blood to clot for 30 minutes then centrifuge for 10 minutes at 1000 x g. Serum should be collected and transferred into plastic vials of 0.2 cc aliquots each. The plastic vials will be snap frozen in LN2 or an alcohol dry ice bath. Samples will be maintained in a cooler containing dry ice and then placed in a ≤ -65°C freezer until shipped for analysis. Samples should be labeled with subject ID, draw date, study number and visit interval (i.e., Day 0, 14, 30 or 60). All sample packages will be sent in a single batch, including VM202 samples, with a temperature tracking recorder. Analysis will be conducted by Charles River Laboratories in accordance with good laboratory practices (GLP). Samples should be sent to:

Charles River Laboratories
Preclinical Services Nevada
6995 Longley Lane
Reno, NV 89511
Phone: (775) 682-2079

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 1-3 hours post injection), Day 21, 30, 60, and Day 90. 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 cc aliquots each. Collect 5 cc of whole blood per patient per timepoint (meaning a transfer to a minimum of 5 vials containing 0.6cc – 1cc aliquots). The vials will be snap frozen in LN2 or an alcohol dry ice bath. 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, 14, 21, 30, 60 or 90). All sample packages will be sent in a single batch, including serum HGF samples) with a temperature tracking recorder. Analysis will be conducted by Charles River Laboratories in accordance with good laboratory practices (GLP). Samples should be sent to:

Charles River Laboratories
Preclinical Services Nevada
6995 Longley Lane
Reno, NV 89511
Phone: (775) 682-2079

4.2.7. PHOTOGRAPH AND MEASUREMENT OF ULCER

Two photographs of any ulcerations or gangrenous areas will be taken for documentation purposes only if present at screening or immediately before treatment on Day 0. If present prior to the first injection, two photographs of each ulceration/gangrene area will be obtained at Day 30, Day 60, Day 90, 6 months and 12 months. A metric ruler (cm and mm) will be photographed in the lower right hand corner of the frame to allow for scale determination. During the monitoring visit, the monitor will retrieve one of the two photographs for each ulceration/gangrene area. The border of all photographs will be labeled with the photograph date, patient's initials, and the patient's study number assignment. Ulcer dimensions will be recorded.

4.2.8. VISUAL ANALOG SCALE (VAS) SCORE

Pain will be measured using the visual analog scale (VAS) at screening, before the first treatment (injection) on Day 0, before the second treatment (injection) on Day 14, at Day 30, Day 60, Day 90, 6 months and 12 months. The VAS scoring instrument is a 10-cm line, oriented horizontally, with the left end indicating "no pain" and the right end representing "pain as bad as it can be". 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.

4.2.9. SHORT FORM MCGILL PAIN QUESTIONNAIRE (SF-MPQ)

Pain will also be characterized using the Short Form version of the McGill Questionnaire (SF-MPQ).[52] This questionnaire reviews 15 dimensions of pain: descriptors 1-11 represent the sensory dimension of pain experience and 12-15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. This test will be administered pre-injection on Day 30, Day 60, Day 90, 6 months and 12 months. The SF-MPQ can be found in Appendix 5.

4.2.10. BRIEF PAIN INVENTORY FOR PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY (BPI-DPN)

The brief pain inventory (BPI-DPN)[53] will be administered before the first treatment (injection) on Day 0, on Day 30, Day 60, Day 90, 6 months and 12 months. The full Questionnaire can be found in Appendix 6.

4.2.11. INJECTION SITE REACTION ASSESSMENT

Local injection sites reactions will be assessed on Day 0 post injection, Day 14, Day 21, Day 30 and Day 60 using the grading defined 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

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).

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization 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 patient 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 patient 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 patients' 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 12 month follow-up visit of the study by a patient 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. ViroMed 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 patient but does not interfere with routine activity.
Moderate:	The AE is discomforting and interferes with routine activity.
Severe:	The AE significantly limits the patient'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 patient, 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 12 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 and the 12 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 48 hours) to the study 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 patient'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 ViroMed 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), Institutional Biosafety Committee (IBC). Upon receipt from ViroMed of an initial or follow-up IND Safety Report or other safety information, the Investigator must promptly notify his or her IRB, IBC.

5.4.2. SPONSOR'S RESPONSIBILITY

All AEs and SAEs will be reported on and annual basis to FDA in accordance with the IND regulation (21 CFR Part 312). All serious unexpected AEs will be reported to FDA as an IND Safety Report with 15 calendar days of the event (21 CFR §312.32). Any unexpected fatal or life-threatening AEs will be reported to the Agency within 7 calendar days.

