A PHASE II, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF VM202 IN SUBJECTS WITH CRITICAL LIMB ISCHEMIA

Protocol VMCLI-II-09-002/E

July 21, 2011

Sponsor:

[redacted]

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- I have read and understand fully the Investigator Brochure.
- I have sufficient time to properly conduct and complete the study within the agreed study period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.
- I will ensure that any staff at my site(s) who are involved in the study conduct are adequately trained regarding this trial's operations, the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the sponsor with a delegation of investigators responsibilities log.
- I understand that the study may be terminated or enrollment may be suspended at any time by ViroMed, Co., Ltd. with or without cause, or by me or my institution if it becomes necessary to protect the best interest of the study patients.

Principal Investigator's Name (print)

Title

Address

Signature / Date

STUDY SYNOPSIS

PROTOCOL TITLE	A Phase II, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects with Critical Limb Ischemia
STUDY PHASE	II
INVESTIGATIONAL AGENT	VM202
DOSE	Two doses will be tested: 8 mg and 16 mg of VM202.
POPULATION	Patients aged ≥ 18 years to ≤ 90 years diagnosed with critical limb ischemia (CLI).
STUDY DESIGN	A phase II, double-blind, randomized, placebo-controlled, multicenter, 12-month study designed to assess the safety and efficacy of unilateral intramuscular injection in the calf of VM202 in patients with critical limb ischemia (CLI). Fifty (50) patients will be randomized in a 2:2:1 ratio to one of three treatment groups: • Low Dose: 8 mg VM202 – 20 patients • High Dose: 16 mg VM202 – 20 patients • Control – placebo (normal saline) – 10 patients Up to twenty sites will participate in the study. Safety will be monitored throughout the study by a Data Safety Monitoring Board (DSMB).
STUDY OBJECTIVES	1. To evaluate the safety of IM administration of VM202 in subjects with moderate or high-risk CLI (Rutherford Clinical Severity Score equal to 4 or 5) who are poor or non- candidates for surgical or percutaneous revascularization. 2. To evaluate potential bioactivity of IM administration of VM202 in subjects with CLI, when compared with placebo, on rest pain (as assessed by frequency of rest pain, pain medication use history, sleeping history, and intensity of rest pain) or leg ulcer healing (as assessed by ulcer surface area, time to complete healing), perfusion (MRA), hemodynamic assessment (ABI & TBI), tissue oxygenation ($TcPO_2$) and the incidence and

extent of lower leg amputation or other surgical interventions

INCLUSION CRITERIA

1. Male or female, between 18 and 90 years of age;
2. Diagnosis of critical limb ischemia (Rutherford Class 4 or 5), including:
   - A resting ankle systolic pressure (in either the dorsalis pedis or posterior tibial arteries) of ≤ 70 mmHg in the affected limb; or
   - A resting toe systolic pressure of ≤ 50 mmHg in the affected limb; or
   - For patients in which measurement of ankle systolic pressure is not feasible (e.g. vessel calcification and non-compressibility), TcPO2 ≤ 30 mmHg;
3. Poor or suboptimal candidate for bypass graft surgery or percutaneous angioplasty;
4. Pain at rest, and/or ischemic ulcers, and/or focal gangrene (< 3 cm^2) for a minimum of 2 weeks,
5. Significant stenosis (≥ 75%) of one or more of the following arteries: superficial femoral, popliteal, or two or more infra-popliteal arteries as verified by angiography within 12 months prior to enrollment;
6. Be willing to maintain current drug therapy for peripheral arterial disease throughout the course of the study including an anti-platelet, hypertension, and statin treatment unless not tolerated;
7. Clinically stable on optimized medical regimen for ≥30 days;
8. Be capable of understanding and complying with the protocol and signing the informed consent document prior to being subjected to any study related procedures;
9. Women who are surgically sterile or at least 1 year postmenopausal or who have been practicing adequate contraception for at least 12 weeks prior to entering the study. If the subject is of child-bearing potential, she must have a negative urine pregnancy test result prior to study enrollment and must agree to repeat pregnancy screening tests during the study. If the subject or the subject's partner(s) is of child bearing potential, the subject and the subject's partner(s) must agree to use a "double barrier" method of birth control while participating in this study.

EXCLUSION CRITERIA

1. Subjects who have undergone a successful revascularization procedure or sympathectomy within 12 weeks prior to study entry. A clinically *unsuccessful* revascularization procedure is defined as one in which:

- the target vessel re-occludes (≥50%, as verified by a second angiogram. Duplex ultrasonography can be used

to determine vessel patency if the patient cannot tolerate a second angiogram), or

- the target vessel remains patent, but there is no resolution of symptoms 6 weeks after the procedure (e.g. no evidence of ulcer healing, no improvement in pressures, no reduction in resting pain);

2. Subjects that will require an amputation in the target leg within 4 weeks of randomization;
3. Subjects with evidence of active infection (e.g., cellulitis, osteomyelitis) or deep ulceration exposing bone or tendon in the extremity planned for treatment;
4. Heart Failure with a NYHA classification of III or IV;
5. Stroke (NIH scale >2) or myocardial infarction within last 3 months;
6. Unstable angina
7. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
8. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
9. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
10. Subjects with advanced liver disease including decompensated cirrhosis, jaundice, ascites or bleeding varices;
11. Subjects currently receiving immunosuppressive medications chemotherapy, or radiation therapy;
12. Positive HIV or HTLV at Screening;
13. Active Hepatitis B or C infection as determined by Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (IgG and IgM; HBcAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV), at Screening;
14. Specific laboratory values at screening including: Hemoglobin < 8.0 g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm^3, AST and/or ALT > 3 times the upper limit of normal or any other clinically significant lab abnormality which in the opinion of the investigator should be exclusionary;
15. Patients with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence); patients with family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
16. Elevated PSA unless prostate cancer has been excluded;

17. Subjects with any co- morbid conditions likely to interfere with assessment of safety or efficacy or with an estimated life expectancy of less than 6 months
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 for the duration of the study;
19. Subjects requiring regular COX-2 inhibitor drug(s) or high dose steroids (excepting inhaled steroids);
20. Major psychiatric disorder in past 6 months;
21. History of drug or alcohol abuse / dependence in the past 2 years;
22. Use of an investigational drug or treatment in past 12 months; concurrent participation in investigational protocol or unapproved therapeutics; and
23. 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, physical exam, cancer screening tests, viral screening, ABI & TBI, $TcPO_2$, 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 a final dose of 8 mg VM202, 16 mg VM202 or placebo by intramuscular injections in the affected calf on Day 0, Day 14, Day 28 and Day 42. VM202 will be delivered in a solution of 0.5 mg VM202 / mL.

TREATMENT GROUP	FINAL DOSE VM202	DOSE VM202 (MG) PER VISIT			
		DAY 0	DAY 14	DAY 28	DAY 42
Low Dose	8 mg	4	4	0	0
High Dose	16 mg	4	4	4	4
Placebo	0	0	0	0	0

Patients in the Low Dose Group (8 mg VM202) will receive:

- Day 0: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 14: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 28: Placebo only (16 injection of 0.5 ml normal saline)
- Day 42: Placebo only (16 injection of 0.5 ml normal saline)

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

- Day 0: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 14: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 28: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 42: 4 mg of VM202 (16 injections of 0.5 ml of VM202)

Patients in the placebo control group will receive 16 injections of 0.5 ml normal saline at each visit.

Determination of HGF serum levels will be made immediately pre-treatment on Day 0, immediately pre-treatment on Day 42, Day 49 and Day 90.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours post injection), Day 42 (pre-injection, and 2 hours post injection), Day 49, Day 90, and at 6 months.

VAS assessment will be performed at Day 0 (pre-injection), Day 14 (pre-injection), Day 28 (pre-injection), Day 42(pre-injection), Day 90, at 6 months, 9 months, and 12 months. VascuQol will be administered on Day 0 (pre-injection), Day 90, at 9 months, and 12 months. . Rutherford classification will be determined at 6 months, 9 months, and 12 months. ABI & TBI will be recorded at Day 0 (pre-injection), Day 28 (pre-injection), Day 90, at 6 months, 9 months, and 12 months. $TcPO_2$ will be measured at Day 0 (pre-injection), 6 months, 9 months, and 12 months. Measurement of ulcer(s) will be performed at Day 0, Day 14, Day 28, Day 42, Day 49, Day 90, at 6 months, 9 months, and 12 months. Retinal fundoscopy will be conducted at 12 months. Adverse events will be recorded throughout the one year follow-up period.

