# Protocol VMNHU-003

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| **Protocol Title:** | **A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 to Treat Chronic Nonhealing Foot Ulcers in Diabetic Patients with Concomitant Peripheral Arterial Disease (PAD)** |
| **Protocol Number:** | VMNHU-003; Version I |
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# A PHASE III, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE SAFETY AND EFFICACY OF VM202 TO TREAT CHRONIC NONHEALING FOOT ULCERS IN DIABETIC PATIENTS WITH CONCOMITANT PERIPHERAL ARTERIAL DISEASE (PAD)

**Protocol VMNHU-003 / I**

**February 04, 2020**

**Sponsor**
Helixmith Co., Ltd.
[redacted]

[redacted]

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## SIGNATURE PAGE

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

[redacted] [redacted] 04-02-2020

*Date (DD-MM-YYYY)*

[redacted] [redacted] 04-Feb-2020

*Date (DD-MM-YYYY)*

## INVESTIGATOR'S AGREEMENT

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

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

Principal Investigator's Name (print)

Title

Address

Signature / Date

## STUDY SYNOPSIS

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|---|---|
| **PROTOCOL TITLE** | A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 to Treat Chronic Nonhealing Foot Ulcers in Diabetic Patients with Concomitant Peripheral Arterial Disease (PAD) |
| **STUDY PHASE** | III |
| **INVESTIGATIONAL AGENT** | VM202 |
| **DOSE** | 16 mg of VM202 administered as a divided Dose of 4 mg each at Day 0, Day 14, Day 28, and Day 42. |
| **POPULATION** | Diabetic patients with confirmed concomitant PAD aged ≥ 18 years to ≤ 80 years diagnosed with nonhealing foot ulcers. |
| **STUDY DESIGN** | A phase III, randomized, double-blind, placebo-controlled, multicenter, 7-month study designed to assess the safety and efficacy of intramuscular (IM) injections in the calf of VM202 in patients with chronic nonhealing foot ulcers. Three hundred patients will be randomized in a 2:1 ratio of VM202 or placebo injections:<br>• Active –VM202 + standard of care – 200 patients<br>• Control – Placebo (VM202 Vehicle) + standard of care – 100 patients<br>Up to thirty (30) 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 efficacy of VM202 in promoting ulcer healing in nonhealing foot ulcers<br>2. To evaluate the safety of IM administration of VM202 in subjects with nonhealing foot ulcers |
| **INCLUSION CRITERIA** | 1. Male or female, between 18 and 80 years of age;<br>2. Documented symptomatic peripheral arterial disease (PAD), with one or more of the following criteria satisfied:<br>• Ankle Brachial Index (ABI) > 0.40 and ≤ 0.90 or > 1.4 (i.e., mild to severe PAD without critical limb ischemia) in target limb;<br>• Toe Brachial Index (TBI) ≤ 0.7 in the target limb;<br>• Toe pressure of < 55 mm Hg in the target limb;<br>• A history of lower extremity PAD with previous related intervention in a leg; |

3. Documented history of Type I or II diabetes with current treatment control (glycosylated hemoglobin $A_{1c}$ [HbA1c] of ≤ 12.0% at Screening) and currently on oral medication, injectable medication and / or insulin;
4. No significant changes anticipated in diabetes medication regimen;
5. At Screening, subject has one ulcer on the target foot that fulfills all of the following criteria:

   - Present for ≥ 2 weeks and ≤ 1 year
   - Full-thickness and not involving bone, tendon, or capsule (probing to tendon or capsule)
   - No sign of infection or osteomyelitis
   - Ulcer must be 0.5 $cm^2$ – 15 $cm^2$ as measured at Screening Visit prior to debridement

   If more than one ulcer is present on the foot, the largest ulcer that fulfills inclusion and exclusion criteria will be considered the target (index) ulcer for the study. Subjects will undergo protocol-defined standardized wound care during screening (for two weeks or longer). Subjects will be considered screen failures and will not receive study injections on Day 0 (baseline) if the target ulcer does not meet all entry criteria (see above) as well as being confirmed as non-healing.

6. Be capable of understanding and complying with the protocol and signing the informed consent document prior to being subjected to any study-related procedures;
7. If female of childbearing potential, negative urine pregnancy test at screening and using acceptable method of birth control during the study.

**EXCLUSION CRITERIA**

1. Will require revascularization in the target leg within 3 months of randomization;
2. In the investigator's assessment, will require an amputation in the target leg within 3 months of randomization;
3. Subjects with target foot ulcer with an etiology of vasculitis, pyoderma gangrenosum, necrobiosis lipoidica, hydrostatic pressure/venous insufficiency, any neoplasms (basalioma, Kaposi's sarcoma, squamous cell carcinoma, etc.), or due to a burn;
4. The study ulcer increased or decreased by 50% or more at baseline from screening (as assessed by comparison of post-debridement photos taken at screening and Day 0);
5. Evidence of active infection (e.g., cellulitis, osteomyelitis) or deep ulceration exposing bone or tendon in the foot planned for treatment;
6. Any gangrene;
7. Current fracture in the target foot;
8. Target ulcer located on an active (hot) Charcot foot;

9. Heart Failure with a NYHA classification of III or IV;
10. Body mass index (BMI) > 45 kg/$m^2$ at Screening;
11. Stroke or myocardial infarction within last 3 months;
12. Unstable angina;
13. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
14. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
15. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
16. Subjects with advanced liver disease including decompensated cirrhosis, jaundice, ascites or bleeding varices;
17. Subjects currently receiving immunosuppressive medications chemotherapy, or radiation therapy;
18. Positive HIV or HTLV at Screening;
19. 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;
20. Clinically significant specific laboratory values at screening (e.g., 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);
21. Glomerular filtration rate (GFR) < 30 mL/min/1.73 $m^2$
22. Subjects with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence for at least 1 year); subjects with medical history and/or family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
23. Subjects with any comorbid conditions likely to interfere with assessment of safety or efficacy or with an estimated life expectancy of less than 1 year;
24. 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;
25. Subjects requiring regular (daily) COX-2 inhibitor drug(s) or steroids (except inhaled steroids or ocular steroids); subjects may be enrolled if willing/able to undergo medication wash-out prior to the first dosing and to refrain from taking these drugs during the study;
26. Major psychiatric disorder in past 6 months;
27. History of drug or alcohol abuse / dependence in the past 2 years;

28. Use of an investigational drug in the past 3 months; use of an investigational biologic in the past 12 months; concurrent participation in investigational protocol or unapproved therapeutics; and
29. Unable or unwilling to give informed consent.

**STUDY PROCEDURES**

Patients will be screened for study eligibility after giving informed consent. Screening should occur at least 7 days and maximal 45 days prior to Day 0 (day of injection). Screening will include assessment of study eligibility, medical history, concomitant medication review, vital signs, physical exam, cancer screening tests, viral screening, ABI and TBI, toe pressure, foot x-ray, 12-lead EKG, retinal fundoscopy, clinical chemistry, hematology, HbA1c, and urine pregnancy test (women of childbearing potential only).

At Screening, standard of care for all wounds on the target foot will be initiated that will continue for the duration of the study, as follows:

- Surgical debridement of necrotic tissue or devitalized tissue
- Use of appropriate off-loading when ambulating
- Maintenance of clean and moist wound environment

The target ulcer will be documented at screening visit before and after debridement. This includes photograph, surface area, depth, perimeter and volume measurements. Subjects will come in once a week for dressing changes and for wound evaluation during screening.

If applicable, the subject will be washed out of prohibited medications prior to Day 0 injections. During washout, screening procedures may be performed. At Day 0, the target ulcer will be documented by photograph, surface area measurement, depth, perimeter and volume. Subjects must have a nonhealing ulcer on Day 0 that meets study entry inclusion criterion #5 and exclusion criterion #4 to be eligible for study participation.

Patients will receive IM injections in the ipsilateral calf of the affected foot of either VM202 or placebo on Day 0, Day 14, Day 28 and Day 42 as follows:

Treatment: Days 0, 14, 28, 42

| TREATMENT GROUP | DOSE VM202 (mg) / VISIT | | | | FINAL DOSE VM202 (mg) |
|---|---|---|---|---|---|
| | DAY 0 | DAY 14 | DAY 28 | DAY 42 | |
| VM202 | 4 | 4 | 4 | 4 | 16 |
| Placebo | 0 | 0 | 0 | 0 | 0 |

0 indicates injections of Placebo

VM202 will be delivered in a solution of 0.5 mg VM202 / mL. All subjects will receive sixteen (16) 0.5-mL injections of VM202 or placebo at each injection visit as follows:

Subjects in the ***VM202 Treatment Arm*** will receive the following IM injections in the calf of the leg with the target ulcer:

- Day 0 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)
- Day 14 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)
- Day 28 – 16 injections of 0.5 mL of VM202 (4 mg of VM202
- Day 42 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)

Subjects in the ***Placebo Group*** will receive 16 injections of 0.5 mL VM202 vehicle in the ipsilateral calf of the affected foot with the target ulcer at each injection visit.

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

Subjects will continue to come to the clinic once a week for dressing changes and wound assessment until the ulcer has healed or study exit, whichever comes first.

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 28, and on Day 60 and Day 90.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 28 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 42 (pre-injection, and 2 hours [± 1 hour] post injection) at Day 60 and at Day 90.

Measurement of target ulcer will be performed at each follow-up visit until complete wound closure is achieved or until study exit. ABI, TBI, and the Cardiff Wound Impact Questionnaire (CWIQ) will be conducted on Day 0, Day 120, and Day 210 Visits. $TcPO_2$ will be assessed as a sub-study at 3 -10 sites on Day 0, Day 120, and Day 210 Visits. Adverse events will be recorded after first study drug administration and throughout the 7-month follow-up period.

**SCHEDULE OF EXAMINATIONS**

Screening (Day -45 to Day -7)
Day 0
Day 14 ± 3 days
Day 28 ± 3 days

Day 42 ± 3 days
Day 60 ± 3 days
Day 74 ± 3 days
Day 90 ± 7 days
Day 120 ± 7 days
Day 210 ± 14 days

**STUDY ENDPOINTS**

The primary study endpoint is the proportion of subjects with a target wound closure by the 4-month follow-up. Complete wound closure is defined as skin re-epithelization without drainage or dressing (primary endpoint), confirmed at a second scheduled or unscheduled visit two weeks (14 ± 5 days) later (secondary endpoint). Active and placebo arms will be compared to determine treatment effect.

Other endpoints will include:

- Time to complete healing of foot ulceration in each group
- Percent change in wound size
- Formation of new ulcers on the target foot
- Change in CWIQ
- Major amputations
- Minor amputations
- Change in ABI
- Change in TBI
- Change in $TcPO_2$ at select sites only

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## ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ABI | Ankle Brachial Index |
| ALT | Alanine Transaminase (SGPT) |
| Anti-HCV | Hepatitis C antibodies |
| AST | Aspartate Transaminase (SGOT) |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| cDNA | Complementary Deoxyribonucleic Acid |
| CBC | Complete Blood Count |
| CDRC | Clinical Data Review Committee |
| CFR | Code of Federal Regulation |
| CLI | Critical Limb Ischemia |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| CS | Clinically Significant |
| CWIQ | Cardiff Wound Impact Questionnaire |
| DBP | Diastolic Blood Pressure |
| DNA | Deoxyribonucleic Acid |
| DP | Dorsal-Plantar / Dorsalis Pedis |
| DPN | Diabetic Peripheral Neuropathy |
| DSMB | Data Safety Monitoring Board |
| ECM | Extracellular Matrix |
| EDC | Electronic Data Capturing |
| EKG | Electrocardiogram |
| EPC | Endothelial Progenitor Cells |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practices |
| GFR | Glomerular filtration rate |
| HBV | Hepatitis B Virus |
| HBcAb | Hepatitis B core antibody |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HCT | Hematocrit |
| HCV | Hepatitis C Virus |
| HEENT | Head, Eyes, Ears, Nose, and Throat |
| Hgb | Hemoglobin |
| HGF | Hepatocyte Growth Factor |
| HIV | Human Immunodeficiency Virus |
| HTLV | Anti-Human T-Cell Lymphotropic Virus |
| IBC | Institutional Biosafety Committee |
| IRB | Institutional Review Board |
| IM | Intramuscular |
| IND | Investigational New Drug |

| | |
|---|---|
| ITT | Intent-to-Treat |
| mITT | Modified Intent-to-Treat |
| MMP | Matrix Metalloproteinases |
| MSC | Mesenchymal Stem Cells |
| NCS | Not Clinically Significant |
| NIH | National Institutes of Health |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| OBA | Office of Biotechnology Activities |
| OSP | Office of Science Policy |
| PAD | Peripheral Arterial Disease |
| PP | Per Protocol |
| PPG | Photoplethysmography |
| PT | Posterior Tibial |
| RBC | Red Blood Cells |
| RNA | Ribonucleic Acid |
| ROS | Reactive Oxygen Species |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAWC | Symposium on Advanced Wound Care |
| SBP | Systolic Blood Pressure |
| SGOT | Serum Glutamic Oxaloacetic Transaminase (same as AST) |
| SGPT | Serum Glutamic Pyruvic Transaminase (same as ALT) |
| SOP | Standard Operating Procedure |
| TAR | Treatment Authorization Request |
| TBI | Toe Brachial Index |
| $TcPO_2$ | Transcutaneous oxygen pressure |
| VEGF | Vascular Endothelial Growth Factor |
| WBC | White Blood Cells |
| WFI | Water for Injection |

## PERSONNEL AND FACILITIES

**STUDY SPONSOR**

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# 1. BACKGROUND

## 1.1. NONHEALING FOOT ULCERS

Over 6.5 million people in the United States have chronic, nonhealing foot ulcers.[1,2] The ulcers initially occur due to trauma, pressure loading, and / or neuropathy. Ulcers fail to heal and become chronic when the energy demands of wound repair cannot be met because of infection and / or when underlying disease inhibits the normal pathways for energy production.

Chronic wounds are unresponsive to standard therapies and persist despite appropriate care.[3,4] The majority (approximately 90%) occur in patients with diabetes, but this attribution can be misleading, as 10% - 50% of these patients have concomitant peripheral arterial disease (PAD).[5-11] Most patients have some form of peripheral neuropathy.[12] A small percentage occurs in patients whose primary condition is ischemic, and in whom revascularization / reperfusion has not resulted in wound healing.[9]

The lifetime risk of developing nonhealing foot ulcers for individuals with diabetes is 15 - 25% with a 50% - 70% recurrence rate within 5 years after the index occurrence.[1,2,9,13,14] The chance of developing an ulcer doubles in patients with concomitant PAD.[6,7,9,14] Figure 1 below depicts the chronic foot ulcer population and the degree to which ischemia and diabetes overlap. The area circled by the thick black line characterizes patients with foot ulcers which suffer from both ischemia and diabetes.