ViroMed 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 primary goal of this study is to determine the maximum tolerated dose that ensures patient safety. Sample size estimations were not based on formal statistical hypotheses testing due to the exploratory nature of this Phase I/II study. Hypothesis testing will not be performed on any endpoint.

6.1. PATIENT CATEGORIZATION

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

Evaluable Patient - Any patient who received the study drug.

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

6.2. STUDY ENDPOINTS

The primary study endpoint is to evaluate safety and tolerability of intramuscular injection in the calf of VM202 in patients with painful DPN. Secondary endpoints include the assessment of the potential of VM202 to reduce the pain associated with DPN.

6.2.1. SAFETY

Any patient who receives VM202 will be included in the safety analysis population. Adverse events, serious adverse events, and adverse events leading to treatment discontinuation will be summarized using descriptive statistics. Categorical variables will be summarized by the number and percentage of patients in each category. Continuous variables will be summarized using n, mean, SD, median, minimum, and maximum values. No statistical testing will be performed.

6.2.2. PHARMACODYNAMICS

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

6.2.3. EFFICACY

This is a phase I /II study, not powered to detect differences in efficacy measures. However, descriptive statistics of clinically meaningful endpoints will be tabulated. Pain as measured by the VAS pain scale, the SF-MPQ and the BPI-DPN will be tracked and presented. The status of preexisting ulcers will also be reported.

7. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

ViroMed will designate a CRO to monitor the progress of this study. The clinical monitor, as a representative of ViroMed, 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 be dated and signed by the person who performed the assessment or procedure, and must contain all information required by the CRF. All data generated during this study and the source documents from which they originated are patient to inspection by ViroMed 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

ViroMed 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 ViroMed 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 ViroMed 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 ViroMed or its designee prior to release of study supplies.

FDA/relevant health authority regulations require that all advertisements for patient recruitment be approved by an IRB prior to implementation. The complete text and format must be submitted to ViroMed 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 ViroMed and its designated CRO.

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 ViroMed 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 site 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 patient 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 patient, 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 patient'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 ViroMed or its designee, prior to submission to an IRB. After approval by ViroMed 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 patient must read, sign and date the informed consent form. The person executing the consent must also sign and date the final consent form page. Patients 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 patient. The informed consent process must be documented in the patient's medical record.

The informed consent must be written in a language in which the patient 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 ViroMed Co., Ltd.

12. CONFIDENTIALITY

In accordance with GCP and with the national data protection laws, all information concerning the patients 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 patient 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 patients, a change may be made preferably after discussion with ViroMed 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 ViroMed 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 ViroMed or its designee. Other errors or omissions will result in queries which will be sent to the investigational site on Data Clarification Forms (DCF) for resolution. A copy of the signed DCF is to be kept by the site with the CRFs. Once the original is received by ViroMed or is 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, ViroMed and its representatives and FDA/relevant health authorities/regulatory agencies. All reports and communications relating to study patients will identify patients only by initials and patient identification number. Complete patient 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 ViroMed or its designee immediately. The investigator will also grant ViroMed representatives the same privileges offered to FDA/relevant health authority or regulatory agents/officers/employees.

The Investigator must provide ViroMed 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 ViroMed or the CRO and the site
- Copies of all SAEs reports submitted to ViroMed or designated CRO
- Copies of all IND Safety Reports submitted to the site by ViroMed
- 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. ViroMed will notify the principal investigator when records are no longer needed. The investigator will not discard any records without notifying ViroMed. If the principal investigator moves from the current investigational site, ViroMed 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 ViroMed 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 ViroMed 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 ViroMed 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 ViroMed. 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

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 ± 7 D	Day 90 ± 7 D	6 months ± 1 mo	12 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	✓											
MNSI ††	✓											
EKG	✓											
Pregnancy test	✓											
Safety and Efficacy Parameters												
Retinal Fundoscopy	✓										✓	✓
Concomitant Medications	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓
Serum Chemistry and hematology	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓
HbA1c	✓						✓		✓	✓	✓	✓
Photograph and measurement of ulcer(s)†††	✓	✓					✓	✓	✓	✓	✓	✓
Visual Analog Scale (VAS) score	✓	✓		✓			✓	✓	✓	✓	✓	
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serum HGF		✓		✓			✓	✓				✓[2]
Copies of VM202 in whole blood		✓	✓***	✓	✓***	✓	✓	✓	✓			✓[1]
SF-MPQ *		✓					✓	✓	✓	✓	✓	
BPI-DPN**		✓					✓	✓	✓	✓	✓	
Treatment												
Injection site reaction assessment			✓	✓	✓	✓	✓	✓				✓[2]
Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