MRA will be conducted as a sub-study at up to two sites on Day 0 (pre-injection) and at 6 and 9 months.

SCHEDULE OF EXAMINATIONS

Screening (Day -60 to Day 0)
Day 0
Day 14 ± 3 days
Day 28 ± 3 days
Day 42 ± 3 days
Day 49 ± 3 days
Day 90 ± 7 days
Month 6 ± 1 month
Month 9 ± 1 month
Month 12 ± 1 month

STUDY ENDPOINTS

The primary study endpoint is to assess the difference in pain level between baseline and the 9 month follow-up as determined by VAS. Active and placebo arms will be compared to determine treatment effect.

Other secondary endpoints will include:

- Difference in pain level between baseline and the 9 month follow-up as determined by VAS by sex and by comorbidities (esp. diabetes or renal dysfunction)
- Change in tissue oxygenation ($TcPO_2$) from baseline to 6, 9 and 12 months following the first treatment
- Change in hemodynamic measures (ABI and TBI) from baseline to Day 28, Day 90, 6 months, 9 months and 12 months following the first treatment
- Change in perfusion (MRA) from baseline to 9 months following the first treatment
- Wound healing (no ulcer: change of skin condition, one ulcer: change of ulcer size, multiple ulcer: change of ulcer number) from baseline to 9 months following the first treatment
- Change in VAS score from baseline to Day 14, Day 28, Day 42, Day 90, at 6 months, 9 months, and 12 months.
- Change in QOL score (VascuQol) at 90 Days, 9 months and 12 months;
- Major limb amputation rate at six months and twelve months following the first treatment
- Mortality at six and twelve months after first treatment

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 their relationship to 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 undergo testing as presented in the American Cancer Society Cancer Screening Guidelines as part of their baseline testing to rule out cancer.

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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)
AUC	Area under the plasma concentration time curve
BP	Blood Pressure
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
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study Visual Acuity Chart
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
GCP	Good Clinical Practices
HBV	Hepatits B Virus
HBcAB	Hepatitis B core antibody
HBsAb	Antibody to Hepatitis B antigen (IgG and IgM)
HBsAg	Hepatitis B surface antigen
HCV	Hepatits C Virus
HGF	hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HTLV	Anti-Human T-Cell Lymphotropic Virus
IBC	Institutional Biosafety Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
NIH	National Institutes of Health
O_2	Oxygen
OBA	Office of Biotechnology Activities
PSA	Prostate Specific Antigen
RBC	Red blood count
RNA	Ribonucleic acid
SGPT	Serum glutamic pyruvic transaminase (same as ALT)
SOP	Standard Operating Procedure
TBI	Toe-brachial index

$TcPO_2$	Transcutaneous pressure of oxygen
VEGF	Vascular endothelial growth factor
WBC	White blood count
WFI	Water for Injection

PERSONNEL AND FACILITIES

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1. BACKGROUND

1.1. PERIPHERAL ARTERIAL DISEASE

The term "peripheral arterial disease" (PAD) is widely used to refer to atherosclerotic disease that obstructs the blood supply to the lower limbs. The clinical manifestations of PAD are a major cause of acute and chronic illness. Patients with PAD experience progressive decrements in functional capacity and quality of life. PAD frequently coexists with coronary and / or cerebrovascular disease, likely due to a similar underlying pathology and shared risk factors (e.g., smoking, hyperlipidemia, hypertension, and diabetes). Patients with PAD have a 20% - 60% increased risk for myocardial infarction (MI), a two- to six-fold increased risk of cardiovascular death, and a 40% increased risk of stroke.[1, 2] This higher level of morbidity and mortality occurs, in part, because many affected patients are asymptomatic and remain undiagnosed for years, allowing the disease to progress unchecked. Clinical symptoms often only manifest when the disease state is advanced.[3]

It is estimated that PAD now affects 8 to 12 million people in the United States. The prevalence of symptomatic PAD increases with age and with number of risk factors. PAD occurs in 1% - 4% of the population over the age of 40, and is reported to be as high as 30% in patients over 70 or in patients older than 50 years with a history of diabetes, smoking, or both.[4-6] As the population ages, this number will increase.

1.2. CRITICAL LIMB ISCHEMIA

Critical limb ischemia (CLI) is the end-stage manifestation of PAD. One to three percent of newly diagnosed PAD patients initially present with CLI; 5%-10% of all other PAD patients eventually progress to CLI. The natural history of CLI has been well documented to have an inexorable downhill course. CLI patients experience ischemic rest pain (Rutherford category 4), ischemic skin lesions, and ulcers or gangrene (Rutherford category 5-6). Amputation of the affected limb remains a common procedure and is likely to occur more frequently due to an aging population.[7] The incidence of major amputations ranges from 120 to 500/million/year.[6] In patients with the comorbidities of diabetes mellitus or renal insufficiency, the rate of amputation can be much greater.[7, 8]

1.3. TREATMENT OPTIONS FOR CLI

The primary treatment goals in patients with CLI are to relieve ischemic pain, heal (neuro) ischemic ulcers, prevent limb loss, improve patient function and quality of life and prolong overall survival. Therefore, reestablishing blood supply to the affected limb, when possible, is critical. In addition to successful revascularization, the institution of lifestyle changes, atherosclerotic risk factor modification, and pharmacologic therapies are also used to reduce cardiovascular morbidity and mortality. Narcotic medications are often used for analgesia and for assistance with sleeping.

1.3.1. REVASCULARIZATION OPTIONS

Revascularization options for patients with CLI range from open surgical procedures (bypass grafts) to various endovascular procedures. The treatment approach depends on a careful evaluation of a patient's current medical condition (comorbidities), the location and extent of the lesion, and the availability of an autologous conduit (e.g. saphenous vein).[9-11] Although arterial bypass surgery has long been considered the preferred first line treatment modality, many of the newer endovascular technologies can be used with similar success rates and with reduced morbidity.[12, 13] Percutaneous transluminal angioplasty (PTA) has been shown to be effective, with limb salvage rates comparable to surgical procedures. Stents placement is usually attempted after failed PTA. Adjunctive therapies such as lasers, thermal angioplasty and atherectomy devices have not yet demonstrated improved efficacy when compared with conventional lower extremity interventions.[14, 15]

1.3.2. AMPUTATION

Amputation is considered when revascularization is not feasible due to the location and extent of atherosclerosis, when a patients is unable to tolerate a procedure, or when a patient is unlikely to have a functional extremity despite restoration of distal flow (e.g. due to dementia, chronic illness, etc.). While amputation does eliminate the source of pain at rest and all necrotic tissue,[11] it is associated with a significantly elevated perioperative and one year mortality rate.[1, 6, 16]

1.3.3. UNMET CLINICAL NEED

In the absence of revascularization options, most patients with CLI require amputation within 6 months. Patients requiring major amputation face a diminished quality of life, an unfavorable natural history and need extensive resources for their post-amputation rehabilitation and course. The 1-year amputation-free survival rate for patients diagnosed with CLI is 45%; the mortality rate is approximately 25% and may be as high as 45% in those who have undergone amputation.[1, 6, 16] Management of this end-stage disease process consumes a significant amount of healthcare resources.[17, 18] Clearly, new therapeutic approaches are required.

1.4. THERAPEUTIC ANGIOGENESIS IN ISCHEMIC LIMB DISEASE

Two key processes determine the amount of blood flow to skeletal muscle in patients with CLI: 1) the degree of arterial occlusion, and 2) the degree to which an endogenous angiogenic response is mounted to compensate for the occlusion. Ischemic tissue injury causes the release of numerous mediators, including growth factors, transcription factors, and signaling molecules known to stimulate angiogenesis and growth of collateral vessels. [19, 20] However, this physiologic response to pathophysiologic processes is often inadequate to prevent clinical manifestations of ischemia.