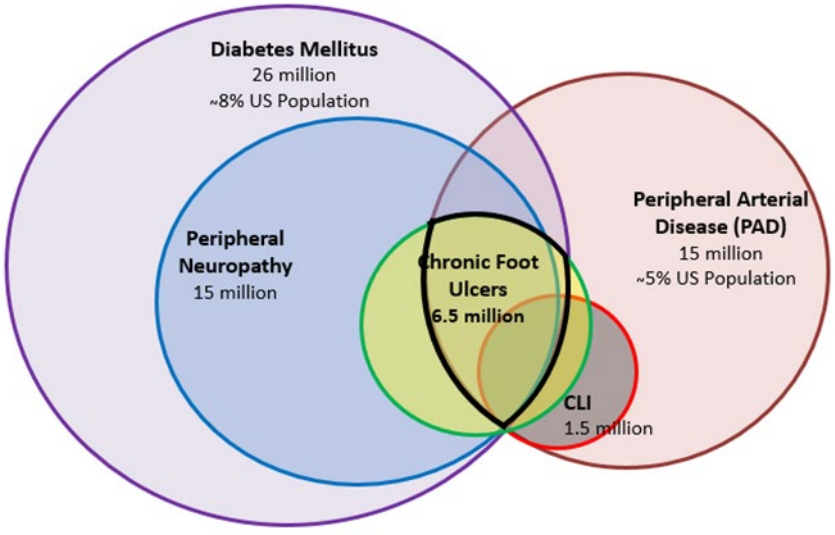


Figure 1. The overlapping relationship of risk factors associated with developing nonhealing ulcers in the United States[1,9,11,13,15-17]

Nonhealing ulcers can significantly affect a patient's quality of life, with patients reporting social isolation, unemployment, depression, and feelings of stigma.[18-21]

Current treatment strategies result in healing approximately 50% of ulcers, regardless of underlying comorbidity(ies), but most ulcers recur.[2,22] Twenty-five percent (25%) of open wounds progress to gangrene or enlarge to such an extent that they require amputation. The five-year mortality rate associated with an index occurrence of a nonhealing ulcer is comparable to or greater than that of many cancers.[10] This significant and growing public health concern costs the US healthcare system over $25 billion annually without accounting for productivity loss.

### 1.1.1. PAD AND DIABETES – TWO ROADS TO A CHRONIC WOUND

Diabetes and PAD are often intertwined conditions.[5,7,12,21,23] PAD is a progressive, atherosclerotic disease that obstructs the blood supply to the lower limbs. It frequently coexists with coronary and / or cerebrovascular disease, likely due to a similar underlying pathology and shared risk factors (e.g., smoking, hyperlipidemia, hypertension, age, and obesity).

The likelihood of developing PAD increases with diabetes.[7,15] Diabetes is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. The metabolic dysfunction arises from defects in insulin secretion (type 1), insulin action (type 2), or a combination of both.[24] Hyperglycemia accelerates atherosclerosis and worsens platelet aggregation, significantly increasing the chances of thrombosis, stroke, peripheral ischemia, and microvasculature and peripheral nerve damage. Independently, either disease process can result in compromised mobility and susceptibility to peripheral tissue damage which can then progress to nonhealing foot ulcers. When PAD and diabetes are present together, morbidity and mortality are greater.

Both conditions can impair the ability of the underlying microvasculature and surrounding tissues to support wound healing. Mitochondrial dysfunction, particularly in endothelial cells, plays a key role in the pathogenesis, because mitochondria provide the energy necessary to sustain wound healing. When they function suboptimally, they do not produce enough energy, and wound healing cannot proceed normally.

## 1.2. WOUND HEALING

Normal wound repair is a relatively linear process (albeit with significant complexity and overlap) which progresses through three general phases:

***Inflammatory***: including platelet aggregation, release of proinflammatory cytokines and recruitment of neutrophils and macrophages;
***Proliferative***: including fibroblast proliferation, angiogenesis, formation of granulation tissue and keratinocyte proliferation, and re-epithelialization; and
***Remodeling***: longest phase; includes myofibroblast transformation and restructure of healed wound to increase strength.

The three phases rely heavily on the microvasculature surrounding the wound area to facilitate nutrient and growth factor transport, oxygen exchange and to provide a conduit for the movement of immune and reparatory cells. In patients suffering from ischemia and/or metabolic derangement, compromised endothelial cells can arrest and even hinder each stage of the repair process. Reactive oxygen species (ROS) generated by mitochondria in response to intracellular hypoxia and / or hyperglycemia worsen and prolong inflammation.[25-28] Endothelial permeability increases, leaving the endothelium and underlying tissues more susceptible to damage by the increased influx of glucose and free radicals. And, although cellular immunity is activated, hypoxic conditions impair the abilities of neutrophils and macrophages to phagocytize bacteria and dying cells. This increases the likelihood of the wounds to become chronically infected.

The proliferative phase can also protract in these patients due to local hypoxic conditions caused either by compromised circulation, reduced erythrocyte function (due to nonenzymatic glycosylation), or both. Reduced oxygen delivery to the wound site hinders angiogenesis and collagen synthesis. In addition, the heightened energy demands (need for additional ATP) required for coordinating new blood vessel formation and tissue regeneration, particularly within granulation tissue, cannot be met by the metabolically compromised mitochondria.

Finally, the remodeling phase is compromised due to local ischemic conditions and because pro-inflammatory cytokines remain persistently high. This causes a sustained overexpression of matrix metalloproteinases (MMPs). In normal wound healing, MMPs orchestrate the turnover of extracellular matrix (ECM) to form a more mature tissue with appropriate tensile strength. Under pathological conditions, however, the overproduction of MMPs causes tissue breakdown making wound enlargement or re-injury more likely.

## 1.3. CURRENT TREATMENT OPTIONS

The standard of care for chronic foot ulcers includes debridement of the wound, management of any infection, revascularization procedures when indicated, mechanical offloading of the ulcer, management of blood glucose, and foot care education. Other adjunctive therapies, such as hyperbaric oxygen, use of advanced wound care products, and negative-pressure wound therapy have shown some benefit, but reports of efficacy are mixed, and their cost-effectiveness has not been demonstrated.[14,29]

## 1.4. UNMET MEDICAL NEED

Chronic foot ulcers are associated with significant morbidity and mortality and present a growing public health concern. At best, even advanced therapies such as human-derived products regulated under 21 CFR 1271 (e.g., AlloDerm, AlloPatch, Cumetra, etc.) and FDA-approved products such as Regranex (BLA 103691, 1997), Apligraf (P950032, 2000), and Dermagraft (P000036, 2001) only result in complete

wound healing in 20% - 50% of patients treated. Clearly, it would be desirable to develop other therapeutic options to treat chronic ulcers.

## 1.5. HEPATOCYTE GROWTH FACTOR (HGF) AND WOUND HEALING

Most foot ulcers are caused by a combination of neuropathy, pressure loading, and/or trauma. Ischemia and / or hyperglycemia are not the initiating factors. However, whether present together or singularly, these comorbidities impair mitochondrial function, reduce the cellular energy supply available for repair, and worsen local inflammatory conditions.

HGF, a multi-functional cytokine with potent neovascularization effects, including vasculogenesis, angiogenesis and arteriogenesis, may be uniquely suited to improve outcomes for chronic wounds. HGF has been described as a 'master trigger' because of its ability to interact with the c-met receptor and modulate the expression of Ets-1, a highly conserved transcription factor which initiates transcription of numerous genes encoding angiogenic modulators such as vascular endothelial growth factor (VEGF).[30-34] More salient for wound repair, HGF can positively affect energy metabolism by minimizing mitochondrial caspase signaling and preventing apoptosis.[35-40] It also triggers antioxidant genes through modulation of intracellular levels of glutathione, a major determinant of cellular redox potential, and of cytoprotective enzymes such as catalase, which further protect against damage from elevated levels of intracellular oxidative stress.[41] Recent research also suggests that HGF has a role in maintaining nerve function and growth and in preserving nerve cell integrity in the face of metabolic derangements.[37,42-46] For diabetics, preservation of sensation may assist with foot care and wound awareness.

During normal wound healing, HGF signaling by damaged cells stimulates the growth of endothelial cells and migration of vascular smooth muscle cells.[47,48] It also mobilizes circulating endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs) to the damaged area.[47-53] These cells, in turn, secrete additional growth factors and antioxidants which facilitate fibroblast proliferation, angiogenesis, formation of granulation tissue and keratinocyte proliferation, and re-epithelialization (see Section 1.2). In the remodeling phase of wound healing, HGF promotes epithelial repair,[54] improves tissue fibrosis, and limits collagen metabolism, thereby decreasing scar formation.[55] In chronic wounds, however, the endogenous signal is insufficient to overcome the onslaught of oxidative stress and the ongoing metabolic dysfunction associated with the underlying pathology(ies).

The challenge associated with delivering a targeted sustained dose of exogenous HGF is 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.[56,57]

One approach to increasing HGF in ischemic tissues is to develop a gene transfer strategy that would allow for persistent expression of HGF protein *in vivo*. Although plasmid DNA is one of the least efficient gene transfer systems currently in use, the

fact that it is associated with limited persistence and no propensity for genomic integration (particularly in skeletal muscle tissue), makes it an attractive option for local targeted delivery.

## 1.6. VM202 FOR THE TREATMENT OF CHRONIC FOOT ULCERS

VM202 is a DNA plasmid that contains novel genomic-cDNA hybrid human hepatocyte growth factor (HGF) coding sequence [redacted] expressing two isoforms of HGF simultaneously, [redacted].

The key feature of HGF[redacted] 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.

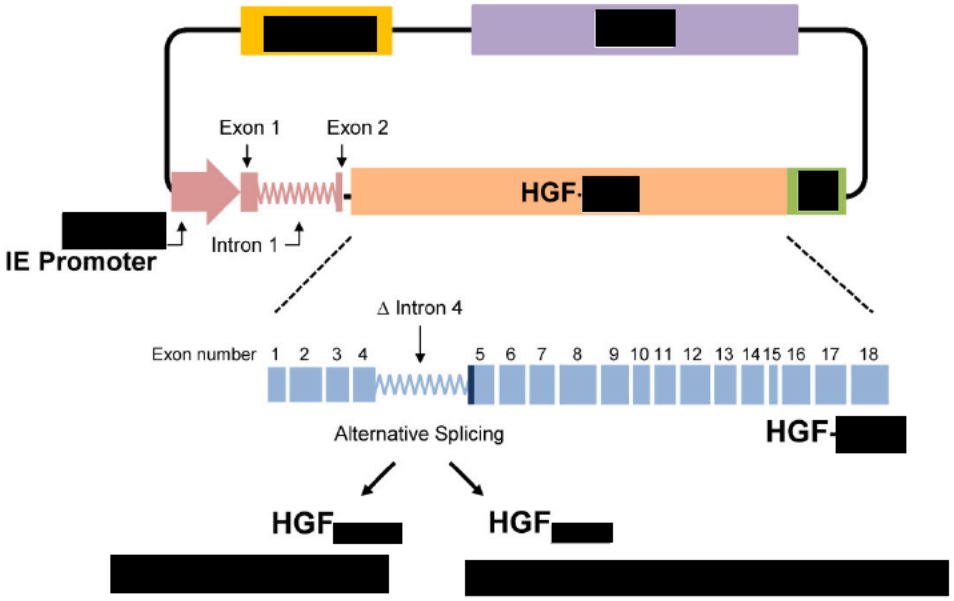


Figure 2. VM202 construct

VM202 is supplied in a sterile glass vial containing [redacted] study product. Before administration, it was reconstituted [redacted] for a final VM202 concentration of 0.5 mg/mL.

### 1.6.1. SAFETY OF VM202

Thus far, review of data available from all clinical studies of VM202 (completed and ongoing) suggests a consistent safety profile at doses ranging from 2 mg VM202 to 64 mg VM202. A total of 165 subjects participating in 5 different studies have received VM202 injections. This includes 18 subjects from the ongoing ALS study (BB IND 15,761). To date, there have been no serious adverse events directly attributed to VM202, no subjects withdrawn due to any documented or perceived drug intolerance, and no immune reactions. VM202 is rapidly eliminated from

circulation and appears to remain active only at the injection site. This is supported by the fact that circulating HGF levels remained fairly constant, relative to baseline (data not yet available for ALS study).

### 1.6.2. VM202 Wound Healing Data - Rationale

Data from the phase I and phase II studies of VM202 in patients with critical limb ischemia (BB IND 13,158) suggest that VM202 promotes wound healing. Results from the phase II study, in particular, showed a statistically significant improvement in wound healing over placebo (see Section 1.6.4). In both studies, however, over half of the patients presenting with ulcers had concomitant diabetes. As was discussed in the previous sections, peripheral ischemia and diabetes often coexist and accelerate pathology. Both conditions create mitochondrial dysfunction, which, in turn damages the endothelial lining of the microvasculature. As HGF is known to be a potent angiogenic and neuroprotective factor capable of upregulating antioxidant mechanisms and interfering with the molecular machinery of mitochondrial apoptotic signaling, it may be uniquely suited to treating nonhealing wounds. In addition, data from the phase I and phase II studies of VM202 in patients with diabetic peripheral neuropathy (DPN, BB IND 13,938) suggest that VM202 may improve nerve health in diabetics. In the phase I study, patients experienced significant improvements in pain over baseline out to 9 months. In the phase II study, a prospective, randomized, placebo-controlled study of two different doses of VM202, subjects receiving 8 mg of VM202 per leg experienced statistically significant pain reduction at 3 months when compared to placebo. Improvement in nerve function could be an important contributing factor in preventing ulcer recurrences.

Considering VM202's excellent safety profile to date, and the early evidence of its wound healing capabilities, this protocol involves a clinical study of VM202 in diabetic patients with concomitant PAD and nonhealing foot ulcers. Sections 1.6.3 and 1.6.4 provide a brief summary of the wound healing results from the phase I and phase II studies of VM202 in Critical Limb Ischemia (CLI) patients, respectively.

### 1.6.3. Phase I Study of VM202 in Patients with Critical Limb Ischemia

The phase I study of VM202 in patients with CLI was a single-center, prospective, dose-escalation study designed to evaluate the safety and tolerability of intramuscular (IM) injections of VM202 in subjects with CLI. The study only enrolled 'no-option' CLI patients with a Rutherford Scale score of 4 or 5. Subjects received 2 mg, 4 mg, 8 mg, or 16 mg VM202. Three subjects were treated per dose cohort, for a total of 12 subjects. For each dose cohort, VM202 was administered as local IM injections with half of the dose administered at Day 1 of the study and the second half administered 2 weeks later. Safety, tolerability, and preliminary efficacy (hemodynamic assessments) were evaluated at screening and at designated time points throughout the study. All 4 dose cohorts were followed for one year from the time of the first dose of study drug administration. Clinical evaluations were conducted at Days 1 (baseline), 15, 28, 59, 91, 180, and 365.

Eight out of 12 (8/12, 75%) subjects enrolled had concomitant diabetes. At baseline, 7 subjects had 15 ulcers. Over half of the subjects with ulcers (4/7, [57%]) had concomitant diabetes. Nine of the fifteen ulcers (9/15 [60%]) completely healed; one (1) ulcer improved (6.7%); and 5/15 (33.3%) worsened. Table 1 lists the incidence and outcome of the ulcers by patient number, dose cohort, and diabetes status.