† Includes: cancer markers; chest X-ray or CT scan of the chest (if patient has a previous history of tobacco use, a CT scan will be performed instead of the chest X-ray) within 3 months; pap smear and mammogram if not performed within past 12 months (females only); PSA (males only); for patients ≥ 50 years old, colonoscopy within past 10 years

†† MNSI - Michigan Neuropathy screening Instrument

††† If present prior to first study drug administration

* SF-MPQ - Short Form McGill Pain Questionnaire

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

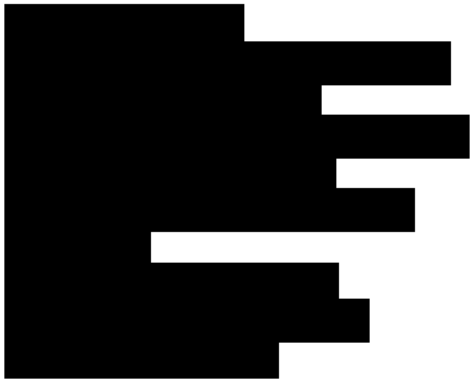
*** 2 hours after injection (± 1 hour)

1 If withdrawal occurred before Day 90 Visit

2 If withdrawal occurred before Day 60 Visit

Appendix 2. Sample Informed Consent

TITLE: A Phase I/II Open Label, Dose-Escalation Study to Assess the Safety and Tolerability of VM202 in Patients with Painful Diabetic Peripheral Neuropathy
Protocol Number: VMDN-001

SPONSOR: 

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

Do I have to take part?

Taking part in this study is entirely voluntary, and you may refuse to participate or withdraw from the study at any time without influencing your regular medical treatment and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect

the standard of care you receive. Regardless of your decision, you will still be treated for your medical condition.

Why is this study being done?

You are being considered to participate in this research study because you have type I or II diabetes with current treatment control and, you are experiencing painful diabetic peripheral neuropathy (DPN) in both lower extremities.

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 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 study in Korea in patients with coronary artery disease and in another study in the United States in patients 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 tolerability of three different doses of VM202.
- If there are any effects of VM202 on your symptoms of painful diabetic neuropathy.

VM202 will be injected into your calf muscle using a syringe with a fine needle. Only one leg will be treated in this study.

Who is in charge of this study?

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

How many people will take part in this research study?
A total of 12 to 14 patients will take part in this study at up to 3 hospitals in the United States.

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. The list of the tests that will be done are listed below. 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 an open label, dose-escalation clinical study. This means that both you and your doctor will know what dose of VM202 you will receive. Four to six subjects will be enrolled into each dosage group starting with the lowest dose group and ending with the highest dose group. Each patient is treated with VM202 twice, with 14 days between treatments. Each injection contains 0.5 ml of fluid with 0.25mg VM202 and will be placed into your right calf unless the study doctor determines that there are reasons to inject your left calf:

Low Dose – 8 injections at each treatment.

Middle Dose - 16 injections at each treatment.

High Dose - 32 injections at each treatment.

What tests, procedures, and diagnostic studies will be done during this study?
There are 9 visits which span 12 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, and heart rate (**vital signs**).

Photograph and Measurement of Ulcer – any ulcerations or gangrenous areas present prior to the first injection will be photographed.

Medication Review – Discussion with your doctor of what medications and dietary supplements you have taken or are currently taking.

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 a short questionnaire about feeling in your legs and feet at Screening. You will be asked to complete brief questionnaires about pain in your feet and legs at some visits.

Cancer Screening – Cancer screening includes testing for cancer markers; pap smear and mammogram if not performed within past 12 months (females only); PSA (males only); for patients ≥ 50 years old, colonoscopy within past 10 years; 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 12 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.

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

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

Visit # 1: Screening/Baseline Evaluations
Screening is a process of evaluating your initial health status and assessing the status of your pain related to diabetic neuropathy. Screening is usually completed within 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, questionnaire, assessment of neuropathy, cancer screening, retinal fundoscopy; urine and tests including a viral screen; photograph and measurement of ulcer, pregnancy test (if you are a female), and 12 lead EKG.

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 to the first available VM202 dose group. You will then be scheduled for the first injection procedure which will be done at your next visit (Visit #2).