A growing area of research has focused on elucidating the molecular mechanisms underlying angiogenesis. The goal is to identify and harness the critical molecular players that initiate and / or regulate angiogenic growth. A number of cytokines such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) have been studied intensively and early phase I/II studies have been conducted. The data thus far have been mixed.[21-26]

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.[27, 28] It is a multi-functional mesenchyme-derived cytokine with potent angiogenic and anti-apoptotic effects [27-30] 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*.[31, 32] Recently, HGF gene transfer has been shown to produce significant augmentation of collateral formation in rabbit hind limb ischemia model.[28] Furthermore, a significant increase in blood flow was achieved by HGF gene transfer both in rat diabetic and non-diabetic hind limb ischemia models.[30, 33]

Because of its pluripotent capabilities, increasing the availability of HGF in ischemic tissues to achieve therapeutic angiogenesis has been a growing area of research. The challenge associated with delivering a targeted sustained dose of exogenous HGF to ischemic tissues 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.[34, 35]

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 in ischemic tissues.

1.5. 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 human clinical trials with $VEGF_{165}$ as the therapeutic gene, known as VMDA-3601.

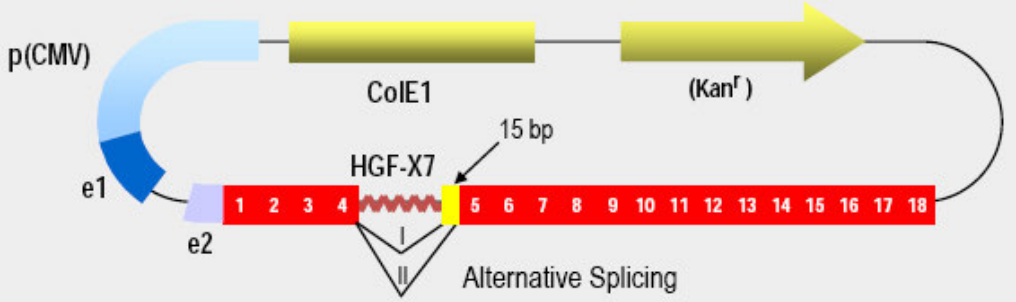

Figure 1. VM202 construct

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.[36-38] This local effect of conventionally injected naked plasmid DNA is well known.[39, 40]

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. VM202 may have the ability to increase perfusion and wound healing, as well as decrease pain due to neuropathy brought on by ischemia.

1.6. 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 intrammyocardial 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-$VEGF_{165}$; $p < 0.001$).

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 6-fold above the human clinical dose of 16 mg (0.23 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 continued clinical investigation of VM202 in patients with critical limb ischemia.

1.7. CLINICAL DATA

VM202was evaluated for treatment of critical limb ischemia in a prospective, dose-escalation Phase I study. The study consisted of four (4) cohorts of three (3) 'no-option' CLI patients. Patients received either 2 mg, 4 mg, 8 mg, or 16 mg VM202. For each dose cohort, VM202 was administered as local intramuscular injections with half of the dose administered at Day 0 of the study and the second half administered 2 weeks later. Preliminary efficacy (hemodynamic assessments), safety and tolerability were evaluated at Baseline (screening) and at designated time points throughout the study. Clinical evaluations were to be conducted at baseline, Days 15, 28, 59, 91, 180, and 365. All dose cohorts were followed for a year from the time of the first dose of study drug administration.

Enrollment is 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 ABI and TBI significantly increased from 0.35 to 0.52 (P=0.005) and 0.15 to 0.24 (P=0.01*)* at 12 months follow-up. TCPO2 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.

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.

VM202 appears to be well tolerated at doses as high as 16 mg. There were no unexpected adverse events in the study. None of the serious adverse events were directly attributable to VM202 (eight SAEs in five subjects, 5/12, 41.7%). There was one amputation caused by osteomyelitis which was assessed as unrelated to VM202.

Preliminary Conclusions. These early data support the feasibility of intramuscular injections of VM202 in subjects with critical limb ischemia. They 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.

1.8. STUDY AND DOSE RATIONALE

Based on the promising results seen in the phase I study, two doses (8 mg and 16 mg final VM202 dose) will be tested and compared to placebo injections in this phase II study. Patients will be treated with a final dose of 8 mg VM202, 16 mg VM202 or placebo by intramuscular injections in the affected calf on Day 0, Day 14, Day 28 and Day 42. VM202 will be delivered in a solution of 0.5 mg VM202 / mL.

As there are currently no approved drugs that can reverse CLI and as most patients have exhausted surgical and endovascular intervention options, inducing angiogenesis in the affected limb with VM202 may result in an increase in tissue perfusion, which, in turn improve wound healing, reduce pain and improve limb salvage rates.

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 CRF 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 II study is to evaluate the safety of IM administration of VM202 in subjects with moderate or high-risk CLI (Rutherford Clinical Severity Score equal to 4 or 5) who are poor or non- candidates for surgical or percutaneous revascularization; and, to evaluate potential bioactivity of IM administration of VM202 in subjects with CLI, when compared with placebo, on rest pain (as assessed by frequency of rest pain, pain medication use history, sleeping history, and intensity of rest pain) or leg ulcer healing (as assessed by ulcer surface area, time to complete healing), perfusion (MRA), hemodynamic assessment (ABI & TBI), tissue oxygenation ($TcPO_2$) and the incidence and extent of lower leg amputation or other surgical interventions.

3.2. STUDY DESIGN

This is a 12 month phase II, double-blind, randomized, placebo-controlled, multicenter study designed to assess the safety and efficacy of VM202 in subjects with critical limb ischemia. Patients with critical limb ischemia will be screened for study eligibility after giving informed consent. Screening will include assessment of study eligibility, a complete medical history, physical exam, cancer screening tests, viral screening, ABI & TBI, $TcPO_2$, 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. With the exception of ulcer measurement, VAS, ABI & TBI and $TcPO_2$ which will be repeated prior to first injection, procedures conducted during screening will represent the baseline reference values. Screening/Baseline assessments should occur within the 60 days prior to Day 0 (day of injection).

Patients who meet the eligibility criteria will be randomly assigned in a 2:2:1 fashion to one of the three treatment arms: Low Dose (8 mg VM202), High Dose (16 mg VM202), or placebo, respectively. Assignment to a treatment arm will be centralized, using an independent predetermined randomization scheme in a double-blinded fashion. Blinding will be achieved by having the study medication (test and control products) prepared by the study pharmacist. Reconstituted VM202 is indistinguishable from saline solution.

Prior to the first injection, vital signs, concomitant medications, serum chemistry and hematology, ulcer evaluation, VAS, ABI & TBI, TcPO2, VascuQol, serum HGF, and copies of VM202 will be determined. MRA will also be conducted as a sub-study at up to two sites.

Patients will receive VM202 or placebo (normal saline) by intramuscular injections in the calf chosen for treatment on Day 0, Day 14, Day 28 and Day 42. VM202 will be delivered in a solution of 0.5 mg VM202 / mL. Study drug will only be administered unilaterally.

Patients in the Low Dose Group (8 mg VM202) will receive:

- Day 0: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 14: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 28: Placebo only (16 injection of 0.5 ml normal saline)
- Day 42: Placebo only (16 injection of 0.5 ml normal saline)

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

- Day 0: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 14: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 28: 4 mg of VM202 (16 injections of 0.5 ml of VM202)
- Day 42: 4 mg of VM202 (16 injections of 0.5 ml of VM202)

Patients in the placebo control group will receive 16 injections of 0.5 ml normal saline at each visit.

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

Table 1. VM202 administration for each study arm

TREATMENT GROUP	FINAL DOSE VM202	DOSE VM202 (MG) PER VISIT			
		DAY 0	DAY 14	DAY 28	DAY 42
Low Dose	8 mg	4	4	0	0
High Dose	16 mg	4	4	4	4
Placebo	0	0	0	0	0

Determination of HGF serum levels will be made immediately pre-treatment on Day 0, immediately pre-treatment on Day 42, Day 49 and Day 90. The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours post injection), Day 42 (pre-injection, and 2 hours post injection), Day 49, Day 90, and at 6 months. VAS assessment will be performed at Day 0 (pre-injection), Day 14 (pre-injection), Day 28 (pre-injection), Day 42(pre-injection), Day 90, at 6 months, 9 months, and 12 months. VascuQol will be administered on Day 0 (pre-injection), Day 90, at 9 months, and 12 months. ABI & TBI will be recorded at Day 0 (pre-injection), Day 28 (pre-injection), Day 90, at 6 months, 9 months, and 12 months. $TcPO_2$ will be measured at Day 0 (pre-injection), 6 months, 9 months, and 12 months. Ulcer measurements will be performed at Day 0, Day 14, Day 28, Day 42, Day 49, Day 90, at 6 months, 9 months, and 12 months. MRA will be conducted as a sub-study at up to two sites on Day 0 (pre-injection) and at 6 and 9 months. Retinal fundoscopy will be conducted at 12 months. Adverse events will be recorded throughout the one year follow-up period.