Table 1. Phase I CLI Study Results: progression / healing of ulcers

| SUBJECT ID | DIABETES | VM202 DOSE | ULCER NUMBER | ULCER MEASUREMENT AT DAY-1 BASELINE OR DAY OF FIRST ONSET ($CM^2$) | LAST ULCER MEASUREMENT ($CM^2$) | LAST MEASURE-MENT |
|---|---|---|---|---|---|---|
| 001101 | N | 2 mg | 1 | 0.24 | 100% Healed by Day 59 | Day 59 |
| 001102 | Y | 2 mg | 1 | 1.19 | 10.2 | Day 365 |
| 001106 | N | 4 mg | 1 | 0.72 | 100% Healed by Day 15 | Day 15 |
| 001111 | Y | 8 mg | 1 | 31 | 164.59 | Day 365 |
| | | | 2 | 32.68 | 100% Healed by Day 365 | Day 365 |
| | | | 3 | 0.54 | 100% Healed by Day 365 | Day 365 |
| | | | 4 | 0.06 | 100% Healed by Day 365 | Day 365 |
| | | | 5 | 0.09 | 3.2 | Day 365 |
| 001112 | Y | 8 mg | 1 | 4.2 | 0.9 | Day 91 |
| | | | 2 | 1.3 | 2.89 | Day 91 |
| | | | 3 | 4.35 | 100% Healed by Day 91 | Day 91 |
| 001113 | Y | 8 mg | 1 | 0.24 | 100% Healed by Day 91 | Day 91 |
| 001114 | N | 16 mg | 1 | 2.72 | 10.5 | Day 365 |
| | | | 2 | 1.62 (Day 28) | 100% Healed by Day 180 | Day 180 |
| | | | 3 | 0.99 (Day 91) | 100% Healed by Day 180 | Day 180 |

### 1.6.4. PHASE II STUDY OF VM202 IN PATIENTS WITH CRITICAL LIMB ISCHEMIA

The phase II study of VM202 subjects with CLI was a multi-center, double-blind, randomized, placebo-controlled, study designed to assess the safety and efficacy of VM202. Patients were randomized 2:2:1 to the Low Dose (8 mg VM202), High Dose (16 mg VM202), or placebo. The enrollment goal (number of patients to be treated) was 50 subjects. Subjects in the Low Dose group received 8 mg of VM202 (delivered as a divided dose of 4 mg on day 0 and Day 14, with Placebo injections on Day 28 and Day 42); subjects in the High Dose group received 16 mg of VM202 (delivered as a divided dose of 4 mg on day 0, Day 14, Day 28, and Day 42). Subjects in the placebo group received only placebo injections on Day 0, 14, 28 and 42. All subjects received the same number (16) and volume of local IM injections at each injection visit. Safety, tolerability, and preliminary efficacy (assessment of pain, wound healing, and other hemodynamic assessments) were evaluated at screening and at designated time points throughout the study. All subjects were

followed for one year from the time of the first dose of study drug administration. Clinical evaluations were conducted at Day 0 (baseline), 14, 28, 42, 49, 90, 180, 270, and 365.

52 subjects were randomized to one of the three treatment arms. Fifty (50) subjects received all study injections. If present prior to the first injection (Day 0), two photographs of each ulceration/gangrene area were obtained pretreatment on Days 14, 28 and 42, and on Day 49, Day 90, 6 months, 9 months and 12 months.

Four subjects in the placebo group (4/10, 40%) had 6 ulcers at study entry. Twelve subjects in the Low Dose had 25 ulcers at baseline (12/20, 60%); and seven subjects in the High Dose group had 14 ulcers at baseline (7/20, 35%). All of the subjects with ulcers in the placebo arm had concomitant diabetes; 8/12 subjects (75%) in the Low Dose arm had concomitant diabetes; and, 3/7 subjects (43%) in the High Dose arm had concomitant diabetes. Table 2 shows the distribution of ulcers in each treatment group.

Table 2. Ulcer distribution by treatment group on Day 0 (baseline)

| Number of ulcers | Number of subjects | | |
|---|---|---|---|
| | Placebo | Low-dose | High-dose |
| 1 | 3/4 (75%) | 4/12 (33%) | 3/7 (43%) |
| 2 | 0/4 (0%) | 5/12 (42%) | 1/7 (14%) |
| 3 | 1/4 (25%) | 0/12 (0%) | 3/7 (43%) |
| 4 | 0/4 (0%) | 3/12 (25%) | 0/7 (0%) |
| Total Number of Ulcers | 6 | 26 | 14 |

Ulcers were evaluated until healed, and, if not healed, to the last available study visit or amputation. If an ulcer was lost due to amputation, the last recorded evaluation of the ulcer was carried forward. Improvement or worsening was determined by changes in ulcer area. The average area at baseline (Day 0) for ulcers in the placebo group was 3.7 $cm^2$ (SD 5.6 $cm^2$), 2.7 $cm^2$ (SD 6.5 $cm^2$) in the Low Dose group, and 2.9 $cm^2$ (SD 4.6 $cm^2$) in the High Dose group. The average increase in wound area was 4.3 $cm^2$ (SD 12.6 $cm^2$).

Improvements were statistically significant for wound healing in both treatment groups. Ulcers improved most in the High Dose group when compared to Placebo ($p < 0.02$). Nine of the 14 ulcers in the High Dose Group (9/14, 64.3%) completely healed. Of the 5 remaining ulcers, 4 improved (4/14, 28.6%) and one worsened (1/14, 7.1%). Improvements were also seen in the Low Dose Group. Fourteen of the 26 ulcers (14/26, 53.8%) present at baseline completely healed. Of the remaining 12 ulcers, 8 improved (8/26, 30.8%), and 4 ulcers worsened (4/26, 15.4%). In the placebo group, only one (1) of the 6 ulcers (16.7%) completely healed from baseline. The 5 other ulcers (5/6, 83.3%) increased in size. Table 3 lists the progression of ulcers at the last available follow-up by treatment group.

Table 3. Progression of ulcers present and documented at baseline by treatment group

| Treatment Arm | Ulcers present at Baseline | Completely Healed n (%) | Ulcers decreased in Size, n (%) | | Ulcers Increased in Size n (%) | | |
|---|---|---|---|---|---|---|---|
| | | | 1 - 50% | 50 - 99% | 1 - 50% | 50 - 99% | ≥ 100% |
| Placebo | 6 | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | 3 (50.0%) | 0 (0.0%) | 2 (33.3%) |
| Low Dose (8mg VM202) | 26 | 14 (53.8%) | 3 (11.5%) | 5 (19.2%) | 1 (3.8%) | 1 (3.8%) | 2 (7.7%) |
| High Dose (16 mg VM202) | 14 | 9 (64.3%) | 3 (21.4%) | 1 (7.1%) | 0 (0.0%) | 0 (0.0%) | 1 (7.1%) |

### 1.6.5. Clinical Experience Conclusions

Data collected to date support the feasibility and safety of IM injections of VM202 in subjects with nonhealing foot ulcers with CLI and diabetes. Results demonstrate statistically significant ulcer healing. To date, there have been no serious adverse events directly attributable to VM202, no subjects have withdrawn due to any documented or perceived drug intolerance, and no immune reactions have been reported. VM202 is rapidly eliminated from circulation and appears to remain active only at the injection site. Continued study of VM202 in nonhealing foot ulcers in diabetic subjects with concomitant PAD is warranted.

## 1.7. Study and Dose Rationale

Based on the excellent safety profile and preliminary efficacy data of VM202 observed in the phase I and phase II CLI studies, we propose using the same dosing scheme utilized in the phase II CLI study in this phase III study.

One dose of VM202 will be tested against placebo (VM202 vehicle). The total dose of VM202 will remain within the dosing scheme of the phase II study (16 mg / leg), delivered as a divided dose of 4 mg IM injections in the ipsilateral calf of the affected foot on Day 0, Day 14, Day 28, and Day 42.

As in all prior/ongoing studies, VM202 will be delivered in a solution of 0.5 mg VM202 / mL. Subjects will be treated with an overall final dose of 16 mg VM202 or placebo. This dosage is well within those supported by the body of pharmacology and toxicology safety studies of VM202. No toxicities were reported in the phase I and II CLI studies, and any other studies. Safety studies in rabbit, rat and mouse models demonstrate that doses approximately 5 (80 mg/70 kg) to 60 (960 mg/70 kg) times the clinical dose (16 mg) proposed in this study are safe and resulted in no toxicities.

## 2. GOOD CLINICAL PRACTICES (GCP) STATEMENT

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

## 3. INVESTIGATIONAL PLAN

### 3.1. STUDY OBJECTIVES

The objective of this Phase III study is to evaluate the safety and efficacy of IM administration of VM202 in the treatment of chronic nonhealing foot ulcers in diabetic patients with concomitant PAD.

### 3.2. STUDY DESIGN

This is a phase III, double-blind, randomized, placebo-controlled, multicenter, 7-month study designed to assess the safety and efficacy of VM202 to treat chronic nonhealing foot ulcers in diabetic patients with concomitant PAD. Subjects with diabetes and a single chronic nonhealing foot ulcer on the target foot will be screened for study eligibility after giving informed consent.

***Initial Screening Activities.*** Prior to full screening, subjects with diabetes will provide informed consent and then undergo target ulcer documentation prior to debridement. Only subjects whose target ulcer meets eligibility criteria (inclusion #5) will be allowed to proceed with the full screening procedures.

***Screening.*** Screening should occur at least 7 days and maximal 45 days prior to Day 0 (day of injection). If the target ulcer criteria are met, the rest of screening will proceed to assess study eligibility in the following order:

- Medical history
- Concomitant medication review
- Vital signs
- Documentation of symptomatic PAD:
    - ABI > 0.40 and ≤ 0.90 or > 1.4 (i.e., mild to severe PAD without critical limb ischemia) in target limb
    - TBI ≤ 0.7 in the target limb
    - Toe pressure of < 55 mm Hg in the target limb
    - A history of lower extremity PAD with previous related intervention in a leg
- Physical exam
- Urine pregnancy testing (women of childbearing potential only)

- Chemistry, hematology, and HbA1c
- Viral screening
- 12-lead EKG
- Foot x-ray
- Fundoscopy
- Cancer screening tests

At Screening, standard of care for all wounds on the target foot will be initiated that will continue for the duration of the study, as follows:

- Surgical debridement of necrotic tissue or devitalized tissue
- Use of appropriate off-loading when ambulating
- Maintenance of a clean and moist wound environment

The target ulcer will be documented at screening visit before and after debridement. This includes photograph and surface area measurement, depth perimeter and volume. Subjects will come in once a week for dressing changes and for wound evaluation during screening. At these visits, vital signs, concomitant medications, target ulcer documentation. Any change in the subject's medical condition should be documented in the medical history.

If applicable, the subject will be washed out of prohibited medications prior to Day 0 injections (see Appendix 3). During washout, screening procedures may be performed. At Day 0, the target ulcer will be documented by photograph, surface area measurement, depth, perimeter and volume before and after debridement. Subjects must have a non-healing ulcer on Day 0 that meets study inclusion criterion # 5 and exclusion criterion #6 to be eligible for study participation.

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

***First Treatment.*** Prior to the first injection, vital signs, concomitant medications, ABI, and TBI will be conducted. $TcPO_2$ will only be assessed as a sub-study at 3 - 10 sites. The target ulcer will be documented by photograph, surface area measurement, perimeter, depth and volume. The Cardiff Wound Impact Questionnaire (CWIQ) will be completed. Study entry criteria should be verified again. In addition, blood will be drawn for determination of serum chemistry and hematology, HbA1c, serum HGF, and copies of VM202.

Subjects will receive IM injections in the ipsilateral calf of the affected foot of either VM202 or placebo on Day 0, Day 14, Day 28 and Day 42 as follows:

Table 4. Treatment: Days 0, 14, 28 and 42

| TREATMENT GROUP | DOSE VM202 (mg) / VISIT | | | | FINAL DOSE VM202 (mg) |
|---|---|---|---|---|---|
| | DAY 0 | DAY 14 | DAY 28 | DAY 42 | |
| VM202 | 4 | 4 | 4 | 4 | 16 |
| Placebo | 0 | 0 | 0 | 0 | 0 |

0 = injections of VM202 vehicle

VM202 will be delivered in a solution of 0.5 mg VM202 / mL.

Subjects in the ***VM202 Treatment Arm*** will receive the following IM injections in the ipsilateral calf of the affected foot with the target ulcer at each injection visit:

- Day 0 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)
- Day 14 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)
- Day 28 – 16 injections of 0.5 mL of VM202 (4 mg of VM202)
- Day 42 –16 injections of 0.5 mL of VM202 (4 mg of VM202)

Subjects in the ***Placebo Group*** will receive 16 injections of 0.5 mL VM202 vehicle in the ipsilateral calf of the affected foot with the target ulcer at each injection visit:

- Day 0 – 16 injections of 0.5 mL of VM202 vehicle
- Day 14 – 16 injections of 0.5 mL of VM202 vehicle
- Day 28 – 16 injections of 0.5 mL of VM202 vehicle
- Day 42 –16 injections of 0.5 mL of VM202 vehicle

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

***Second, Third and Fourth Treatments.*** Prior to the study injections on Day 14, 28 and 42, vital signs, and concomitant medications will be documented. The target ulcer will be documented by photograph, surface area measurement, depth and volume. In addition, blood will be drawn for determination of copies of VM202, serum HGF (Day 28 only), and serum chemistry and hematology (Day 42 only). The occurrence of injection site reactions and AEs will be assessed prior to the study injections.

***Post Injections.*** 1 to 3 hours post injection on Days 0, 14, 28 and 42, vital signs, and blood draw for determination of copies of VM202 will be performed, and the occurrence of injection site reactions and AEs will be assessed.

Subjects will continue to come to the clinic once a week for dressing changes and wound assessment until the ulcer has healed or study exit, whichever comes first. At these visits, vital signs, concomitant medications, target ulcer documentation

(photograph, surface area, depth, perimeter and volume measurements), and the occurrence of injection site reactions (if the visit occurs within 60 days) and AEs will be assessed.

All subjects will be assessed at Day 60, Day 74, Day 90, Day 120 and Day 210; at all these visits, vital signs, concomitant medications, assessment of AEs and, if applicable, target ulcer documentation (photograph, surface area, depth, perimeter and volume measurements) will be conducted.

The occurrence of injection site reactions will be assessed on Day 60.

Blood will be drawn for determination of serum HGF, and copies of VM202 on Days 60 and 90. Blood will be drawn for determination of serum chemistry and hematology on Days 90, 120 and 210. Blood will be drawn for determination HbA1c on Days 120 and 210.

ABI, TBI, and CWIQ will be determined on Day 120, and 210. $TcPO_2$ will be assessed as a sub-study at 3 -10 sites at these visits.