Visit # 2 – First Injection Procedure (injection of VM202 into the calf muscle)

Before Injection Procedure:
The following tests will be performed before you have your injection procedure done: medication review, questionnaires, vital signs, photograph and measurement of ulcer and blood tests including HGF and VM202.

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 solution at sites evenly distributed over your calf muscle. The number of injections depends on which dosage group you are enrolled in; you will receive 8, 16 or 32 injections

Each injection will take 20 – 30 seconds. Each site will be marked with an indelible marker. The entire injection procedure is expected to take 30 – 60 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 including HGF and VM202, and assessment of side effects.

Before you go home detailed 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/Final Injection Procedure (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, questionnaire, vital signs, and blood tests including HGF and VM202.

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 solution at sites evenly distributed over your calf muscle. If the marks made to identify the first injection sites are still visible, they will guide the doctor to inject at locations that were not injected previously. The number of injections depends on which dosage group you are enrolled in; you will receive 8, 16 or 32 injections.

Each injection will take 20 – 30 seconds. The entire injection procedure is expected to take 30 – 60 minutes.

After Injection Procedure:
After the injection procedure is performed, the following tests and/or evaluations will be done: vital signs, blood tests including HGF and 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 including HGF and 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, questionnaires, vital signs, blood tests including HGF and VM202, photograph and measurement of any ulcers which were present before the first injection, injection site reaction assessment, 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, questionnaires, vital signs, blood tests including HGF and VM202, photograph and measurement of any ulcers which were present before the first injection, injection site reaction assessment, and assessment of side effects.

Visit # 7 – 90 Days after the First Injection Procedure

At this visit, the following tests or evaluations will be done: medication review, questionnaires, vital signs, blood tests including VM202, photograph and measurement of any ulcers which were present before the first injection, and assessment of side effects.

Visit # 8 – 6 Months after the First Injection Procedure

At this visit, the following tests or evaluations will be done: medication review, questionnaires, vital signs, blood tests, photograph and measurement of any ulcers which were present before the first injection, and assessment of side effects.

Visit # 9 – 12 Months after the First Injection Procedure

At this visit, the following tests or evaluations will be done: retinal fundoscopy, medication review, questionnaires, vital signs, blood tests, retinal fundoscopy, photograph and measurement of any ulcers which were present before the first injection, and assessment of side effects.

After you have completed your 12-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 12 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, 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 12 times over approximately 13 months. Each time your blood is drawn roughly 1 to 2 tablespoons of blood will be taken.

Risks from cancer screening

Cancer screening includes testing for cancer markers; pap smear and mammogram if not performed within past 12 months (females only); PSA (males only); for patients ≥50 years old, colonoscopy within past 10 years; 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 patients) hives and itching (approximately 0.5% of patients) 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. ViroMed 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 patient 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 (ViroMed 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, an IRB and/or research ethics committee(s).

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).

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, ViroMed Co., Ltd., its subcontractors, or by regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that I will not be referred to by name in any report concerning the study. I 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; 1 copy to be kept with hospital record.

Appendix 3. 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 patient. 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 patient 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. Patients, 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 patient can at the great toe (e.g. examiner's DIP joint of the first finger versus patient'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 patient 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 patient 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 patient 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 patient'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 patient, 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 4. Test Article Administration

1. ***Test article preparation*** - VM202 is supplied in a sterile glass vial containing 2.2 mg of lyophilized study product. Before administration, it will be reconstituted with 4.4 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. The final doses of 4 mg, 8 mg, and 16 mg will be divided evenly between the Day 0 administration and the Day 14 administration. Individual injections will be 0.5 mL. VM202 will be administered via 0.5 mL intramuscular injections on Day 0 and then again on Day 14 in the right calf (unless medically contra-indicated) as follows by patient cohort:

   Table 4. Single dose preparation and delivery of VM202

COHORT	NUMBER OF VIALS VM202 RECONSTITUTED	TOTAL VOLUME TO BE INJECTED	NUMBER OF INJECTIONS	VOLUME / SINGLE INJECTION
I – 2 mg VM202	1	4 mL	8	0.5 mL
II -4 mg VM202	2	8 mL	16	0.5 mL
III - 8 mg VM202	4	16 mL	32	0.5 mL

2. ***Test material administration*** – Patients will receive injections of VM202 on Day 0 and Day 14. A fine needle (e.g. 27 gauge, 1") suitable for IM injections will be used. Only one leg will be treated in this study. Unless there are medical contraindications, the right leg should be treated. Distribute injection sites evenly over the calf muscle. Inject as follows:

   Cohort I Eight 0.5 mL injections on Day 0, and eight 0.5 mL injections on Day 14
   Cohort II Sixteen 0.5 mL injections on Day 0, and sixteen 0.5 mL injections on Day 14.
   Cohort III Thirty-two 0.5 mL injections on Day 0, and thirty-two 0.5 mL injections on Day 14.