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

3.3. PATIENT POPULATION

Fifty (50) patients meeting the following study entry criteria will be enrolled.

3.3.1. INCLUSION CRITERIA

1. Male or female, between 18 and 90 years of age;
2. Diagnosis of critical limb ischemia (Rutherford Class 4 or 5), including:
   - A resting ankle systolic pressure (in either the dorsalis pedis or posterior tibial arteries) of ≤ 70 mmHg in the affected limb; or
   - A resting toe systolic pressure of ≤ 50 mmHg in the affected limb; or
   - For patients in which measurement of ankle systolic pressure is not feasible (e.g. vessel calcification and non-compressibility), TcPO2 ≤ 30 mmHg;
3. Poor or suboptimal candidate for bypass graft surgery or percutaneous angioplasty;
4. Pain at rest, and/or ischemic ulcers, and/or focal gangrene (< 3 cm^2) for a minimum of 2 weeks;
5. Significant stenosis (≥ 75%) of one or more of the following arteries: superficial femoral, popliteal, or two or more infra-popliteal arteries as verified by angiography within 12 months prior to enrollment;
6. Be willing to maintain current drug therapy for peripheral arterial disease throughout the course of the study including an anti-platelet, hypertension and statin treatment unless not tolerated;
7. Clinically stable on optimized medical regimen for ≥30 days;
8. Be capable of understanding and complying with the protocol and signing the informed consent document prior to being subjected to any study related procedures;
9. Women who are surgically sterile or at least 1 year postmenopausal or who have been practicing adequate contraception for at least 12 weeks prior to entering the study. If the subject is of child-bearing potential, she must have a negative urine pregnancy test result prior to study enrollment and must agree to repeat pregnancy screening tests during the study. If the subject or the subject's partner(s) is of child bearing potential, the subject and the subject's partner(s) must agree to use a "double barrier" method of birth control while participating in this study.

3.3.2. EXCLUSION CRITERIA

1. Subjects who have undergone a successful revascularization procedure or sympathectomy within 12 weeks prior to study entry. A clinically *unsuccessful* revascularization procedure is defined as one in which:
   - the target vessel re-occludes (≥50%, as verified by a second angiogram. Duplex ultrasonography can be used to determine vessel patency if the patient cannot tolerate a second angiogram), or
   - the target vessel remains patent, but there is no resolution of symptoms 6 weeks after the procedure (e.g. no evidence of ulcer healing, no improvement in pressures, no reduction in resting pain);

2. Subjects that will require an amputation in the target leg within 4 weeks of randomization;
3. Subjects with evidence of active infection (e.g., cellulitis, osteomyelitis) or deep ulceration exposing bone or tendon in the extremity planned for treatment;
4. HF with a NYHA classification of III or IV;
5. Stroke (NIH scale > 2) or myocardial infarction within last 3 months;
6. Unstable angina
7. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
8. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
9. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
10. Subjects with advanced liver disease including decompensated cirrhosis, jaundice, ascites or bleeding varices;
11. Subjects currently receiving immunosuppressive medications chemotherapy, or radiation therapy;
12. Positive HIV or HTLV at Screening;
13. Active Hepatitis B or C infection as determined by Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (IgG and IgM; HBcAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV), at Screening;
14. Specific laboratory values at Screening including: Hemoglobin < 8.0 g/dL, WBC < 3,000 cells per microliter, platelet count <75,000/mm^3, AST and/or ALT > 3 times the upper limit of normal or any other clinically significant lab abnormality which in the opinion of the investigator should be exclusionary;
15. Patients with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence); patients with family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
16. Elevated PSA unless prostate cancer has been excluded;
17. Subjects with any co- morbid conditions likely to interfere with assessment of safety or efficacy or with an estimated life expectancy of less than 6 months
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 for the duration of the study;
19. Subjects requiring regular COX-2 inhibitor drug(s) or high dose steroids (excepting inhaled steroids);
20. Major psychiatric disorder in past 6 months;
21. History of drug or alcohol abuse / dependence in the past 2 years;
22. Use of an investigational drug or treatment in past 12 months; concurrent participation in investigational protocol or unapproved therapeutics; and
23. 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 person executing the consent 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 randomization, 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 (carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), CA19-9, and CA125 (females only)); 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
- Retinal Fundoscopy - fluorescein angiography may be conducted in cases where fundoscopy alone is deemed insufficient
- 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
- ECG
- Visual Analog Scale (VAS) score
- ABI & TBI
- $TcPO_2$

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

After providing written informed consent, potential study participants will undergo Screening assessments. The site will complete a Treatment Authorization Form (TAF) for patients determined to be eligible for study participation. The TAF includes the patient identification number, demographic information (gender, date of birth) and indication that the patient meets all inclusion and exclusion criteria. The completed TAF will be faxed to ViroMed or its designee. ViroMed or its designee will confirm whether the patient can be treated, update the TAF with specific treatment instructions, and return it to the investigational site by fax. Upon receipt, the Investigator will schedule the patient to undergo the study treatment. Note: adherence to this process is mandatory to track enrollment and to assure proper randomization.

3.4.5. RANDOMIZATION & BLINDING

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

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

4. Send another sealed envelope to the Sponsor with the site number, subject number and kit number on the outside and the assigned treatment inside, to be opened by the Sponsor or designee only in the case of a medical emergency.

Blinding will be achieved by having the study medication (VM202) prepared by the study pharmacist. Reconstituted VM202 is indistinguishable from saline solution.. The site pharmacist prepares the vials according to the instructions in the kit (which vials to reconstitute with water for injection [WFI]. The drug depot, site pharmacist and select individuals at Synteract (but not including study monitors) will be unblinded to the treatment assignments. The subject and study personnel, including core lab, investigator and study coordinators, will remain blinded until all data has been entered into the database and the database is locked.

IN CASE OF EMERGENCY ONLY, i.e. SERIOUS ADVERSE EVENT (SAE) AND ONLY WHEN THIS INFORMATION INFLUENCES THE PATIENT'S MANAGEMENT, the Investigator may open the sealed envelope to immediately start the appropriate treatment (to be recorded in the case report form [CRF]).

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

3.4.6. DAY 0 – 1ST INJECTIONS

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

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Visual Analog Scale (VAS) score
- VascuQol
- ABI & TBI
- $TcPO_2$
- Photograph and measurement of ulcer(s) – if present
- MRA – sub-study to be only at designated site(s) –to be completed within 7 days prior to Day 0

3.4.6.2. 1ST DOSE OF VM202 / PLACEBO

- Intramuscular injections of VM202 in calf (unilateral)

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 14 ± 3 DAY –2ND INJECTIONS

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

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Visual Analog Scale (VAS) score
- Photograph and measurement of ulcer(s) – if present
- Injection site assessment
- Adverse event assessment

3.4.7.2. 2ND DOSE OF VM202 / PLACEBO

- Intramuscular injections of VM202 in calf (unilateral, same leg as 1st injection)

3.4.7.3. POST-INJECTION

- Vital Signs
- Injection site assessment
- Adverse event assessment

3.4.8. DAY 28 ± 3 DAY –3RD INJECTIONS

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

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Visual Analog Scale (VAS) score
- ABI & TBI
- Photograph and measurement of ulcer(s) – if present
- Injection site assessment
- Adverse event assessment

3.4.8.2. 3RD DOSE OF VM202 / PLACEBO

- Intramuscular injections of VM202 in calf (unilateral, same leg as 1st injection)

3.4.8.3. POST-INJECTION

- Vital Signs
- Injection site assessment
- Adverse event assessment

3.4.9. DAY 42 ± 3 DAY – 4TH INJECTIONS

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

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

3.4.9.2. 4TH DOSE OF VM202 / PLACEBO

- Intramuscular injections of VM202 in calf (unilateral, same leg as 1st injection)