***Note, if the ulcer has healed, the subject needs to return to the clinic in 14 days (± 5 days) in order to confirm complete wound closure at two consecutive study visits two weeks apart. If target foot ulcer healing is first documented on Day 210, the subject will return for one additional visit 14 ± 5 days after Day 210 for a confirmation of ulcer healing visit. This confirmation visit may coincide with a pre-specified visit or may require an unscheduled visit.***

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

## 3.3. SUBJECT POPULATION

A total of 300 evaluable subjects with *diabetes mellitus* (DM) and concomitant PAD meeting the following study entry criteria will be enrolled.

### 3.3.1. INCLUSION CRITERIA

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

1. Male or female, between 18 and 80 years of age;
2. Documented history of symptomatic PAD, with one or more of the following criteria satisfied:

    - ABI > 0.40 and ≤ 0.90 or > 1.4 (i.e., mild to severe PAD without critical limb ischemia) in target limb;
    - TBI ≤ 0.7 in the target limb;
    - Toe pressure of < 55 mm Hg in the target limb;
    - A history of lower extremity PAD with previous related intervention in a leg;

3. Documented history of Type I or II diabetes with current treatment control (HbA1c of ≤ 12.0% at Screening) and currently on oral medication, injectable medication and / or insulin;
4. No significant changes anticipated in diabetes medication regimen;
5. At Screening, subject has one ulcer on the target foot that fulfills all of the following criteria:

    - Present for ≥ 2 weeks and ≤1 year
    - Full- thickness and not involving bone, tendon, or capsule (probing to tendon or capsule)
    - No sign of infection or osteomyelitis
    - Ulcer must be 0.5 $cm^2$ – 15 $cm^2$ as measured at Screening Visit prior to debridement

    If more than one ulcer is present on the foot, the largest ulcer that fulfills inclusion and exclusion criteria will be considered the target (index) ulcer for the study. Subjects will undergo protocol-defined standardized wound care during screening (for two weeks or longer). Subjects will be considered screen failures and will not receive study injections on Day 0 (baseline) if the target ulcer does not meet all entry criteria (see above) as well as being confirmed as non-healing.

6. Be capable of understanding and complying with the protocol and signing the informed consent document prior to being subjected to any study related procedures;
7. If female of childbearing potential, negative urine pregnancy test at screening and using acceptable method of birth control during the study.

### 3.3.2. EXCLUSION CRITERIA

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

1. Will require revascularization in the target leg within 3 months of randomization;
2. In the investigator's assessment, will require an amputation in the target leg within 3 months of randomization;
3. Subjects with target foot ulcer with an etiology of vasculitis, pyoderma gangrenosum, necrobiosis lipoidica, hydrostatic pressure/venous insufficiency, any neoplasms (basalioma, Kaposi's sarcoma, squamous cell carcinoma, etc.), or due to a burn;
4. The study ulcer increased or decreased by 50% or more at baseline from screening (as assessed by comparison of post-debridement photos taken at screening and Day 0);
5. Evidence of active infection (e.g., cellulitis, osteomyelitis) or deep ulceration exposing bone or tendon in the foot planned for treatment;
6. Any gangrene;

7. Current fracture in the target foot;
8. Target ulcer located on an active (hot) Charcot foot;
9. Heart Failure with a NYHA classification of III or IV;
10. Body mass index (BMI) > 45 kg/$m^2$ at Screening;
11. Stroke or myocardial infarction within last 3 months;
12. Unstable angina;
13. Uncontrolled hypertension defined as sustained systolic blood pressure (SBP) > 200 mmHg or diastolic BP (DBP) > 110 mmHg at baseline/screening evaluation;
14. Ophthalmologic conditions pertinent to proliferative retinopathy or conditions that preclude standard ophthalmologic examination;
15. Inflammatory disorder of the blood vessels (inflammatory angiopathy, such as Buerger's disease);
16. Subjects with advanced liver disease including decompensated cirrhosis, jaundice, ascites or bleeding varices;
17. Subjects currently receiving immunosuppressive medications chemotherapy, or radiation therapy;
18. Positive HIV or HTLV at Screening;
19. 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;
20. Clinically significant specific laboratory values at screening (e.g., 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);
21. Glomerular filtration rate (GFR) < 30 mL/min/1.73 $m^2$
22. Subjects with a recent history (< 5 years) of or new screening finding of malignant neoplasm except basal cell carcinoma or squamous cell carcinoma of the skin (if excised and no evidence of recurrence for at least 1 year); subjects with medical history and/or family history of colon cancer in any first degree relative are excluded unless they have undergone a colonoscopy in the last 12 months with negative findings;
23. Subjects with any comorbid conditions likely to interfere with assessment of safety or efficacy or with an estimated life expectancy of less than 1 year;
24. 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;
25. Subjects requiring regular (daily) COX-2 inhibitor drug(s) or steroids (except inhaled steroids or ocular steroids); subjects may be enrolled if willing/able to undergo medication wash-out prior to the first dosing and to refrain from taking these drugs during the study;
26. Major psychiatric disorder in past 6 months;
27. History of drug or alcohol abuse / dependence in the past 2 years;

28. Use of an investigational drug in the past 3 months; use of an investigational biologic in the past 12 months; concurrent participation in investigational protocol or unapproved therapeutics; and
29. Unable or unwilling to give informed consent.

## 3.4. STUDY PROCEDURES

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

### 3.4.1. INFORMED CONSENT

The investigator or designee with appropriate delegation will explain the study purpose, procedures, and subject's responsibilities to the potential participant. The subject's willingness and ability to meet the follow-up requirements will be determined and written informed consent will be obtained (Appendix 2). The subject will sign and date the informed consent form. The investigator or designee will also sign and date the consent form. The original informed consent form will be retained with the subject records; a copy will be provided to the subject.

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

### 3.4.2. SUBJECT IDENTIFICATION

To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form. All subjects that give informed consent (sign the informed consent form) will be assigned a unique identifier in the following format: XX-YY-ZZZ. XX is the 2-digit assigned site number, YY is the sequential subject ID number, and ZZZ are the subject initials (initials of first name/middle name (if applicable)/last name). For example, the first subject named John Simon Doe at site 11 will be assigned 11-01-JSD. Subject ID numbers will not be reused (e.g., if the subject is determined to be a screen failure).

### 3.4.3. SCREENING (DAY -45 TO DAY -7)

Prior to full screening, subjects with diabetes and PAD will provide informed consent and then undergo target ulcer documentation (photograph, surface area, depth, perimeter and volume measurements) prior to debridement. Only subjects whose target ulcer meets eligibility criteria (inclusion #5) will be allowed to proceed with the full screening procedures.

Full screening procedures involve, in the following order:

- Evaluation of eligibility criteria
- Medical history
- Concomitant medication review
    - ***Start of prohibited concomitant medication washout (if applicable)***
- Vital signs

- Documentation of symptomatic PAD:
    - ABI > 0.40 and ≤ 0.90 or > 1.4 (i.e., mild to severe PAD without critical limb ischemia) in target limb;
    - TBI ≤ 0.7 in the target limb
    - Toe pressure of < 55 mm Hg in the target limb
    - A history of lower extremity PAD with previous related intervention in a leg;
- Physical exam, including height
- Urine pregnancy testing (women of childbearing potential only)
- Serum chemistry (including eGFR), hematology, and HbA1c
- Viral screening– HIV, Anti-Human T-Cell Lymphotropic Virus (HTLV), Hepatitis B core antibody (IgG and IgM; HBcAb), antibody to Hepatitis B antigen (HBsAb), Hepatitis B surface antigen (HBsAg) and Hepatitis C antibodies (Anti-HCV).
- 12-lead EKG
- Foot x-ray
- Fundoscopy
- Cancer screening should be conducted per the current American Cancer Society Guidelines for the Early Detection of Cancer. Testing is described in Section 4.1.3

### 3.4.4. STANDARD OF CARE

At screening, standard of care for all wounds on the target foot will be initiated that will continue for the duration of the study/until the ulcer has completely healed:

- Surgical debridement of necrotic tissue or devitalized tissue
- Use of appropriate off-loading when ambulating
- Maintenance of a clean and moist wound environment

Detailed instructions can be found in Appendix 4.

#### 3.4.4.1. WOUND ASSESSMENT AND DRESSING CHANGES DURING SCREENING

During the Screening period, subjects will come in once a week for dressing changes and wound evaluation. If a study visit is already scheduled for that week, the dressing change and wound evaluation will occur as part of the study visit. At these visits, the following assessments will be performed:

- Documentation of target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement
- Vital signs (except for weight)
- Concomitant medications
- Assessment of pre-treatment AEs

### 3.4.5. PROHIBITED CONCOMITANT MEDICATIONS/TREATMENTS

#### 3.4.5.1. MEDICATION THAT MAY INTERFERE WITH VM202 BIOACTIVITY

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

#### 3.4.5.2. MEDICATIONS/TREATMENT THAT MAY INTERFERE WITH ASSESSMENT OF VM202 EFFECT ON ULCER HEALING

Subjects must refrain from using the following medications/ undergoing the following therapies for the duration of the study (Appendix 3):

- Gels or creams with growth factors, e.g., Regranex® gel (becaplermin)
- Larval debridement
- Skin substitutes, e.g., Dermagraft®, Apligraf®
- Hyperbaric oxygen therapy
- Hydrotherapy
- Negative pressure wound therapy
- Electrical stimulation therapy

#### 3.4.5.3. SCREEN FAILURES

Subjects not meeting all study entry criteria will be designated as screen failures. End of study procedures will not be performed for these subjects, but their reason for discontinuation will be recorded in EDC.

#### 3.4.5.4. RE-SCREENING

Subjects whose target foot ulcer was initially not eligible (e.g., ulcer surface area was too large or too small; ulcer was infected) may be re-screened if the target ulcer remains open 2 weeks after screen failure ***and*** now meets inclusion and exclusion criteria. Any subject who has been screen failed may only undergo one re-screening.

Subjects who failed to meet any other inclusion or exclusion criteria may not be re-screened without sponsor permission.

The following screening assessments, if completed during the first screening and found to meet eligibility criteria, may not need to be repeated when the subject returns for re-screening:

- Viral screening (Hepatitis B and C, HIV, HTLV) if performed within 6 months of signing the new informed consent;

- Cancer screening assessments if performed within the timeframe stipulated in protocol Section 4.1.3 before signing the new informed consent; for fecal occult blood test, a negative result within 12 months of signing the new informed consent will not need to be repeated;
- Ophthalmological examination if performed within 3 months of signing the new informed consent;
- Target foot x-ray if performed within 6 months of signing the new informed consent and the subject has not sustained any new trauma to the foot

All other screening assessments will need to be repeated.

### 3.4.6. TREATMENT AUTHORIZATION

After providing written informed consent, potential study participants will undergo screening assessments. If the subject meets all inclusion criteria and none of the exclusion criteria, the subject will be assigned to study treatment using the IWRS. Refer to the IWRS manual for instructions.

### 3.4.7. RANDOMIZATION AND BLINDING

A randomization schedule with subjects allocated to VM202 (treatment) or placebo (control) in a 2:1 ratio will be used.

The Pharmacist will review the subject's treatment allocation and assigned kit number in IWRS. All documents related to investigational product and treatment allocation will be kept in a secure location with access limited to Pharmacy personnel responsible for preparing the syringes with assigned study treatment.

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

This is a double-blind study. The patients, Investigators, study site staff, or Sponsor or any of the Sponsor's representatives or vendors will not know the assigned treatment. Blinding will be achieved by having the study medication (VM202) prepared by the study pharmacist or designee. Reconstituted VM202 is indistinguishable from VM202 vehicle (placebo). The site pharmacist or designee prepares the vials according to the instructions. The site pharmacist or designee and select individuals at the CRO (but excluding blinded study monitors and the blinded clinical trial manager) will be unblinded to the treatment assignments. The subject and study personnel, including core labs, principal investigator, co-investigators, study coordinators, study monitors, data managers, and the clinical trial manager will remain blinded until all data have been entered into the database and the database is locked.

IN CASE OF EMERGENCY ONLY, i.e., SERIOUS ADVERSE EVENT (SAE) AND ONLY WHEN THIS INFORMATION INFLUENCES THE SUBJECT'S

MANAGEMENT AND WHEN KNOWLEDGE OF THE TREATMENT ASSIGNMENT IS ESSENTIAL TO THE WELFARE OF THE PATIENT, the Investigator or designee may request unblinding of that patient. Whenever feasible, the Sponsor (or the Sponsor's representative) should be consulted in advance of breaking the blind for any patient. In any case, the Sponsor (or the Sponsor's representative) must be notified of the unblinding, and the Investigator or designee will document the reason(s) necessary to break the blind for any patient. Complete instructions on this process are detailed in the Study Reference Manual (VMNHU-003 Subject Emergency Unblinding Communication Plan).

### 3.4.8. DAY 0 – 1ST INJECTIONS

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

The first assessment will entail:

- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume)
    - If eligibility is confirmed, the blinded study coordinator will randomize the subject using IWRS and notify the pharmacist or his/her representative to prepare the randomly assigned study medication.
    - If the subject is no longer eligible, the subject will exit the study and will be designated a screen failure.
    - If a subject withdraws from the study after being randomized but prior to being dosed, the subject will be designated early terminated in IWRS. However, because the subject has not received any study drug, no Early Termination Visit will be conducted.

If the subject is confirmed to be eligible per inclusion criterion #5 and exclusion criterion #4, the following procedures will be performed prior to injection:

- Vital signs
- Concomitant medications
- Serum chemistry and hematology
- HbA1c
- Serum HGF
- Copies of VM202 in whole blood
- ABI
- TBI
- $TcPO_2$ (as a sub-study at 3 -10 sites)
- Completion of CWIQ

#### 3.4.8.2. 1ST DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in the ipsilateral calf of the affected foot with the target ulcer will be administered.

#### 3.4.8.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

The following procedures will be performed 1-3 hours post injection:

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

### 3.4.9. WOUND ASSESSMENT AND DRESSING CHANGES AFTER DAY 0

Following Day 0, subjects will come in once a week for dressing change and wound evaluation. If a study visit is already scheduled for that week, the dressing change and wound evaluation will occur as part of the study visit.
At these visits, the following assessments will be performed:

- Documentation of target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Vital signs (except for weight)
- Concomitant medications
- Injection site assessment (visits prior to Day 60)
- Adverse event assessment

### 3.4.10. DAY 14 ± 3 DAYS – 2ND INJECTIONS

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

The following procedures will be performed prior to injection:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

#### 3.4.10.2. 2ND DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in the ipsilateral calf of the affected foot with the target ulcer will be administered.

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

The following procedures will be performed 1-3 hours post injection:

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

### 3.4.11. DAY 28 ± 3 DAYS – 3RD INJECTIONS

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

The following procedures will be performed prior to injection:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum HGF
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

#### 3.4.11.2. 3RD DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in the ipsilateral calf of the affected foot with the target ulcer will be administered.

#### 3.4.11.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

The following procedures will be performed 1-3 hours post injection:

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

### 3.4.12. DAY 42 ± 3 DAYS – 4TH INJECTIONS

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

The following procedures will be performed prior to injection:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum chemistry and hematology
- Copies of VM202 in whole blood
- Injection site assessment
- Adverse event assessment

#### 3.4.12.2. 4TH DOSE OF VM202 OR PLACEBO

Sixteen (16) IM injections of randomly assigned study medication in the ipsilateral calf of the affected foot with the target ulcer will be administered.