3. Inject the entire amount of the drug 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. ***Second test material administration*** – Second administration should also be distributed evenly over the calf, and, as much as is possible, at different injection sites. If the marks made to identify previous injection sites are visible, every effort should be made to inject at other locations. Day 14 injections should be distributed as evenly as possible over the calf.

Appendix 5. Short Form McGill Pain Questionnaire

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

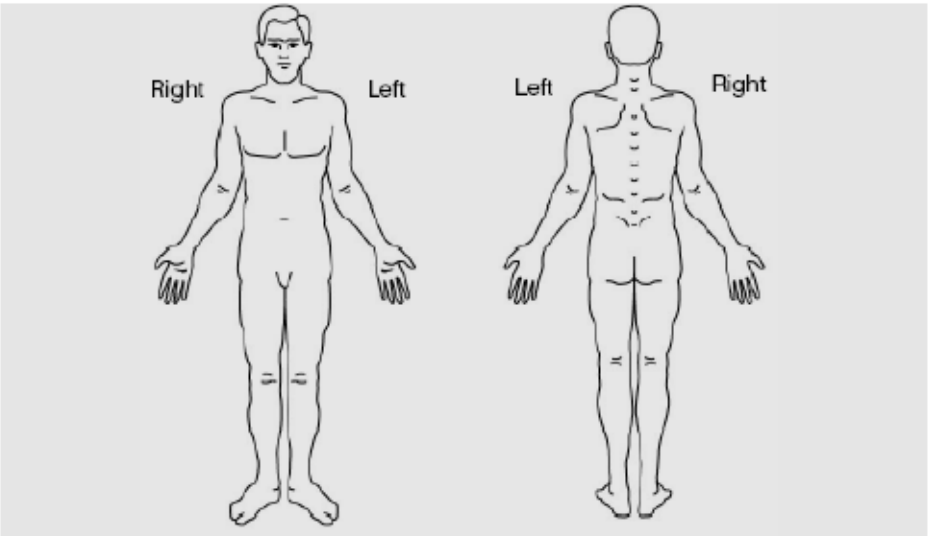
Appendix 6. Brief Pain Inventory for Patients with Diabetic Peripheral Neuropathy (BPI-DPN)

Brief Pain Inventory (Short Form) for Diabetic Peripheral Neuropathy
BPI-DPN

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 everyday 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 due to your diabetes by circling the one number that best describes your pain at its WORST in the past 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 due to your diabetes by circling the one number that best describes your pain at its LEAST in the past 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 due to your diabetes 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 due to your diabetes 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

7) What treatments or medications are you receiving for your pain due to diabetes?

8) In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much RELIEF 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 due to your diabetes 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

Appendix 7. Guidelines for the Early Detection of Cancer

American Cancer Society Guidelines for the Early Detection of Cancer

The following cancer screening guidelines are recommended for those people at average risk for cancer (unless otherwise specified) and without any specific symptoms.

People who are at increased risk for certain cancers may need to follow a different screening schedule, such as starting at an earlier age or being screened more often. Those with symptoms that could be related to cancer should see their doctor right away.

Cancer-related Checkup

For people aged 20 or older having periodic health exams, a cancer-related checkup should include health counseling, and depending on a person's age and gender, might include exams for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some non-malignant (non-cancerous) diseases.

Special tests for certain cancer sites are recommended as outlined below.

Breast Cancer

- Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.
- Clinical breast exam (CBE) should be part of a periodic health exam, about every 3 years for women in their 20s and 30s and every year for women 40 and over.
- Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam (BSE) is an option for women starting in their 20s.
- Women at high risk (greater than 20% lifetime risk) should get an MRI and a mammogram every year. Women at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

Colon and Rectal Cancer

Beginning at age 50, both men and women should follow 1 of these 5 testing schedules:

- yearly fecal occult blood test (FOBT)* or fecal immunochemical test (FIT)
- flexible sigmoidoscopy every 5 years
- yearly FOBT* or FIT, plus flexible sigmoidoscopy every 5 years**
- double-contrast barium enema every 5 years
- colonoscopy every 10 years

*For FOBT, the take-home multiple sample method should be used. **The combination of yearly FOBT or FIT flexible sigmoidoscopy every 5 years is preferred over either of these options alone.