3.4.9.3. POST-INJECTION

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

3.4.10. DAY 49 ± 3 DAYS

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Copies of VM202 in whole blood
- Serum HGF
- Photograph and measurement of ulcer(s) – if present
- Injection site assessment
- Adverse event assessment

3.4.11. DAY 90 ± 7 DAYS

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Serum HGF
- Copies of VM202 in whole blood
- Visual Analog Scale (VAS) score
- VascuQol
- ABI & TBI

- Photograph and measurement of ulcer – if present
- Adverse event assessment

3.4.12. 6 MONTHS ± 1 MONTH

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Photograph and measurement of ulcer – if present
- Visual Analog Scale (VAS) score
- Copies of VM202 in whole blood
- ABI & TBI
- $TcPO_2$
- MRA – sub-study to be only at designated site(s) - to be completed within 7 days of the Month 6 Visit
- Rutherford Classification
- Adverse event assessment

3.4.13. 9 MONTHS ± 1 MONTH

- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Visual Analog Scale (VAS) score
- VascuQol
- ABI & TBI
- Photograph and measurement of ulcer(s) – if present
- $TcPO_2$
- MRA – sub-study to be only at designated site(s)) - to be completed within days of the Month 9 Visit
- Rutherford Classification
- Adverse event assessment

3.4.14. 12 MONTHS ± 1 MONTH

- Retinal fundoscopy
- Concomitant Medications
- Vital Signs
- Serum Chemistry and hematology
- Visual Analog Scale (VAS) score
- VascuQol
- ABI & TBI
- Photograph and measurement of ulcer(s) – if present
- $TcPO_2$
- Rutherford Classification
- 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 treatment arm if discontinuation occurs prior to the 90 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 90
- Copies of VM202 in whole blood if discontinued prior to Day 90
- Injection site reaction assessment if discontinued prior to Day 49
- 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, ColE1 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°C and 8°C in an appropriately locked room accessible only to the pharmacist or a duly designated person. Since VM202 does not contain preservatives, opened vials of VM202 and VM202 reconstituted with water for injection (WFI) must be used within 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. PLACEBO

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

3.6.3. PRODUCT ACCOUNTABILITY

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

Investigational drugs are to be used only in accordance with this protocol and under supervision of the 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.

3.6.4. 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. Patients assigned to either the placebo arm or the Low Dose arm will receive normal saline injections. The placebo group will receive only normal saline injections; the Low Dose arm will receive VM202 for the first two injection visits (Day 0 and Day 14), and then normal saline for the next two injection visits (Day 28 and Day 42). Visually, normal saline is indistinguishable from reconstituted VM202. 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 peripheral arterial disease history to include all events and interventions for critical limb ischemia and to excluded other (e.g. structural abnormalities such as fibromuscular dysplasia or connective tissue disorders, inflammatory conditions, thromboembolic disease, impingement/entrapment, venous claudication, etc.).

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
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 6).

4.1.4. VIRAL SCREENING

Each site will be responsible for Screening Viral Testing. Assays will include: HIV_1, HIV_2, HTLV, HBV and HCV as determined by screening for the HBsAg, HBsAB, HBcAb (IgM plus IgG), and Anti-HCV..

4.1.5. URINALYSIS

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

4.1.6. 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.

4.1.7. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

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

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

Abstention, the rhythm method or contraception by a partner are not 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.

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.

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 42, on Day 49, and Day 90. 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 $\leq$ -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 2 hours post injection), Day 42 (pre-injection, and 2 hours post injection), Day 49, Day 90, and 6 months. 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. 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, pretreatment on Days 14, 28 and 42, Day 90, 6 months, 9 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 as detailed in the study manual.

4.2.8. PATIENT QUESTIONNAIRE (VASCUQOL)

The VascuQol patient questionnaire was specifically developed for use in patients with lower limb ischemia.[42] This questionnaire has 25 questions that review five domains: activity level, symptoms, pain, emotional status and social items. VascuQol was found to be better at detecting improvement in symptoms, disease severity than SF-36 in CLI patients and correlated well with the Rutherford classification.[43] This test will be administered pre-injection on Day 0, at Day 90, 9 months, and 12 months. The VascuQol can be found in Appendix 5.

4.2.9. ANKLE BRACHIAL INDEX (ABI) AND TOE BRACHIAL INDEX (TBI)

Ankle-Brachial Index (ABI) and Toe Brachial Index (TBI) will be determined at screening, before the first treatment (injection) on Day 0, before the third injection on Day 28, on Day 90, 6 months, 9 months and 12 months. ABI and TBI will be determined as described in the Study Manual.

4.2.10. TRANSCUTANEOUS OXYGEN PRESSURE (TCPO2)

Transcutaneous oxygen pressure ($TcPO_2$) will be measured at screening, before the first treatment (injection) on Day 0, at 6, 9 and at 12 months. $TcPO_2$ measurement sites will include the anterior and posterior calf and dorsum of the foot. Because $TcPO_2$ measurements are instrument dependent, investigators should use the same instrument for all $TcPO_2$ assessments and follow the standard procedures defined by their instrument's manufacturer. If a sensor placement site is unavailable due to amputation or areas of ulceration/gangrene, sensor placement site will be assigned a clinically equivalent default $TcPO_2$ value of zero pressure ("0 mmHg"). Hard copy instrumentation printout will be included in the source documentation to support the $TcPO_2$ data. The limb/chest $TcPO_2$ index will be calculated by using the lesser of the lower limb measurements.

4.2.11. 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 pretreatment on Days 14, 28 and 42, on Day 49, Day 90, 6 months, 9 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 measured and recorded as detailed in the Study Manual.

4.2.12. INJECTION SITE REACTION ASSESSMENT

Local injection sites reactions will be assessed on Day 0 post injection, pre and post injection on Days 14, 28 and 42, and on Day 49 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 2.

Table 2. 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.	Life-threatening consequences; major invasive intervention indicated (e.g., complete	Death

ADVERSE EVENT	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
			hyperbaric oxygen)	resection , tissue reconstruction, flap, or grafting	
Alergic reaction / hypersensitivity	Transient flushing or rash; drug fever < 38°C (<100.4°F)	Rash; flushing ; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medications(s) indicated; allergy-related edema/ angioedema; hypotension	Anaphylaxis	Death

4.2.13. MRA

MRA will be conducted as a sub-study at up to two sites on Day 0 (pre-injection) and at 6 and 9 months (see Appendix 3).

5. EVALUATION OF ADVERSE EVENTS

5.1. DEFINITIONS

An Adverse Event (AE) is the development of an untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to an investigational product, whether or not considered causally related to the product.

An untoward medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or clinically significant abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).
An **adverse reaction** means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

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

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization 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 / or Synteract, 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). Per the 2010 FDA Guidance Document for Industry and Investigators "Safety Reporting Requirements for INDs and BA/BE Studies," events categorized as 'possibly' or 'probably' related will be treated as 'suspected adverse reactions.' Events categorized as 'definitely' related will be treated as an 'adverse reaction.'

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

Any incidents of neoplasia or retinopathy will be reported to FDA in an expedited report (within 7 days of occurrence).

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 objective of this Phase II study is to evaluate the safety of IM administration of VM202 in subjects with moderate or high-risk CLI (Rutherford Clinical Severity Score equal to 4 or 5) who are poor or non- candidates for surgical or percutaneous revascularization; and, to evaluate potential bioactivity of IM administration of VM202 in subjects with CLI, when compared with placebo, on rest pain (as assessed by frequency of rest pain, pain medication use history, sleeping history, and intensity of rest pain) or leg ulcer healing (as assessed by ulcer surface area, time to complete healing), perfusion (MRA), hemodynamic assessment (ABI & TBI), tissue oxygenation (TcPO2) and the incidence and extent of lower leg amputation or other surgical interventions.

6.1. GENERAL METHODS

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

6.2. STUDY ENDPOINTS

6.2.1. PRIMARY ENDPOINT

The primary study endpoint is to assess the difference in pain level between baseline and the 9 month follow-up as determined by VAS. Active and placebo arms will be compared to determine treatment effect. The primary analysis will be conducted in the efficacy analysis dataset. A secondary analysis will be conducted in the ITT analysis dataset, and further analyses conducted as necessary to explore any inconsistency between the two results.