#### 3.4.12.3. POST-INJECTION (2 HOURS ± 1 HOUR POST INJECTION)

The following procedures will be performed 1-3 hours post injection:

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

### 3.4.13. DAY 60 ± 3 DAYS

The following procedures will be performed:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Copies of VM202 in whole blood
- Serum HGF
- Injection site assessment
- Adverse event assessment

### 3.4.14. DAY 74 ± 3 DAYS

The following procedures will be performed:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Adverse event assessment

### 3.4.15. DAY 90 ± 7 DAYS

The following procedures will be performed:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum chemistry and hematology
- Copies of VM202 in whole blood
- Serum HGF
- Adverse event assessment

### 3.4.16. DAY 120 ± 7 DAYS

The following procedures will be performed:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum chemistry and hematology
- HbA1c
- ABI
- TBI
- $TcPO_2$ (as a sub-study at 3 -10 sites)
- CWIQ
- Adverse event assessment

### 3.4.17. DAY 210 ± 14 DAYS

The following procedures will be performed:

- Retinal fundoscopy
- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum chemistry and hematology
- HbA1c
- ABI
- TBI
- $TcPO_2$ (as a sub-study at 3 -10 sites)
- CWIQ
- Adverse event assessment

### 3.4.18. CONFIRMATION OF ULCER HEALING

If the ulcer heals, healing must be confirmed 14 days (± 5 days) after healing was first reported. This visit may coincide with a pre-specified visit or may require an unscheduled visit:

- Concomitant medications
- Vital signs (except for weight)
- Documentation of the healed ulcer (photograph)
- Injection site assessment (if visit occurs prior to Day 60)
- Adverse event assessment

## 3.5. STUDY COMPLETION

### 3.5.1. COMPLETED SUBJECTS

Each subject in the study will be considered completed when all assessments through 7 months have been performed in accordance with the study protocol.

### 3.5.2. DISCONTINUED SUBJECTS

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

Possible reasons for study discontinuation include the following:

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

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

Additional subjects may be enrolled if subjects discontinue prior to the 4 Month visit in order to achieve a 300-subject dataset with 4-month data.

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

Subjects that withdraw after receiving any treatment injections but prior to study completion will undergo the following, if possible:

- Vital signs
- Concomitant medications
- Documentation of the target ulcer (photograph and measurements of surface area, depth, perimeter and volume) before and after debridement.
- Serum chemistry and hematology
- Serum HGF if discontinued prior to Day 90
- Copies of VM202 in whole blood if discontinued prior to Day 90
- Injection site reaction assessment if discontinued prior to Day 60
- Adverse event assessment

In case of a subject lost-to-follow-up, the investigator/designee must do his/her best to contact the subject (by phone or letter) at least twice. If no response is obtained from the subject, the investigator is encouraged to contact one of the subject's

relatives or his/her general practitioner. Documentation of these contacts must be recorded in the subject medical chart. It can be, for instance, the acknowledgement of receipt of a letter sent to the subject.

### 3.5.3. PREMATURE STUDY TERMINATION

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

## 3.6. INVESTIGATIONAL DRUG PRODUCT AND ACCOUNTABILITY

### 3.6.1. INVESTIGATIONAL DRUG PRODUCT

VM202 is a DNA plasmid containing a novel genomic cDNA hybrid human hepatocyte growth factor (HGF) coding sequence (HGF[redacted]) expressing two isoforms of HGF, [redacted] The key feature of HGF[redacted] 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 [redacted] base pairs, a [redacted] enhancer / promoter, a growth hormone [redacted] terminator sequence, [redacted] originator, and [redacted] resistance gene, on a [redacted] backbone.

VM202 is supplied in a sterile glass vial containing [redacted] study product. VM202 should be stored in a refrigerator at temperatures between 2°C and 8°C in an appropriately locked room accessible only to the pharmacist, or a duly designated person. Since VM202 does not contain preservatives, opened vials of VM202 and VM202 reconstituted with WFI must be used within 12 hours. A complete description of test article administration can be found in Appendix 7.

### 3.6.2. PLACEBO

The placebo will be sterile VM202 vehicle. Components of VM202 vehicle are provided in Table 5. VM202 excipients are supplied in a sterile glass vial in liquid form. Each vial is only to be used for one subject. Visually, VM202 vehicle is indistinguishable from reconstituted VM202.

Table 5. Components of VM202 Vehicle

| COMPONENT | FUNCTION | COMPOSITION |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

### 3.6.3. PRODUCT ACCOUNTABILITY

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

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

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

### 3.6.4. DOSE AND ADMINISTRATION

VM202 is supplied in a sterile glass vial containing [redacted] study product. Before administration, it will be reconstituted with [redacted] by the study pharmacist for a final VM202 concentration of 0.5 mg / mL. Each reconstituted vial is only to be used for one subject. The VM202 arm will receive only VM202 injections. The placebo group will receive only VM202 vehicle injections. All subjects will receive 16 injections in ipsilateral calf of the affected foot with the target ulcer at each injection visit (Days 0, 14, 28 and 42). A complete description of test article administration can be found in Appendix 7.

### 3.7. PRIOR AND CONCOMITANT MEDICATION

All concomitant medications (taken within 60 days of the first injection) will be recorded at each study visit. For each medication taken, the following information will be collected:

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

## 4. EXAMINATIONS AND EVALUATIONS

### 4.1. EVALUATIONS CONDUCTED AT BASELINE ONLY

#### 4.1.1. MEDICAL HISTORY

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

The Investigator will perform an especially detailed assessment of past diabetes and PAD history to include all events and interventions prior to study enrollment. Care should be taken to exclude ulcers due vasculitis, pyoderma gangrenosum, necrobiosis lipoidica, hydrostatic pressure/venous insufficiency, any neoplasms (basalioma, Kaposi's sarcoma, squamous cell carcinoma etc.), or a burn.

#### 4.1.2. PHYSICAL EXAM

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

#### 4.1.3. CANCER SCREENING

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

1. Cervical Cancer Screening - Papanicolaou (PAP) smear
   - Women < 21 years – no screening required
   - Women that have undergone a complete hysterectomy – no screening required
   - Women between the ages of 21 and 65 (inclusive), testing within the last 3 years
   - Women > 65 years old with regular screening within the last 10 years with normal results – no screening required. Any abnormal finding in the past 10 years requires screening at study entry.

2. Breast Cancer Screening (women only) - mammogram
   - Women between the ages of 45 and 54 (inclusive) – normal findings within one year
   - Women ≥ 55 – normal findings within 2 years

3. Lung Cancer Screening - For subjects ≥ 55 years and ≤ 74 years: low dose chest CT scan (LDCT w/o contrast) conducted within 3 months prior to signing the informed consent form **IF** the subject has a ≥ 30 pack year smoking history **AND** is still smoking **or** quit within the last 15 years. If results are not available, screening needs to be performed.

   A pack year is number of cigarette packs smoked per day multiplied by the number of years the subject has smoked (e.g., someone who smoked a pack of cigarettes per day for 30 years has a 30 pack-year smoking history, as does someone who smoked 2 packs a day for 15 years).

4. Colon Cancer - For subjects ≥ 50 years: fecal occult blood test. A positive fecal occult blood test requires follow-up testing which is beyond the scope of this study. If follow-up testing rules out cancer, the subject will be able to participate in the study if the subject is still interested.

   Subjects with a medical history or family history of colon cancer in any first-degree relative must have documentation of a negative colonoscopy performed within the past 12 months.

#### 4.1.4. VIRAL SCREENING

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

#### 4.1.5. FOOT X-RAY

X-rays of the target foot will be taken in two projections: dorsal-plantar (DP) and oblique. These can be done under weight bearing or non-weight bearing conditions, at the investigator's discretion.

#### 4.1.6. 12-LEAD EKG

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

#### 4.1.7. PREGNANCY TEST (WOMEN OF CHILDBEARING POTENTIAL ONLY)

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

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

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

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### 4.2. EVALUATIONS CONDUCTED THROUGHOUT THE STUDY

#### 4.2.1. DOCUMENTATION OF TARGET ULCER

At each visit at which the target ulcer is present, a photograph of the ulcer will be taken before and after debridement. Measurements of the surface area, depth, perimeter and volume of the target ulcer will be performed. Instructions can be found in Appendix 5.

#### 4.2.2. RETINAL FUNDOSCOPY

Proliferative retinopathy, defined as the presence of new proliferating blood vessels (neovascularization) arising from the retina or optic disc and growing on the retinal surface or into the vitreous cavity, will be assessed by retinal fundoscopy at Screening for eligibility and repeated at Day 210. Retinal fundoscopy must be performed by an ophthalmologist within 3 months of Screening.

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

#### 4.2.3. CONCOMITANT MEDICATIONS

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

### 4.2.4. VITAL SIGNS

Vital signs consisting of blood pressure (while subject is sitting), temperature, weight, heart rate, and respiratory rate will be measured and recorded at Screening and at every study visit through the 7-month follow-up. Weight will not be measured during Wound Assessment and Dressing Change or Confirmation of Wound Closure visits.

### 4.2.5. SERUM CHEMISTRY, HEMATOLOGY AND HBA1C

Evaluation of serum chemistry and hematology will be conducted at Screening, Day 0, Day 42, Day 90, Day 120 (4 months) and Day 210 (7 months). Evaluations will be conducted by a local laboratory at each site.

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

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

HbA1c will be determined at Screening, Day 0, Day 120 (4 months) and Day 210 (7 months) at a local laboratory at each site. Laboratory testing by visit is provided in Appendix 1.

### 4.2.6. SERUM HGF

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 28, Day 60, and Day 90.

A minimum 6 cc blood draw will be taken at each time point. Allow blood to clot for 30 – 60 minutes at room temperature then centrifuge for 10 minutes at 1000 x g. Divide the isolated serum into six (6) equal aliquots of ~0.3 mL each. (0.5-mL plastic storage tubes provided). Samples should be labeled with study number, subject ID, draw date and time, and visit interval (i.e., Day 0, Day 28, Day 60 or 90). Samples will be maintained in a cooler containing dry ice and then placed in a ≤ -65°C freezer until shipped for analysis.

At the request of the Sponsor or its designee, serum HGF samples will be batched with VM202 samples and shipped in a special container with temperature tracking recorder to [redacted] for analysis.

[redacted]

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

### 4.2.7. Copies of VM202 in Whole Blood

The number of copies of VM202 in whole blood will be determined by PCR at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 28 (pre-injection, and 2 hours [± 1 hour] post injection), Day 42 (pre-injection, and 2 hours [± 1 hour] post injection), Day 60, and Day 90.

Six (6) cc of whole blood will be collected in EDTA-coated tubes, inverted >5 times and transferred to plastic sterile and or RNase and DNase free vials of ~0.6 – 1 cc aliquots each for a total of 5 aliquots per time point. These will be maintained in a ≤ --65°C freezer until shipped for analysis. Samples should be labeled with study number, subject ID, draw date and time, and visit interval (i.e., Day 0 pre, Day 0 post, Day 14 pre, Day 14 post, Day 28 pre, Day 28 post, Day 42 pre, Day 42 post, Day 60, and Day 90).

At the request of the Sponsor or its designee, VM202 samples will be batched with serum HGF samples and shipped in a special container with temperature tracking recorder to [redacted] analysis.

[redacted]

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

### 4.2.8. Ankle Brachial Index (ABI), Toe Brachial Index (TBI) and Toe Pressure in the Target Limb

Ankle-Brachial Index (ABI) and Toe Brachial Index (TBI) will be determined in the target limb at Screening, before the first treatment (injection) on Day 0, Day 120 (4 months) and Day 210 (7 months). Toe pressure will be determined at Screening in the target limb. Instructions can be found in Appendix 6.

### 4.2.9. Transcutaneous Oxygen Pressure ($TcPO_2$)

Transcutaneous oxygen pressure ($TcPO_2$) will be measured before the first treatment (injection) on Day 0, Day 120, and Day 210 Visits as a sub-study at 3 -10 sites. $TcPO_2$ 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.

### 4.2.10. CARDIFF WOUND IMPACT QUESTIONNAIRE (CWIQ)

The CWIQ is a measure designed to assess the impact of ulcers on patient health-related quality of life (HRQoL). There is a total of 3 domains:

- Social life (14 items, graded on a 5-point Likert scale)
- Well-being (7 items, graded on a 5-point Likert scale)
- Physical symptoms and daily living (24 items, graded on a 5-point Likert scale)

In addition, there are Overall Quality of Life questions (2 items graded on a 11-point Likert scale).

The CWIQ will be completed by the subject at Day 0, Day 120 (4 months) and Day 210 (7 months). The score data will be summarized based on the CWIQ scoring instructions. The questionnaire can be found in Appendix 8.

### 4.2.11. INJECTION SITE REACTION ASSESSMENT

Local injection sites reactions will be assessed on Day 0 post injection, Day 14 pre and post injection, Day 28 pre and post injection, Day 42 pre and post injection, Day 60, and at each wound assessment/dressing change visit after the first injection visit and prior to Day 60. Injection site reactions will be reported on the Injection Site Adverse Event form. The location (calf area) and temporal relationship to the most recent study injections will determine whether the event is an injection site reaction or adverse event.

Table 6. Injection Reaction Assessment

| ADVERSE EVENT | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 | GRADE 5 |
|---|---|---|---|---|---|
| Injection site reaction | Pain, itching, erythema | Pain or swelling, with inflammation or phlebitis | Ulceration or necrosis that is severe; operative intervention indicated | | |
| Ulceration | | Superficial ulceration < 2 cm size; local wound care; medical intervention indicated | Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen) | Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting | Death |

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

# 5. EVALUATION OF ADVERSE EVENTS

## 5.1. DEFINITIONS

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

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

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

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

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

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization (admission to hospital with a stay > 24 hours) or prolongation of hospitalization which is not specifically required by the protocol or is elective. Hospitalization for elective treatment of a pre-existing condition that has not worsened is not considered to be an AE. Hospital admissions or surgery planned before any study drug is administered are not to be considered AEs unless there is unexpected deterioration of the subject's condition after study drug treatment (e.g., surgery must be performed earlier than planned).
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

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

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

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

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

## 5.2. ASSESSMENT OF ADVERSE EVENTS (AEs)

All AEs, regardless of severity, occurring following the first study drug administration and the 7-month follow-up visit of the study by a subject must be recorded in the AE form of the EDC. Any events occurring before the injections will be added to the medical history. This will include the following information:

- Description of the AE
  Every effort must be made to report the underlying condition or unifying diagnosis for the event. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when possible. Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE. In addition, AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause (i.e., a "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record; events occurring secondary to the primary event should be described in the narrative description of the case [e.g., orthostatic hypotension → fainting and fall to floor → head trauma → neck pain; the primary AE is orthostatic hypotension]).
- Date of onset
- Duration
- Frequency
- Severity
- Seriousness (yes/no)
- Treatment
- Outcome
- Relationship to study medication, injection procedure and/or underlying disease

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

### 5.2.1. AE CAUSALITY

The study investigator will determine whether an AE is related or unrelated to study medication, the procedure (IM 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 worst intensity of the AE/SAE will be reported using the following criteria:

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

## 5.3. REPORTING/RECORDING OF AEs

Throughout the course of the study, all efforts will be made by the investigator to remain alert to possible AEs. The first concern will be the safety of the subject, and for providing appropriate medical intervention. The period of observation for collection of AEs occurs following the first study drug administration until the 7-month follow-up visit. Any AE should be recorded in the EDC. Any events occurring before the injections will be added to the medical history.