All positive tests should be followed up with colonoscopy.

People should talk to their doctor about starting colorectal cancer screening earlier and/or undergoing screening more often if they have any of the following colorectal cancer risk factors:

- a personal history of colorectal cancer or adenomatous polyps

- a strong family history of colorectal cancer or polyps (cancer or polyps in a first-degree relative [parent, sibling, or child] younger than 60 or in 2 first-degree relatives of any age)
- a personal history of chronic inflammatory bowel disease
- a family history of an hereditary colorectal cancer syndrome (familial adenomatous polyposis or hereditary non-polyposis colon cancer)

Cervical Cancer

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years. Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.
- Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or a weakened immune system should continue to have screening as long as they are in good health.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or pre-cancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.

Endometrial (Uterine) Cancer

The American Cancer Society recommends that at the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting to their doctors. For women with or at high risk for hereditary non-polyposis colon cancer (HNPCC), annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35.

Prostate Cancer

Both the prostate-specific antigen (PSA) blood test and digital rectal examination (DRE) should be offered annually, beginning at age 50, to men who have at least a 10-year life expectancy. Men at high risk (African-American men and men with a strong family of one or more first-degree relatives [father, brothers] diagnosed before age 65) should begin testing at age 45. Men at even higher risk, due to multiple first-degree relatives affected at an early age, could begin testing at age 40. Depending on the results of this initial test, no further testing might be needed until age 45.

Information should be provided to all men about what is known and what is uncertain about the benefits, limitations, and harms of early detection and treatment of prostate cancer so that they can make an informed decision about testing.

Men who ask their doctor to make the decision on their behalf should be tested. Discouraging testing is not appropriate. Also, not offering testing is not appropriate.

References

American Cancer Society. *Cancer Facts & Figures 2007.* Atlanta, Ga: American Cancer Society; 2007.

Saslow D, Boetes C, Burke W, et al for the American Cancer Society Breast Cancer Advisory Group. American

Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57:75-89. [Free full text article available at: http://caonline.amcancersoc.org/cgi/content/full/57/2/75]. Accessed March 28, 2007.

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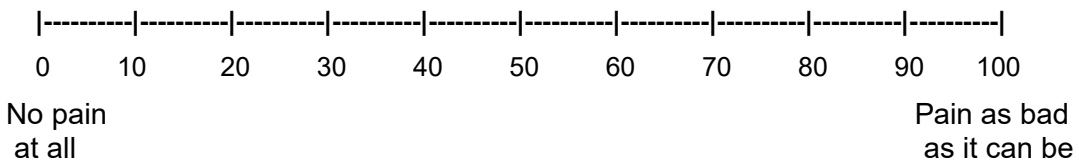
Revised: 03/28/2007

Appendix 8. Visual Analog Scale

Completion of the VAS is based on pain that the subject is experiencing in the right leg (pain below the knee which may include the calf, foot, or both). If the right leg is medically contraindicated, the left leg will be assessed. A score of $\geq$ 4 cm (40 mm) is required in order to be eligible for the study.

The VAS will be completed by the subject. The subject should be asked: "How do you currently rate your pain **in your leg (below the knee – this includes pain in your foot)** that will undergo/underwent study injections? Please place one tick mark on the line below."



The subject should be instructed to indicate his or her current level of pain in the affected leg associated with diabetic neuropathy 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.

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 Days 0 and 14, 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. Laboratory Tests by Visit

Table 5. Schedule of laboratory evaluations

Parameters	Screen	Day 0	Day 14	Day 21	Day 30	Day 60	Day 90	6 Months	12 Months	Early Withdrawal
HbA1c	✓				✓		✓	✓	✓	✓
Serum HGF		✓ - pre	✓ - pre		✓	✓				✓ (< Day 60)
VM202		✓ - pre ✓ - post	✓ - pre ✓ - post	✓	✓	✓	✓			✓ (< Day 90)
Hematology										
HCT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hemoglobin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RBC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WBC with differential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Platelets	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MCV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MCH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MCHC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chemistry										
Albumin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alkaline Phosphatase	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ALT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AST	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bicarbonate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BUN	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Calcium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chloride	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Creatinine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GGT	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Globulin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Glucose	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LDH	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Phosphorus	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Potassium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sodium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total Bilirubin	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Uric Acid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