6.2.2. SECONDARY EFFICACY ENDPOINTS

Other secondary endpoints will include:

- Difference in pain level between baseline and the 9 month follow-up as determined by VAS by sex and by comorbidities (esp. diabetes or renal dysfunction)
- Change in tissue oxygenation ($TcPO_2$) from baseline to 6, 9 and 12 months following the first treatment
- Change in hemodynamic measures (ABI and TBI) from baseline to Day 28, Day 90, 6 months, 9 months and 12 months following the first treatment
- Change in perfusion (MRA) from baseline to 9 months following the first treatment
- Wound healing (no ulcer: change of skin condition, one ulcer: change of ulcer size, multiple ulcer: change of ulcer number) from baseline to 9 months following the first treatment
- Change in VAS score from baseline to Day 14, Day 28, Day 42, Day 90, at 6 months, 9 months, and 12 months.
- Change in QOL score (VascuQol) at 90 Days, 9 months and 12 months;
- Major limb amputation rate at six months and twelve months following the first treatment
- Mortality at six and twelve months after first treatment

6.2.3. 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.

6.2.4. DATA SAFETY MONITORING AND INTERIM ANALYSES

For ethical reasons, and to ensure study integrity, an interim examination of key safety data will be performed when approximately half of the patients (n=25) have 6 months data. The primary objective of this analysis will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either active treatment arm. An independent data safety monitoring board (DSMB) will perform the review. The DSMB Chair will review a limited set of unblinded tables and listings, including all reported SAEs, monthly through to the full DSMB interim analysis (at 25-patients) and then every three months thereafter. The DSMB chair may request additional data for review and/or additional meetings of the committee as he / she sees fit.

6.3. 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.

7. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

ViroMed has designated Synteract 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 to Synteract.

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 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 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.

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 and Synteract
- 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.

18. REFERENCES

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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 ± 3 D		3rd Injection Day 28 ± 3 D		4th Injection Day 42 ± 3 D		Day 49 ± 3 D	Day 90 ± 7 D	6 mo ± 1 mo	9 mo ± 1 mo	12 mo ± 1 mo	Early Withdrawal
		Pre-dose	Post-dose	Pre-dose	Post-dose	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	✓														
ECG	✓														
Pregnancy test	✓														
Safety and Efficacy Parameters															
Retinal Fundoscopy	✓													✓	✓
Vital Signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Serum Chemistry and hematology	✓	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Copies of VM202 in whole blood		✓	✓**					✓	✓**	✓	✓	✓			✓[1]
Serum HGF		✓						✓		✓	✓				✓[1]
Visual Analog Scale (VAS) score	✓	✓		✓		✓		✓			✓	✓	✓	✓	
VascuQol		✓									✓		✓	✓	
ABI & TBI	✓	✓				✓					✓	✓	✓	✓	
$TcPO_2$	✓	✓										✓	✓	✓	
Photograph and measurement of ulcer(s)††	✓	✓		✓		✓		✓		✓	✓	✓	✓	✓	✓
Rutherford Classification	✓											✓	✓	✓	
MRA (at designated site(s) only) †††		✓										✓	✓		
Treatment															
Injection site reaction assessment			✓	✓	✓	✓	✓	✓	✓	✓					✓[2]
Adverse Events			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

† Includes: cancer markers (carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), CA19-9, and CA125 (females only)); 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

†† If present prior to first study drug administration

††† 7 days prior to Day 0; ±7 days to Month 6 and Month 9

** 2 hours after injection (± 1 hour)

1 If withdrawal occurred before Day 90 Visit

2 If withdrawal occurred before Day 49 Visit

Appendix 2. Sample Informed Consent

TITLE: A Phase II, Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 in Subjects with Critical Limb Ischemia
Protocol #: VMCLI-II-09-002

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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 critical limb ischemia and are not a good candidate for a revascularization procedure.

Because the blood vessels in your body have narrowed or become blocked, not enough blood flows to your legs, causing pain, swelling, and possibly an infection that is slow to heal. The growth of new blood vessels to supply blood to your limbs would help increase blood flow that may reduce pain, swelling, and infection. Stimulating the growth of new blood vessels may also stimulate growth or regeneration of nerves and may reduce pain. Researchers have discovered that a protein called hepatocyte growth factor (HGF) that your body naturally produces in small amounts can cause the growth of new blood vessels and protect nerves. Unfortunately, your body only makes a small amount of this protein and not always in the areas where you need it. Researchers have found a way to increase the amount of HGF in your legs. They have isolated the genes responsible for directing the production of HGF, and have designed a product that can be injected into your leg.

In the research study the HGF gene will be injected into your calf muscle cells to evaluate if it changes your pain related to critical limb ischemia. 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 increase the blood flow to your foot ant reduce pain. This study will examine whether VM202 injected into your leg is safe and tolerable at either low or high dose, and also will collect preliminary information about whether the plasmid increases HGF and relieves your critical limb ischemia. This study is intended to help determine:

- The safety and tolerability of a low and high dose of VM202; and,
- if VM202 can improve your critical limb ischemia and reduce your pain.

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 50 patients will take part in this study at up to 20 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 a double-blind, placebo-controlled, randomized clinical study. If you agree and are medically eligible to participate you will be "randomly" assigned (like drawing numbers out of a hat or flipping a coin) to one of three groups as listed below. "Double-blind" means that you and your doctor will not know the treatment you are getting in the study. However, your doctor can find out if needed. "Placebo controlled" means not all participants will be assigned to a treatment group that will receive the study drug. Some participants may only receive saline injections. What group you are assigned to is done by a computer and is not known by your doctor until the study is completed.

You will be randomly assigned to one of three possible study groups:

- **Low Dose** VM202 Treatment Group – if you are selected for this group, you will receive 8 mg of VM202 over the course of the first two injection visits (4 mg of VM202 at the Day 0 visit and 4 mg of VM202 at the Day 14 visit). Each individual injection contains 0.5 mL of fluid with 0.25mg VM202. You will receive 16 injections for a total of 8 milliliters (8 mL) of VM202 (which is about a teaspoon and a half of fluid) at the first two injection visits. On the next two injection visits (Day 28 and Day 42) you will receive saline injections (sixteen 0.5 mL injections for a total of 8 mL at each injection visit). Approximately forty percent of patients will be selected for this group.

- **High Dose** VM202 Treatment Group – if you are selected for this group, you will receive 16 mg of VM202 over the course of the four injection visits (4 mg of VM202 at the Day 0 visit, 4 mg of VM202 at the Day14 visit, 4 mg of VM202 at the Day 28 visit, and 4 mg of VM202 at the Day 42 visit). Each individual injection contains 0.5 mL of fluid with 0.25mg VM202. You will receive a total of 8 milliliters (8 mL) of VM202 (which is about a teaspoon and a half of fluid) at each of the four injection visits. Approximately forty percent of patients will be selected for this group.

- **Placebo** Control Group – if you are selected for this group, you will not receive VM202. You will only receive injections of saline. At each of the four injection visits, you will receive sixteen injections of 0.5 mL of saline for a total of 8 milliliters (8 mL) of saline

(which is about a teaspoon and a half of fluid). Approximately twenty percent of patients will be selected for this group.

All patients (regardless of which group they assigned to) will receive sixteen 0.5 mL injections at each of the four injection visits.

What tests, procedures, and diagnostic studies will be done during this study?

There are 10 visits which span 12 months total time from visit #2 to visit #10. 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 critical limb ischemia – 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 ECG – An electrocardiogram (ECG) 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 ECG 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**).

Measuring blood pressure in your leg (ABI & TBI) – The ankle-brachial index (ABI) and the toe-brachial (TBI) index is the ratio of the blood pressure in the lower legs to the blood pressure in the arms. Compared to the arm, lower blood pressure in the leg is a symptom of blocked arteries. Blood pressure measurements are taken at the arms and ankles or toes. You may experience some minor discomfort associated with compressing the artery with the cuff. It will last only a few seconds.

Transcutaneous oxygen pressure ($TcPO_2$) – Transcutaneous oxygen pressure ($TcPO_2$) is a measurement of how much oxygen reaches your skin. It requires that a small device be placed on the skin for 15 – 20 minutes. There is no pain or risk associated with this procedure.