## 5.4. REPORTING / RECORDING OF SAEs

### 5.4.1. INVESTIGATOR'S RESPONSIBILITY

SAEs will be recorded following the first study drug administration through the 7-month follow-up visit. Any serious adverse event that occurs during this investigation, whether or not related to the study medication, must be reported as soon as possible but no later than 3 working days after the investigator first learns of the event to the Sponsor and CRO. However, if the EDC is inaccessible, then in order to report an SAE within the required timeframe, a paper SAE form must be used and submitted to [redacted] or scanned and emailed to [redacted] Once the EDC becomes accessible, the data must be entered into EDC as per standard procedure. If secondary or tertiary diagnoses occur concurrent to the primary SAE (e.g., during a hospitalization period), these additional diagnoses should be recorded in the follow-up reports to the index SAE.

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

The Investigator will be required to provide complete information (including the Investigator's opinion of the relationship of the SAE to the study medication) concerning each SAE to the CRO and Sponsor within 5 working days of first learning of the event. The investigator or designee will provide copies of related source documentation such as results/reports, hospitalization records, and other relevant information involving the SAE.

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

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

### 5.4.2. SPONSOR'S RESPONSIBILITY

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

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

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

# 6. STATISTICAL METHODS

## 6.1. SAMPLE SIZE CALCULATION

The sample size for the primary efficacy endpoint is calculated based on the hypothesis for the primary efficacy endpoint. The primary study endpoint is the proportion of subjects with a target wound closure at 4 months.

The statistical hypotheses for the first primary efficacy endpoint are:

$H_0$: $P_t = P_c$ versus $H_a$: $P_t \neq P_c$

where $P_t$ and $P_c$ are the proportions of subjects with a target wound closure by the 4-month follow-up for the VM202 and placebo groups, respectively.

The hypothesis testing will be at two-sided 0.05.

Based on prior VM202 studies, the percentage of subjects achieving complete wound closure by the 4-month (i.e., 4-month responder rate) for VM202 (treatment arm) is assumed to range from 50% to 60%, and that for the Placebo group is assumed to range from 20% to 30%. Table 7 below summarizes the statistical power for a sample size of 200 VM202 and 100 Placebo subjects based on Fisher's exact test with a two-sided significance level of 0.05 for the statistical hypothesis.

Table 7. Statistical power by estimated responder rates for Treatment ($p_t$) and Control ($p_c$) arms

| $p_t$ | $p_c$ | Statistical Power |
|---|---|---|
| 0.50 | 0.20 | >.999 |
| 0.50 | 0.25 | 0.985 |
| 0.50 | 0.30 | 0.898 |
| 0.55 | 0.20 | >.999 |
| 0.55 | 0.25 | 0.999 |
| 0.55 | 0.30 | 0.982 |
| 0.60 | 0.20 | >.999 |
| 0.60 | 0.25 | >.999 |
| 0.60 | 0.30 | 0.998 |

Except for the assumption of $p_t = 0.50$ and $p_c = 0.30$, the statistical power for all assumptions of $p_t$ and $p_c$ is > 0.95. For the assumption of $p_t = 0.50$ and $p_c = 0.30$, the statistical power is about 90%.

## 6.2. ANALYSIS POPULATION

### 6.2.1. INTENT-TO-TREAT POPULATION (ITT)

This subset includes all subjects who are randomized. All baseline characteristics will be summarized based on ITT. Subjects in the ITT will be analyzed according to

original treatment assignment, regardless of actual treatment received. The primary analyses of the primary efficacy endpoint will be based on this ITT population.

### 6.2.2. SAFETY POPULATION

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

### 6.2.3. MODIFIED ITT (MITT) POPULATION

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

- Received any study drug injections
- Had at least one post-baseline wound assessment
- Have no safety or efficacy parameter results prior to dosing on Day 0 that would have made the subject ineligible for participation if the results had been known or disclosed at Screening. This determination will be made in a blinded fashion by the Clinical Data Review Committee (CDRC, members to be determined) prior to analyses.

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

### 6.2.4. PER PROTOCOL (PP) POPULATIONS

#### 6.2.4.1. PP1

The first Per Protocol (PP1) population is a subset of mITT. It includes all mITT subjects who meet the following criterion:

- Have not used the protocol-specified prohibited concomitant medications or treatments such as COX-2 inhibitor drug(s) or non-specific COX-1/COX-2-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs), anti-VEGF agents (e.g., Lucentis®, Avastin®, Eylea®), steroids (except inhaled steroids or ocular steroids), Regranex® gel (becaplermin), larval debridement, skin substitutes (e.g., Dermagraft®, Apligraf®), hyperbaric oxygen therapy, hydrotherapy, negative pressure wound therapy, or electrical stimulation therapy which may affect the wound healing. The use and effect of protocol-specified prohibited concomitant medications will be determined by the CDRC in a blinded fashion prior to analyses.

#### 6.2.4.2. PP2

The second Per Protocol population is a further subset of the mITT. It includes all subjects in the first PP population who also meet all of the following criteria:

- Meets major protocol eligibility criteria determined by the CDRC in a blinded fashion prior to analyses
- Received all injections based on the randomized treatment.
- Maintained standard of care for their wounds for the duration of the study, as follows:
  - Surgical debridement of necrotic tissue or devitalized tissue
  - Use of appropriate off-loading when ambulating
  - Maintenance of moist wound environment
- Additional criteria, if any, established by the CDRC before unblinding of the randomization code.

The PP populations will be used in the sensitivity analyses for the primary efficacy endpoint.

## 6.3. STUDY ENDPOINTS

### 6.3.1. PRIMARY ENDPOINT

The primary study endpoint is the proportion of subjects with a target wound closure by the 4-month follow-up. Complete wound closure is defined as skin re-epithelialization without drainage or dressing (primary endpoint), confirmed at a second scheduled or unscheduled visit two weeks (14 ± 5 days) later (secondary endpoint). Active and placebo arms will be compared to determine treatment effect.

### 6.3.2. OTHER ENDPOINTS

Other exploratory endpoints will include:

- Time to complete wound closure of foot ulcer
- Proportion of subjects with a target wound closure prior to or at 7 months
- Percent change in wound volume at 2 months, 2.5 months, 3 months, 4 months, and 7 months
- Percent change in wound perimeter, area and wound depth at 2 months, 2.5 months, 3 months, 4 months, and 7 months
- Proportion of subjects with formation of new ulcers on the target foot at 2 months, 2.5 months, 3 months, 4 months, and 7 months
- Time to the major amputations
- Time to the minor amputation
- Change in ABI at 4 months, and 7 months
- Change in TBI at 4 months, and 7 months
- Change in $TcPO_2$ at 4 months, and 7 months

- Change in each domain score (quality of life, social life, well-being, physical symptoms and daily living) of CWIQ from Day 0 at 4 months and 7 months

### 6.3.3. SAFETY

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

### 6.3.4. PHARMACOKINETICS

HGF serum levels will be determined immediately pre-treatment on Day 0, immediately pre-treatment on Day 28, on Day 60 and Day 90.

The number of copies of VM202 in whole blood will be determined at Day 0 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 14 (pre-injection, and 2 hours [± 1 hour] post injection), Day 28 (pre-injection, and 2 hours [± 1 hour] post injection), at Day 42 (pre-injection, and 2 hours [± 1 hour] post injection), Day 60 and Day 90.

### 6.3.5. DATA SAFETY MONITORING BOARD (DSMB) AND INTERIM ANALYSIS

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

An interim futility analysis will be performed by an independent statistician when 50% of subjects who receive study drug injections reach the 4-month follow-up visit. The analysis will concern only the primary endpoint data and will present the percentages of subjects with complete wound closure by the 4-month follow-up by treatment group and the conditional power for success at the final analysis. The study will not be stopped due to the possible finding of VM202 efficacy superiority based on the interim analysis, so the significance level for the final analysis remains at 0.05. Details of the interim analysis are provided in the Statistical Analysis Plan.

## 6.4. SUBJECT CATEGORIZATION

**Screen Failure** - Any subject who was consented and entered into the Screening process appropriately, but subsequently did not meet the entry criteria in order to be treated. Subjects who fail screening will not be followed for safety or efficacy

assessment, and no other study procedures will be performed. Screen failures will be replaced.

**Evaluable Subject** - Any subject who received the study drug.

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

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

## 7. ACCESS TO STUDY DOCUMENTS AND STUDY MONITORING

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

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

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

During the study, the clinical monitor will visit the study facilities regularly, and utilize telephone and written communications on an ongoing basis to maintain current knowledge of the study. During periodic visits to the study site, the monitor will review source documents and worksheets to verify the accuracy and completeness of the information provided on the case report forms (CRFs). Study worksheets and source documents must contain all data provided on the CRFs. All data generated during this study and the study worksheets/source documents from which they originated are subject to inspection by the Sponsor or its representatives, the FDA and other regulatory agencies.

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

## 8. QUALITY CONTROL AND ASSURANCE

The Sponsor employees and/or their contracted representatives utilize Standard Operating Procedures (SOPs) designed to ensure that research procedures and documentation are

consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and Good Clinical Practice guidance.

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

## 9. INSTITUTIONAL REVIEW BOARD

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

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

The investigator is responsible for notifying the IRB of any serious adverse events as required by the IRB. A copy of the notification must be forwarded to the CRO.

Status reports must be submitted to the IRB at least once a year (or more frequently as required by the IRB) and the IRB must be notified of completion or termination of the study. A final report must be provided to the IRB and the Sponsor within 2 months of study completion or termination. This report should include: any deviations from the protocol, the number of participants evaluated, the number of participants who withdrew or were withdrawn and the reasons for withdrawal, any significant adverse events and the investigator's summation of the study.

## 10. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC)

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

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

## 11. INFORMED CONSENT PROCESS

It is the responsibility of the investigator or his/her qualified designee to inform each subject, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. A sample informed consent form containing the required elements of informed consent is provided in Appendix 2. Any changes made to this sample must be approved by the Sponsor or its designee, prior to submission to an IRB. After approval by the Sponsor or its designee, the informed consent must be submitted to and approved by an IRB. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the informed consent form. The person executing the consent must also sign and date the final consent form page. One original informed consent form is to be retained by the study site and a copy is to be given to the subject. The informed consent process must be documented in the subject's medical record.

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

## 12. CONFIDENTIALITY

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

The investigator acknowledges that any and all information acquired from the Sponsor or its designee or developed or acquired in connection with the study are strictly confidential. The investigator will not disclose any confidential information to any third party nor use confidential information for any purpose without first obtaining the consent of Sponsor in

writing. Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his/her center, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

## 13. PROTOCOL AMENDMENTS

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

## 14. DATA MANAGEMENT

Electronic data capture (EDC) will be utilized for this study. Study worksheets will be provided by the Sponsor or its designee to the site before data collection. In order to facilitate data entry, the worksheets coincide with the data entry pages in the EDC system. The design of the data entry screens will follow the same flow as the provided worksheets in order to insure minimal issues during data entry. The use of worksheets is optional; sites may elect to use other source documents that contain data recorded on the CRF. Note, study worksheets and/or source documents must contain all data provided on the CRFs. If used, appropriate worksheets will be completed and initialed or signed where indicated at each examination. All worksheets will be completed in a legible manner in black/blue ink. Any corrections to the worksheets will be made by drawing a single line through the incorrect entry, recording the correct information, and initialing and dating the change.

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

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

All clinical data generated in the study will be submitted to the Sponsor or designated CRO for quality assurance review and statistical analysis. All worksheets and data entered into the EDC system will be reviewed for completeness and evident recording errors will be

rectified by contact with the appropriate clinical site. Computerized data checks will be used to identify unusual data entries for verification prior to statistical analysis.
To minimize the amount of missing data, investigators will be trained on the deleterious effect that missing data have on trial integrity and credibility and that missing data could diminish the scientific value of all subjects' altruistic contributions.

## 15. RECORD KEEPING AND RETENTION

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

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

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

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

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

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

All study-related records must be maintained for at least 2 years after a marketing application (NDA/BLA) is approved for the drug; or if an application is not approved for the drug, until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified. The Sponsor will notify the principal investigator when records are no longer needed. The investigator will not discard any records without notifying the Sponsor. If the principal investigator moves from the current investigational site, the Sponsor should be notified of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

## 16. INVESTIGATOR FINAL REPORT

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

## 17. STUDY REPORT AND PUBLICATION

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

Sponsor. At the end of the study, a clinical study report will be written by the Sponsor or its designee.

## 18. REFERENCES


1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA : the journal of the American Medical Association 2005;293:217-28.
2. Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society 2009;17:763-71.
3. Lazarus GS, Cooper DM, Knighton DR, Percoraro RE, Rodeheaver G, Robson MC. Definitions and guidelines for assessment of wounds and evaluation of healing. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society 1994;2:165-70.
4. Chronic cutaneous ulcer and burn wounds - developing products for treament. In: FDA, ed. FDA Guidance Document; 2006:22.
5. Peripheral arterial disease in people with diabetes. Diabetes care 2003;26:3333-41.
6. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747-55.
7. Althouse AD, Abbott JD, Forker AD, et al. Risk Factors for Incident Peripheral Arterial Disease in Type 2 Diabetes: Results From the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) Trial. Diabetes care 2014;37:1346-52.
8. Madanchi N, Tabatabaei-Malazy O, Pajouhi M, Heshmat R, Larijani B, Mohajeri-Tehrani MR. Who are diabetic foot patients? A descriptive study on 873 patients. Journal of diabetes and metabolic disorders 2013;12:36.
9. Brechow A, Slesaczeck T, Munch D, et al. Improving major amputation rates in the multicomplex diabetic foot patient: focus on the severity of peripheral arterial disease. Therapeutic advances in endocrinology and metabolism 2013;4:83-94.
10. Morbach S, Furchert H, Groblinghoff U, et al. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes care 2012;35:2021-7.
11. Hinchliffe RJ, Andros G, Apelqvist J, et al. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes/metabolism research and reviews 2012;28 Suppl 1:179-217.
12. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. Journal of the American Academy of Dermatology 2014;70:1 e-18; quiz 9-20.
13. Reiber GE, Raugi GJ. Preventing foot ulcers and amputations in diabetes. Lancet 2005;366:1676-7.
14. Greer N, Foman NA, MacDonald R, et al. Advanced wound care therapies for nonhealing diabetic, venous, and arterial ulcers: a systematic review. Annals of internal medicine 2013;159:532-42.
15. Lower extremity disease among persons aged > or =40 years with and without diabetes--United States, 1999-2002. MMWR Morbidity and mortality weekly report 2005;54:1158-60.
16. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Journal of vascular surgery 2007;45 Suppl S:S5-67.