Additional imaging study – One to two hospitals in this study will be conducting an additional imaging test called magnetic resonance angiogram (MRA). This study is being done to determine how well blood is flowing through your legs. An MRA is a type of magnetic resonance imaging (MRI) scan that uses a magnetic field and pulses of radio wave energy to provide pictures of blood vessels inside the body. With MRA, both the blood flow and the condition of the blood vessel walls can be seen. You will lie on your back on a table that is part of an MRI scanner. Your leg may be held with straps to help you remain still. The table will slide into a space that contains the magnet. Some MRI machines (open MRI) are now made so that the magnet does not surround the person being tested. Open MRI is less confining than a standard MRI but may not provide the same quality of image. Inside the scanner, you may hear a fan and feel air moving. You may also hear tapping or thumping noises as the MRA scans are taken. You may want to ask for ear plugs to reduce the noise. If contrast material is needed, the technologist will put it in an IV in your arm. The material may be given over 1 to 2 minutes. Then more MRI scans are done. An MRA test usually takes 30 to 90 minutes but can take as long as 2 hours.

Visit # 1: Screening/Baseline Evaluations

Screening is a process of evaluating your initial health status and assessing the status of your critical limb ischemia. Screening is usually completed within one month 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, medication review, questionnaire, assessment of critical limb ischemia, cancer screening, retinal fundoscopy; urine and blood tests including a viral screen; ABI & TBI, $TcPO_2$, photograph and measurement of ulcer, pregnancy test (if you are a female), and 12 lead ECG.

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

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

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

Before Injection Procedure:

The following tests will be performed before you have your injection procedure done: medication review, questionnaires, ABI & TBI, $TcPO_2$, vital signs, photograph and measurement of ulcer, MRA (only if your hospital is participating in the small sub-study), 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 or placebo at 16 sites evenly distributed over your calf muscle.

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, VM202 blood test, 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 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, photograph and measurement of ulcer, injection site reaction assessment, and assessment of side effects, and blood tests.

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 or placebo at 16 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.

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, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 4 – Third Injection Procedure – Day 28 (14 Days After the Second Injection Procedure)

Before Injection Procedure:

The following tests will be performed before you have your injection procedure done: medication review, questionnaire, vital signs, photograph and measurement of ulcer, ABI & TBI, injection site reaction assessment, and assessment of side effects, and blood tests.

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 or placebo at 16 sites evenly distributed over your calf muscle. If the marks made to identify the second injection sites are still visible, they will guide the doctor to inject at locations that were not injected previously.

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, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 5 – Fourth/Last Injection Procedure – Day 42 (14 Days After the Third Injection Procedure)

Before Injection Procedure:

The following tests will be performed before you have your injection procedure done: medication review, questionnaire, vital signs, photograph and measurement of ulcer, injection site reaction assessment, and assessment of side effects 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 or placebo at 16 sites evenly distributed over your calf muscle. If the marks made to identify the second injection sites are still visible, they will guide the doctor to inject at locations that were not injected previously.

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, VM202 blood test, injection site reaction assessment, and assessment of side effects.

Before you go home you will receive detailed discharge instructions.

Visit # 6 –Day 49 (7 days after the fourth/last injection procedure)
At this visit, the following tests or evaluations will be done: medication review, vital signs, photograph and measurement of ulcer, blood tests including HGF and VM202, injection site reaction assessment, and assessment of side effects.

Visit # 7 – Day 90
At this visit, the following tests or evaluations will be done: medication review, vital signs, questionnaires, ABI & TBI, photograph and measurement of ulcer, blood tests including HGF and VM202, and assessment of side effects.

Visit # 8 – 6 months
At this visit, the following tests or evaluations will be done: medication review, vital signs, questionnaire, ABI & TBI, $TcPO_2$, MRA (if applicable to your hospital), photograph and measurement of ulcer, blood tests including VM202, and assessment of side effects.

Visit # 9 – 9 months
At this visit, the following tests or evaluations will be done: medication review, vital signs, questionnaires, ABI & TBI, $TcPO_2$, MRA (if applicable to your hospital), photograph and measurement of ulcer, MRA (only if your hospital is participating in the small sub-study), blood tests, and assessment of side effects.

Visit # 10 – 12 months – Final Visit
At this visit, the following tests or evaluations will be done: medication review, vital signs, questionnaires, ABI & TBI, $TcPO_2$, photograph and measurement of ulcer, blood tests, 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; current fecal occult blood test; 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 ECG

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 critical limb ischemia will improve. Knowledge from this study may help us better understand how to treat people with critical limb ischemia.

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, Synteract 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?

You do not have to take part in this study to receive treatment for critical limb ischemia. If you decide not to take part in this study, there are other treatments for critical limb ischemia, which include surgery, angioplasty, amputation, skin grafting, and medications such as aspirin, clopidogrel (Plavix), and cholesterol-lowering agents such as atorvastatin (Lipitor). Your doctor will discuss these other treatments with you.

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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. MRA (select sites only)

MRI Measurements

Magnetic Resonance Imaging (MRI): MRI will be used to quantify the changes in the blood flow and muscle mass of the treated leg. Both large vessel (>500 Mm) and capillary level blood flow (perfusion) will be evaluated.

Safety screening: All participants who undergo MRI scans that include contrast agent injections will be required to have normal kidney function. A measurement of glomerular filtration rate (GFR) taken no earlier than 24 hrs prior to the contrast injection will be used to determine kidney function. No subject with GFR < 60 mL/min/1.73 m^2 will be administered contrast agent. The staff nurse of the Northwestern University MRI research facility (CAMRI) where these scan are performed will perform point-of-care (iSTAT) to determine GFR on the same day as the MRI scan. MRI scans that do not required the administration of MRI contrast agent may be evaluated using the non-contrast MRI scans (i.e. to evaluate muscle mass). Prior to the visit, participants will be interviewed to ensure they do not have contraindications to MRI testing (presence of metal or electrical devices in their body, such as a cardiac pacemaker, defibrillation wires, or metal foreign objects).

MRI Scan Protocol: Participants will be positioned on the MRI table. An intravenous catheter will be inserted into the arm for infusion of the gadolinium-based MRI contrast agent. A signal-reception coil will be placed to cover the low leg of the participant. Cross-sectional images will be acquired along the length of the participant's legs. These images will be acquired to cover from the knee to the mid-leg, covering the entire calf muscle.

Calf Muscle Area

2D T1 weighted single slice acquired at the mid-calf. The localization will be kept consistent by measuring a 2D slice located at a fixed distant from the top of the tibia. A 2.5 mm thick transverse image will be acquired at the point of maximal muscle cross-sectional area. The distal end of the tibia will be used to scan a point located 66% of the distance from the distal to the proximal tibial. This point represents maximum muscle area on > 95% of individuals.

Perfusion

Calf muscle will be calculated using a standard imaging technique. A multi-phase interleaved, multi-echo MRI pulse sequence (SR-FLASH) and (IR-FLASH) will be acquired in conjunction with an injection of MRI contrast agent (0.1 mmol/kg b.w.). Two slices will be prescribed for this scan. They will be separated by 5 cm with the lower of the two sliced co-localized at the level of the muscle mass image. Immediately prior to the images acquisitions participants will be asked to perform 50 heel-rises in the MRI scanning area. They will do this by balancing against the wall with their fingertips and raising up and down on their toes once per second until they have complete 50 heel-rises, or are too tired to continue (whichever comes first).

Angiography (Collateralization)

Time-resolved MRA images will be acquired, following the perfusion scans in conjunction with a second, single dose injection of contrast agent (Gd-DTPA or equivalent). These will be acquired as a second, single dose (0.1 mmol/kg b.w.) contrast injection. A time-series of T1 weighted, 3D Fast Low Angle Shot gradient-recalled will be acquired of the peripheral

vasculature from the knee to the ankle. This region will cover the region of interest for analysis of collateral formation. The size and number collaterals will be counted and scored.

Appendix 4. Test Article Administration

1. ***Test article preparation***

VM202 - 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. For the Low Dose treatment arm, the final doses of 8 mg of VM202 will be divided evenly between the Day 0 administration and the Day 14 administration, with the Day 28 and Day 42 injections consisting of normal saline (see description of normal saline below). The High Dose treatment arm will receive final doses of 16 mg of VM202 divided evenly between the Day 0, Day 14, Day 28 and Day 42 administrations. Individual injections will be 0.5 mL. All injections will be 0.5 mL administered by intramuscular injections.