17. Faglia E. Characteristics of peripheral arterial disease and its relevance to the diabetic population. The international journal of lower extremity wounds 2011;10:152-66.
18. Goodridge D, Trepman E, Sloan J, et al. Quality of life of adults with unhealed and healed diabetic foot ulcers. Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society 2006;27:274-80.
19. Snyder RJ, Hanft JR. Diabetic foot ulcers--effects on QOL, costs, and mortality and the role of standard wound care and advanced-care therapies. Ostomy/wound management 2009;55:28-38.
20. Winkley K, Sallis H, Kariyawasam D, et al. Five-year follow-up of a cohort of people with their first diabetic foot ulcer: the persistent effect of depression on mortality. Diabetologia 2012;55:303-10.
21. Lozano FS, Gonzalez-Porras JR, March JR, Lobos JM, Carrasco E, Ros E. Diabetes mellitus and intermittent claudication: a cross-sectional study of 920 claudicants. Diabetology & metabolic syndrome 2014;6:21.
22. Sargen MR, Hoffstad O, Margolis DJ. Geographic variation in Medicare spending and mortality for diabetic patients with foot ulcers and amputations. Journal of diabetes and its complications 2013;27:128-33.
23. Jude EB, Eleftheriadou I, Tentolouris N. Peripheral arterial disease in diabetes--a review. Diabetic medicine : a journal of the British Diabetic Association 2010;27:4-14.
24. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 2014;383:1068-83.
25. Pedersen BL, Baekgaard N, Quistorff B. Muscle mitochondrial function in patients with type 2 diabetes mellitus and peripheral arterial disease: implications in vascular surgery. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2009;38:356-64.
26. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. American journal of physiology Cell physiology 2004;287:C817-33.
27. Aldakkak M, Stowe DF, Heisner JS, Spence M, Camara AK. Enhanced Na+/H+ exchange during ischemia and reperfusion impairs mitochondrial bioenergetics and myocardial function. Journal of cardiovascular pharmacology 2008;52:236-44.
28. Di Marco E, Gray SP, Chew P, et al. Pharmacological inhibition of NOX reduces atherosclerotic lesions, vascular ROS and immune-inflammatory responses in diabetic Apoe(-/-) mice. Diabetologia 2014;57:633-42.
29. Alexiadou K, Doupis J. Management of diabetic foot ulcers. Diabetes therapy : research, treatment and education of diabetes and related disorders 2012;3:4.
30. Paumelle R, Tulasne D, Kherrouche Z, et al. Hepatocyte growth factor/scatter factor activates the ETS1 transcription factor by a RAS-RAF-MEK-ERK signaling pathway. Oncogene 2002;21:2309-19.
31. Hashiya N, Jo N, Aoki M, et al. In vivo evidence of angiogenesis induced by transcription factor Ets-1: Ets-1 is located upstream of angiogenesis cascade. Circulation 2004;109:3035-41.
32. Cooper CD, Newman JA, Gileadi O. Recent advances in the structural molecular biology of Ets transcription factors: interactions, interfaces and inhibition. Biochemical Society transactions 2014;42:130-8.

33. Gille J, Khalik M, Konig V, Kaufmann R. Hepatocyte growth factor/scatter factor (HGF/SF) induces vascular permeability factor (VPF/VEGF) expression by cultured keratinocytes. J Invest Dermatol 1998;111:1160-5.
34. Morishita R, Aoki M, Yo Y, Ogihara T. Hepatocyte growth factor as cardiovascular hormone: role of HGF in the pathogenesis of cardiovascular disease. Endocr J 2002;49:273-84.
35. Nakagami H, Morishita R, Yamamoto K, et al. Hepatocyte growth factor prevents endothelial cell death through inhibition of bax translocation from cytosol to mitochondrial membrane. Diabetes 2002;51:2604-11.
36. Trusolino L, Bertotti A, Comoglio PM. MET signalling: principles and functions in development, organ regeneration and cancer. Nature reviews Molecular cell biology 2010;11:834-48.
37. Ishihara N, Takagi N, Niimura M, et al. Inhibition of apoptosis-inducing factor translocation is involved in protective effects of hepatocyte growth factor against excitotoxic cell death in cultured hippocampal neurons. Journal of neurochemistry 2005;95:1277-86.
38. Ishigaki A, Aoki M, Nagai M, et al. Intrathecal delivery of hepatocyte growth factor from amyotrophic lateral sclerosis onset suppresses disease progression in rat amyotrophic lateral sclerosis model. Journal of neuropathology and experimental neurology 2007;66:1037-44.
39. Jin M, Yaung J, Kannan R, He S, Ryan SJ, Hinton DR. Hepatocyte growth factor protects RPE cells from apoptosis induced by glutathione depletion. Investigative ophthalmology & visual science 2005;46:4311-9.
40. Tulasne D, Foveau B. The shadow of death on the MET tyrosine kinase receptor. Cell death and differentiation 2008;15:427-34.
41. Kannan R, Jin M, Gamulescu MA, Hinton DR. Ceramide-induced apoptosis: role of catalase and hepatocyte growth factor. Free radical biology & medicine 2004;37:166-75.
42. Hashimoto N, Yamanaka H, Fukuoka T, et al. Expression of HGF and cMet in the peripheral nervous system of adult rats following sciatic nerve injury. Neuroreport 2001;12:1403-7.
43. Tsuchihara T, Ogata S, Nemoto K, et al. Nonviral Retrograde Gene Transfer of Human Hepatocyte Growth Factor Improves Neuropathic Pain-related Phenomena in Rats. Mol Ther 2008.
44. Kadoyama K, Funakoshi H, Ohya W, Nakamura T. Hepatocyte growth factor (HGF) attenuates gliosis and motoneuronal degeneration in the brainstem motor nuclei of a transgenic mouse model of ALS. Neuroscience research 2007;59:446-56.
45. Li M, Ona VO, Guegan C, et al. Functional role of caspase-1 and caspase-3 in an ALS transgenic mouse model. Science 2000;288:335-9.
46. Niimura M, Takagi N, Takagi K, et al. Prevention of apoptosis-inducing factor translocation is a possible mechanism for protective effects of hepatocyte growth factor against neuronal cell death in the hippocampus after transient forebrain ischemia. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2006;26:1354-65.
47. Bussolino F, Di Renzo MF, Ziche M, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol 1992;119:629-41.

48. Nakagami H, Kaneda Y, Ogihara T, Morishita R. Hepatocyte growth factor as potential cardiovascular therapy. Expert Rev Cardiovasc Ther 2005;3:513-9.
49. Gao YF, Ha XQ, Lu TD, Han JP. Effects of hepatocyte growth factor-mediated activation of Dll4-Notch-Hey2 signaling pathway. Chinese medical journal 2011;124:127-31.
50. Matsumoto K, Nakamura T. Emerging multipotent aspects of hepatocyte growth factor. J Biochem 1996;119:591-600.
51. Jayasankar V, Woo YJ, Pirolli TJ, et al. Induction of angiogenesis and inhibition of apoptosis by hepatocyte growth factor effectively treats postischemic heart failure. J Card Surg 2005;20:93-101.
52. van de Kamp J, Jahnen-Dechent W, Rath B, Knuechel R, Neuss S. Hepatocyte growth factor-loaded biomaterials for mesenchymal stem cell recruitment. Stem cells international 2013;2013:892065.
53. Le Goff A, Ji Z, Leclercq B, et al. Anti-apoptotic role of caspase-cleaved GAB1 adaptor protein in hepatocyte growth factor/scatter factor-MET receptor protein signaling. The Journal of biological chemistry 2012;287:35382-96.
54. D'Angelo F, Bernasconi E, Schafer M, et al. Macrophages promote epithelial repair through hepatocyte growth factor secretion. Clinical and experimental immunology 2013;174:60-72.
55. Xiao Z, Xi C. Hepatocyte growth factor reduces hypertrophy of skin scar: in vivo study. Advances in skin & wound care 2013;26:266-70.
56. Kawaida K, Matsumoto K, Shimazu H, Nakamura T. Hepatocyte growth factor prevents acute renal failure and accelerates renal regeneration in mice. Proceedings of the National Academy of Sciences of the United States of America 1994;91:4357-61.
57. Liu ML, Mars WM, Zarnegar R, Michalopoulos GK. Uptake and distribution of hepatocyte growth factor in normal and regenerating adult rat liver. Am J Pathol 1994;144:129-40.
58. Snyder RJ, Kirsner RS, Warriner RA, 3rd, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. Ostomy/wound management 2010;56:S1-24.

# APPENDICES

## TABLE OF APPENDICES

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

## SCHEDULE OF EVALUATIONS: BASELINE THROUGH ALL STUDY INJECTIONS

| PROCEDURE | Screening / Baseline (-45 D to -7 D) | Wound Assessments & Dressing Changes - Weekly†† | 1st Injection Day 0 | | 2nd Injection Day 14 ± 3 D | | 3rd Injection Day 28 ± 3 D | | 4th Injection Day 42 ± 3 D | | Confirmation of Ulcer Healing (14D ± 5D after visit in which ulcer was not measureable) | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pre-dose | Post-dose | Pre-dose | Post-dose | Pre-dose | Post-dose | Pre-dose | Post-dose | | |
| **Baseline Evaluation** | | | | | | | | | | | | |
| Informed Consent | ✓ | | | | | | | | | | | |
| Medical History | ✓ | | | | | | | | | | | |
| Physical Exam | ✓ | | | | | | | | | | | |
| Cancer screening† | ✓ | | | | | | | | | | | |
| Viral screening – HIV, HTLV, HBV, HCV | ✓ | | | | | | | | | | | |
| Foot x-ray | ✓ | | | | | | | | | | | |
| Retinal Fundoscopy | ✓ | | | | | | | | | | | |
| EKG | ✓ | | | | | | | | | | | |
| Urine Pregnancy test (women of childbearing potential only) | ✓ | | | | | | | | | | | |
| **Safety and Efficacy Parameters** | | | | | | | | | | | | |
| Vital Signs | ✓ | ✓* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* | ✓ |
| Concomitant Medications | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Photograph and measurement of ulcer in target leg | ✓ | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Serum Chemistry and hematology | ✓ | | ✓ | | | | | | ✓ | | | ✓ |
| ABI & TBI | ✓ | | ✓ | | | | | | | | | |
| Toe pressure | ✓ | | | | | | | | | | | |
| $TcPO_2$ | | | ✓ | | | | | | | | | |
| CWIQ | | | ✓ | | | | | | | | | |
| HbA1c | ✓ | | ✓ | | | | | | | | | |
| Study Injections | | | ✓ | | ✓ | | ✓ | | ✓ | | | |
| Copies of VM202 in whole blood | | | ✓ | ✓** | ✓ | ✓** | ✓ | ✓** | ✓ | ✓** | | ✓[1] |
| Serum HGF | | | ✓ | | | | ✓ | | | | | ✓[1] |
| **Treatment** | | | | | | | | | | | | |
| Injection site reaction assessment | | ✓[3] | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓[3] | ✓[2] |
| Adverse Events | | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

† Cancer screening: see Section 3.4.3

†† Ulcer assessment and dressing changes to be conducted once weekly. Confirmation of ulcer healing to be conducted 2 weeks (± 5 days) after visit in which ulcer is not measureable

* Excluding weight

** 2 hours after injection (± 1 hour)

1 If withdrawal occurred before Day 90 Visit

2 If withdrawal occurred before Day 60 Visit

3 If visit occurs after first injection visit and before Day 60

## SCHEDULE OF EVALUATIONS: POST STUDY INJECTIONS THROUGH STUDY COMPLETION

| PROCEDURE | Wound Assessments & Dressing Changes - Weekly†† | Day 60 ± 3 D | Day 74 ± 3 D | Day 90 ± 7 D | Day 120 ± 7 D | Day 210 ± 14 D | Confirmation of Ulcer Healing (14D ± 5D after visit in which ulcer was not measureable) | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|
| **Baseline Evaluation** | | | | | | | | |
| Informed Consent | | | | | | | | |
| Medical History | | | | | | | | |
| Physical Exam | | | | | | | | |
| Cancer screening† | | | | | | | | |
| Viral screening – HIV, HTLV, HBV, HCV | | | | | | | | |
| Foot x-ray | | | | | | | | |
| Retinal Fundoscopy | | | | | | ✓ | | |
| EKG | | | | | | | | |
| Urine Pregnancy test (women of childbearing potential only) | | | | | | | | |
| **Safety and Efficacy Parameters** | | | | | | | | |
| Vital Signs | ✓* | ✓ | ✓ | ✓ | ✓ | ✓ | ✓* | ✓ |
| Concomitant Medications | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Photograph and measurement of ulcer in target leg | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Serum Chemistry and hematology | | | | ✓ | ✓ | ✓ | | ✓ |
| ABI & TBI | | | | | ✓ | ✓ | | |
| $TcPO_2$ | | | | | ✓ | ✓ | | |
| CWIQ | | | | | ✓ | ✓ | | |
| HbA1c | | | | | ✓ | ✓ | | |
| Study Injections | | | | | | | | |
| Copies of VM202 in whole blood | | ✓ | | ✓ | | | | ✓[1] |
| Serum HGF | | ✓ | | ✓ | | | | ✓[1] |
| **Treatment** | | | | | | | | |
| Injection site reaction assessment | ✓[3] | ✓ | | | | | ✓[3] | ✓[2] |
| Adverse Events | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

† Cancer screening: see Section 3.4.3
†† Ulcer assessment and dressing changes to be conducted once weekly. Confirmation of ulcer healing to be conducted 2 weeks (± 5 days) after visit in which ulcer is not measureable
* Excluding weight
** 2 hours after injection (± 1 hour)
1 If withdrawal occurred before Day 90 Visit
2 If withdrawal occurred before Day 60 Visit
3 If visit occurs after first injection visit and before Day 60

## SCHEDULE OF LABORATORY EVALUATIONS

| Parameters | Screen | Day 0 | Day 14 | Day 28 | Day 42 | Day 60 | Day 74 | Day 90 | Day 120 | Day 210 | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | |
| HbA1c | ✓ | ✓ | | | | | | | ✓ | ✓ | |
| Serum HGF | | ✓ pre-injection | | ✓ pre-injection | | ✓ | | ✓ | | | ✓[1] |
| VM202 | | ✓ pre & post injection | ✓ pre & post injection | ✓ pre & post injection | ✓ pre & post injection | ✓ | | ✓ | | | ✓[1] |
| HTLV, HIV-1, HIV-2 | ✓ | | | | | | | | | | |
| Hepatitis B, Hepatitis C[†] | ✓ | | | | | | | | | | |
| Hematocrit | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Hemoglobin | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| RBC | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| WBC with differential | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Platelets | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Albumin | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Alkaline Phosphatase | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| ALT | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| AST | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Bicarbonate | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| BUN | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Calcium | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Chloride | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Creatinine | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| eGFR | ✓ | | | | | | | | | | |
| Glucose | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Potassium | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Sodium | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Total Protein | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Total Bilirubin | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | ✓ | ✓ |

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

1 If withdrawal occurs before Day 90 Visit

# Appendix 2. Sample Informed Consent

**TITLE: A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Assess the Safety and Efficacy of VM202 to Treat Chronic Nonhealing Foot Ulcers in Diabetic Patients with Concomitant Peripheral Arterial Disease (PAD)**

SPONSOR: Helixmith Co., Ltd.