Placebo - Patients assigned to either the placebo arm or the Low Dose arm will receive normal saline injections. The placebo group will receive only normal saline injections; the Low Dose arm will receive VM202 for the first two injection procedures (Day 0 and Day 14), and then normal saline for the next two injection visits (Day 28 and Day 42). Visually, normal saline is indistinguishable from reconstituted VM202.

Table 3. Single dose preparation and delivery, Day 0 and Day 14

TREATMENT ARM	NUMBER OF VIALS RECONSTITUTED	TOTAL VOLUME TO BE INJECTED	NUMBER OF INJECTIONS	VOLUME / SINGLE INJECTION
Low Dose 8 mg VM202	2 Vials VM202, reconstituted with WFI	8 mL	16	0.5 mL
High Dose 16 mg VM202	2 Vials VM202, reconstituted with WFI	8 mL	16	0.5 mL
Placebo – Normal Saline	NA	8 mL	16	0.5 mL

Table 4. Single dose preparation and delivery, Day 28 and Day 42

TREATMENT ARM	NUMBER OF VIALS RECONSTITUTED	TOTAL VOLUME TO BE INJECTED	NUMBER OF INJECTIONS	VOLUME / SINGLE INJECTION
Low Dose 8 mg VM202	NA – Normal Saline	8 mL	16	0.5 mL
High Dose 16 mg VM202	2 Vials VM202, reconstituted with WFI	8 mL	16	0.5 mL
Placebo – Normal Saline	NA	8 mL	16	0.5 mL

2. ***Test material administration*** – Patients will receive injections of VM202 or placebo on Day 0, Day 14, Day 28, and Day 42. A fine needle (e.g. 27 gauge, 1") suitable for IM injections will be used. Only one leg will be treated in this study. Distribute injection sites evenly over the calf muscle, carefully avoiding fascia.

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

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

Appendix 5. VascuQol

APPENDIX: VASCUQOL QUESTIONS (US ENGLISH VERSION)

The following questions are about how you have been affected by the poor circulation in your legs in the past two weeks. You will be asked about the symptoms you have had, the way that your activities have been affected, and how you have been feeling.

For each question please read all of the answers and then check the one that applies best to you.

For example:

19. In the last two weeks, problems caused by poor circulation in my legs have made me feel frustrated....
    All of the time
    Most of the time
    A good bit of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time

So if you had felt frustrated "hardly any of the time" your answer would be:
    All of the time
    Most of the time
    A good bit of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time

If you are not sure about how to answer a question then please give the best answer you can. There are no right or wrong answers.

Please answer every question.

Thank you

1. During the past two weeks, I have had pain in my leg (or foot) when walking....
   All of the time
   Most of the time
   Much of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time
2. During the past two weeks, I have been worried that I might injure my leg....
   All of the time
   Most of the time
   Much of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time
3. During the past two weeks, cold feet have given me....
   A very great deal of discomfort or distress
   A great deal of discomfort or distress
   A good deal of discomfort or distress
   A moderate amount of discomfort or distress
   Some discomfort or distress
   Very little discomfort or distress
   No discomfort or distress
4. During the past two weeks, because of the poor circulation to my legs, my ability to exercise or to play sports has been....
   Totally limited, couldn't exercise at all
   Extremely limited
   Very limited
   Moderately limited
   A little limited
   Only very slightly limited
   Not at all limited
5. During the past two weeks, my legs felt tired or weak....
   All of the time
   Most of the time
   Much of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time
6. During the past two weeks, because of the poor circulation in my legs I have been restricted in spending time with my friends or relatives....
   All of the time
   Most of the time
   Much of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time
7. During the past two weeks, I have had pain in the foot (or leg) after going to bed at night
   All of the time
   Most of the time
   Much of the time
   Some of the time
   A little of the time
   Hardly any of the time
   None of the time
8. During the past two weeks, pins and needles or numbness in my leg (or foot) have caused me....
   A very great deal of discomfort or distress
   A great deal of discomfort or distress
   A good deal of discomfort or distress
   A moderate amount of discomfort or distress
   Some discomfort or distress
   Very little discomfort or distress
   No discomfort or distress
9. During the past two weeks, the distance I can walk has improved....
   Not at all—check this if the distance is unchanged or has decreased
   ❑ A little
   ❑ Somewhat
   ❑ Moderately
   ❑ A good deal
   ❑ A great deal

❑ A very great deal

10. During the past two weeks, because of the poor circulation in my legs, **my ability to walk has been....**
    Totally limited, couldn't walk at all
    Extremely limited
    Very limited
    Moderately limited
    A little limited
    Only very slightly limited
    Not at all limited
11. During the past two weeks, **being (or becoming) housebound has concerned me....**
    A very great deal
    A great deal
    A good deal
    Moderately
    Somewhat
    A little
    Not at all
12. During the past two weeks, **I have been concerned about having poor circulation in my legs....**
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time
13. During the past two weeks, **I have had pain in the foot (or leg) when I am resting**
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time
14. During the past two weeks, because of the poor circulation in my legs, **my ability to climb stairs has been....**
    Totally limited, couldn't climb stairs at all
    Extremely limited
    Very limited
    Moderately limited
    A little limited
    Only very slightly limited
    Not at all limited
15. During the past two weeks, because of the poor circulation in my legs, **my ability to participate in social activities has been....**
    Totally limited, couldn't socialize at all
    Extremely limited
    Very limited
    Moderately limited
    A little limited
    Only very slightly limited
    Not at all limited
16. During the past two weeks, because of the poor circulation in my legs **my ability to do routine household work has been....**
    Totally limited, couldn't perform housework at all
    Extremely limited
    Very limited
    Moderately limited
    A little limited
    Only very slightly limited
    Not at all limited
17. During the past two weeks, **ulcers or sores on my leg (or foot) have caused me pain or distress....**
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time—(pick this one if you do not have leg ulcers)
18. Because of the poor circulation in my legs, **the range of activities that I would have liked to do in the past two weeks has been....**
    Severely limited—most activities not done
    Very limited
    Moderately limited—several activities not done
    Slightly limited
    Very slightly limited—very few activities not done
    Hardly limited at all
    Not limited at all—have done all the activities that I wanted to
19. During the past two weeks, **problems caused by poor circulation in my legs has made me feel frustrated....**
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time
20. During the past two weeks, **when I have had pain in the leg (or foot) it has given me....**
    A very great deal of discomfort or distress
    A great deal of discomfort or distress
    A good deal of discomfort or distress
    A moderate amount of discomfort or distress
    Some discomfort or distress
    Very little discomfort or distress
    No discomfort or distress
21. During the past two weeks, **I have felt guilty about relying on friends or relatives**
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time

22. During the past two weeks, because of the poor circulation to my legs, my ability to go shopping or carry bags has been....
    Totally limited, couldn't go shopping at all
    Extremely limited
    Very limited
    Moderately limited
    A little limited
    Only very slightly limited
    Not at all limited
23. During the past two weeks, I have worried I might be in danger of losing a part of my leg or foot....
    All of the time
    Most of the time
    Much of the time
    Some of the time
    A little of the time
    Hardly any of the time
    None of the time
24. During the past two weeks, the distance I can walk became less
    - ❑ A very great deal
    - ❑ A great deal
    - ❑ A good deal
    - ❑ Moderately
    - ❑ Somewhat
    - ❑ A little
    - ❑ Not at all—check this if the distance is unchanged or has increased
25. During the past two weeks, I have been depressed about the poor circulation in my legs....
    - ❑ All of the time
    - ❑ Most of the time
    - ❑ Much of the time
    - ❑ Some of the time
    - ❑ A little of the time
    - ❑ Hardly any of the time
    - ❑ None of the time

Domains: Activity items—4,9,10,14,16,18,22,24
Symptom items—3,5,8,17
Pain items—1,7,13,20
Emotional items—2,11,12,19,21,23,25
Social items—6,15

Each domain is scored 1-7: = the total of domain item scores divided by the number of questions in the domain.

The total King's College Hospital's VascuQol score is also scored 1-7 = the total of all the item scores divided by 25.

Copies of the translated versions in UK English, Canadian French and English, French, Dutch, Italian, German and Swedish are available from the author.

Appendix 6. 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.

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