[redacted]

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

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

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

***Why is this study being done?***
You are being considered to participate in this research study because you have type I or II diabetes with current treatment control, peripheral arterial disease [narrowing of blood vessels that reduce the blood flow to your limbs], and, you have a chronic, nonhealing ulcer on one of your feet.

Ulcers initially occur due to trauma, pressure loading [force applied to the skin], and / or neuropathy [problems with the nerves in your feet]. Ulcers don't heal because of infection and / or when your diabetes and poor circulation interfere with normal healing.

Researchers have discovered that a protein called hepatocyte growth factor (HGF) that your body naturally produces in small amounts may cause the growth of new blood vessels, protect nerves, and stimulate wound healing. 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 leg. 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 helps ulcer healing. The product being used in this study is called VM202. VM202 is an experimental drug that is not yet approved by regulatory authorities (the US Food and Drug Administration [FDA]). VM202 is a plasmid (a small piece of DNA), which includes the HGF genes.

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

This study is intended to help determine the safety and efficacy of VM202 in subjects with a chronic, nonhealing ulcer. VM202 will be injected into your calf muscles in one leg (the leg with the ulcer on your foot), using a syringe with a fine needle.

***Who is in charge of this study?***
The Principal Investigator is [INSERT PRINCIPAL INVESTIGATOR NAME]. This study is sponsored and funded by Helixmith Co., Ltd. [INSERT PRINCIPAL INVESTIGATOR NAME] is being paid by Helixmith Co., Ltd. to conduct this study. Together with your doctor, Helixmith

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 300 patients will take part in this study at up to 30 research centers 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. If you do not meet all of the study entry criteria, you will not be able to participate in the study and your study doctor will discuss with you other options that you may have for treatment of your medical condition. The study doctor will tell you whether you are able to participate in this study after the initial test results are received and reviewed.

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

You will be randomly assigned to one of two possible study groups. In each study group, you will receive 16 injections in one calf at the Day 0, Day 14, Day 28 and Day 42 visits. The contents of the injections depend on your study group:

- **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 Day 14 visit, 4 mg of VM202 at the Day 28 visit, and 4 mg of VM202 at the Day 42 visit). At all 4 injection visits, you will receive 16 injections of 0.5 mL of VM202 in one calf. The total volume of all of the injections is about 2 teaspoons of fluid. Approximately sixty-five percent (65%) of patients will be assigned to this group.

- **Placebo Control Group** – if you are selected for this group, you will not receive VM202. You will only receive injections of saline. At all 4 injection visits, you will receive 16 injections of 0.5 mL of saline in one calf. The total volume of all of the injections is about 2 teaspoons of fluid. Approximately thirty-five percent (35%) of patients will be assigned to this group.

***What tests, procedures, and diagnostic studies will be done during this study?***
There are 10 visits which span 7 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

1 to 2 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.

You will also need to come in once a week for dressing changes and assessment of your ulcer, unless that visit coincides with a pre-specified visit described above. The study doctor will provide you with dressings and instructions to clean the wound at home between visits if necessary.

Please note: after your ulcer heals, you will need to come in 2 weeks later to confirm that your ulcer is truly healed. This confirmation visit may coincide with a pre-specified visit or may require an additional visit. Even after the ulcer heals, you will still be asked to attend all visits described below.

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

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

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

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

**Assessment of the ulcer –** A photograph of the ulcer will be taken, and the size of the ulcer will be determined. Please note, the photograph is a close-up of your ulcer; no one will be able to identify you in the photo.

**Foot X-ray –** Two X-rays will be taken of your foot with the ulcer.

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

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

**Questionnaire –** You will be asked to complete a short questionnaire the effects of your ulcer on your life.

**Measurement of blood pressure in your leg (ABI, TBI and toe pressure) –** 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 and 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 ($TcPO_2$), at Select sites Only – Omit section if not applicable –** 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.

**Cancer screening** – Cancer screening may include pap smear and mammogram depending on your age and screening status (females only); and a CT scan of the chest depending on your current smoking status and tobacco use history (all subjects). Please ask your study doctor, which tests you may need.

If you are 50 years of age or older, fecal occult blood test [stool samples will be tested for the presence of blood] - if you have a personal or family history of colon cancer in any first degree relative, you must have undergone a colonoscopy in the past 12 month with negative findings.

**Retinal fundoscopy (specific eye exam) –** An ophthalmologist (eye doctor) will dilate your pupils and perform a retinal examination with retinal photographs at Screening. If your ophthalmologist determines that a more detailed image of the blood vessels in your eye is necessary to determine if you are eligible for study participation, he / she may conduct another test called fluorescein angiography. This involves injecting a dye into a vein in your arm; the dye then circulates through the bloodstream and to the blood vessels of your eye. Retinal photographs of the back of your eye will be taken again at 7 months, but the fluorescein angiography will not be repeated. If dilating eye drops are used, they may impair focusing of the eyes for several hours. Therefore, arrangements should be made for someone else to drive after the examination. Wearing sunglasses or tinted lenses may make dilated pupils more comfortable. You should tell the examiner if you are allergic to any medications, are taking any medications, or have glaucoma or a family history of glaucoma.

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

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

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

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

**Visit # 1: Screening Evaluations**
Screening is a process of evaluating your initial health status and assessing your ulcer. Screening is usually completed within 1 week before the first study injections if you qualify for this study. If you agree to take part in this research study, you will first sign this consent form, and then undergo screening. Screening will involve the following procedures: medical history, physical exam, vital signs, medication review, ulcer assessment, foot x-rays, measurement of blood pressures in your leg, cancer screening, retinal fundoscopy, blood tests including a viral screen, urine pregnancy test (if you are a female of childbearing age), and a 12-lead EKG.

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

Please note: Starting at this visit, you will receive standard of care treatment for your ulcer which includes removal of dead or damaged tissue, the use of an appropriate off-loading device (boot or sandal that will be keep the pressure off your ulcer), and the ulcer will be kept clean and moist using a special dressing.

It takes approximately 2 to 4 weeks to get all of the screening test results. After your doctor has reviewed the results of these tests, he/she will determine whether you are eligible for participation in the study. If you are eligible for the study and you do wish to continue, you will be assigned by chance (randomly) to receive VM202 or placebo. You will then be scheduled for the first set of injections which will be done at your next visit (Visit #2).

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

*Before Injection Procedure:*
The following tests will be performed before you have your injection procedure done: ulcer assessment, photograph of your ulcer, medication review, completion of questionnaire, vital signs, measuring blood pressures in your leg, measurement of how much oxygen reaches your skin (select sites), and blood tests including HGF and VM202.

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

*After Injection Procedure:*

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

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

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

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

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

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

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

**Visit # 4 – Third Injection Procedure (injections of VM202 or placebo into your calf muscles; 14 Days after the Second Injection Procedure)**

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

*Injection Procedure:*

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

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

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

**Visit # 5 – Fourth (Last) Injection Procedure (injections of VM202 or placebo into your calf muscles; 14 Days after the Third Injection Procedure)**

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

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

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

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

**Visit # 6 – 60 Days after the First Injection Procedure**
At this visit, the following tests or evaluations will be done: ulcer assessment and photograph, medication review, vital signs, blood tests for HGF and VM202, injection site reaction assessment and assessment of side effects.

**Visit # 7 – 74 Days after the First Injection Procedure**
At this visit, the following tests or evaluations will be done: ulcer assessment, medication review, vital signs, and assessment of side effects.

**Visit # 8 – 90 Days (3 Months) after the First Injection Procedure**
At this visit, the following tests or evaluations will be done: ulcer assessment, medication review, vital signs, blood tests including HGF and VM202, and assessment of side effects.

**Visit # 9 – 4 Months after the First Injection Procedure**
At this visit, the following tests or evaluations will be done: ulcer assessment, medication review, vital signs, completion of questionnaire, measuring blood pressures in your leg, measurement of how much oxygen reaches your skin (select sites), blood tests, and assessment of side effects.

**Visit # 10 – 7 Months after the First Injection Procedure**
At this visit, the following tests or evaluations will be done: retinal fundoscopy, ulcer assessment, medication review, vital signs, completion of questionnaire, measuring blood pressures in your leg, measurement of how much oxygen reaches your skin (select sites), blood tests, and assessment of side effects.

After you have completed your 7-month follow-up visit, you do not have to return for any more visits.

***Medication Use during the Study***
The study doctor will review your current medications/therapies with you. The following therapies are not allowed during the study:

- Gels or creams with growth factors, e.g., Regranex® gel (becaplermin)
- Larval debridement
- Skin substitutes, e.g., Dermagraft®, Apligraf®
- Hyperbaric oxygen therapy
- Hydrotherapy
- Negative pressure wound therapy
- Electrical stimulation therapy

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

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

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

***How long will I be in this research study?***
Your last follow up visit will be approximately 7 months after your first injection procedure. After this visit, you will have completed this study.

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

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

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

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

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

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care. If you do decide to stop your participation in the study, you should talk to your doctor immediately so he/she can advise you of any additional tests that may be needed for your safety. Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if he/she determines that it is no longer in your best interest to continue. The Sponsor or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified, and your study doctor will discuss with you other options you may have.

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

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

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

***Risks to women who can get pregnant or are breastfeeding***

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

The following birth control measures are acceptable:

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

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

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

***Risks from taking a blood sample***

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

***Risks from foot X-ray***

A foot X-ray is a safe and painless test that uses a small amount of radiation. The average dose of two foot X-rays is 0.2 mrem. In comparison, most people receive 300 mrem every year from natural background sources of radiation.

***Risks from cancer screening***
Cancer screening may include pap smear and mammogram if not performed within past 12 months (females only) and CT scan of the chest. All subjects 50 years of age or older will undergo a fecal occult blood test. If you have a personal or family history of colon cancer in any first degree relative, you must have undergone a colonoscopy in the past 12 months with negative findings.

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). Some discomfort can be associated with a Pap smear and mammography (if you are female). Risks from colonoscopy 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, the drops may produce a brief stinging sensation when put in the eyes and a medicinal taste in the mouth caused by the medication draining from the tear ducts into the throat. Dilating eye drops rarely produce nausea, vomiting, dryness of the mouth, flushing, dizziness, or an attack of narrow-angle glaucoma. If glaucoma is suspected, drops generally are not used.

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

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

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

***Are there benefits to taking part in this research study?***
There may be no direct benefit to you by participating in this study. However, it is possible that your ulcer may heal faster.

Knowledge from this study may help us better understand how to treat people with chronic nonhealing ulcers.

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

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

***Will I need to pay for the tests and procedures?***
Participation in this study will be of no cost to you. All medical exams, urine and blood tests, and study evaluations and procedures that are required for this research study are provided to you at no cost to you. You will also not need to pay for the VM202/placebo injections. Helixmith Co., Ltd., 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 will still receive medical care for your condition although you would not be able to get the VM202 product.

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

***What about confidentiality?***
The personal information obtained about you during the course of this study will remain confidential. When recording the results of the study you will be referred to only by a unique subject identifier code number and your initials. Except when required by law, you will not be

identified by name, social security number, address, telephone number, or any other direct personal identifier in study records.

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

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

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

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

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

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

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

***What alternatives are there to participation in this study?***
The standard of care for chronic foot ulcers includes debridement of the wound, management of any infection, revascularization procedures when indicated, mechanical offloading of the ulcer, management of blood glucose, and foot care education.

Other adjunctive therapies, such as hyperbaric oxygen, use of advanced wound care products, and negative-pressure wound therapy have shown some benefit, but reports of efficacy are mixed, and their cost-effectiveness has not been demonstrated.

Note: You do not have to take part in this study to receive treatment for your condition.

**STATEMENT OF CONSENT**

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

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

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

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

Original copy for site file; 1 copy for subject.

# Appendix 3. Medications/Therapies Excluded from Use During the Study

## WASHOUT TABLE FOR COX-2 INHIBITORS, STEROIDS, & ANTI-VEGF

| Drug | Example of Common Name(s) | Maximum Dose Allowed During Study | Washout Period |
|---|---|---|---|
| **Cox-2 specific Inhibitors** | | | |
| celecoxib | Celebrex | none | 2 weeks |
| **Non-Steroidal Anti-inflammatory Drugs (NSAIDs: nonspecific inhibitors of both Cox-1 and Cox-2)** | | | |
| acetylsalicylic acid | Aspirin, Arthritis Foundation Safety Coated Aspirin, Bayer Aspirin, Bayer Children's Aspirin, Ecotrin | 81 mg daily | 2 weeks for doses over 81 mg daily |
| diclofenac | Voltaren, Arthrotec, Cambia, Cataflam, Flector, Pennsaid, Solaraze, Zipsor | none | 2 weeks |
| diflunisal | Dolobid | none | 2 weeks |
| etodolac | Lodine | none | 1 week |
| fenoprofen | Nalfon | none | 1 week |
| flurbiprofen | Ansaid | none | 1 week |
| ibuprofen | Motrin, Advil, Caldolor, Profen | none | 1 week |
| indomethacin | Indocin | none | 1 week |
| ketoprofen | Nexcede, Orudis | none | None for topical formulation, 1 week for all others |
| ketorolac | Sprix, Acuvail, Acular | none | 1 week |
| mefenamic acid | Ponstel | none | 1 week |
| meloxicam | Mobic | none | 1 week |
| nabumetone | Relafen, Relifex and Gambaran | none | 1 week |
| naproxen sodium | Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inza, Midol Extended Relief, Miranax, Naposin, Naprelan, Naprogesic, Naprosyn, Narocin, Proxen, Synflex, Xenobid | none | 2 weeks |
| oxaprozin | Daypro | none | 1 week |
| piroxicam | Feldene | none | 1 week |
| sulindac | Clinoril | none | 1 week |
| tolmetin | Tolectin | none | 1 week |
| **Steroids** | | | |
| Corticosteroids (injected, oral, topical) | Prednisone, betamethasone, dexamethasone, cortisone, triamcinolone | none† | 1 week |
| **Anti-Vascular Endothelial Growth Factor (VEGF) Agents** | | | |
| Anti-VEGF Agents | Eylea, Lucentis, Avastin | none | 30 days |

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

## OTHER PROHIBITED MEDICATIONS/THERAPIES DURING STUDY PARTICIPATION

Subjects must refrain from using the following medications/ undergoing the following therapies for the duration of the study:

- Gels or creams with growth factors, e.g., Regranex® gel (becaplermin)
- Larval debridement
- Skin substitutes, e.g., Dermagraft®, Apligraf®
- Hyperbaric oxygen therapy
- Hydrotherapy
- Negative pressure wound therapy
- Electrical stimulation therapy

Subject must agree to remain off of these medications/treatments until completion of the 7-month follow-up visit.

# Appendix 4. Standardized Wound Care

Starting at screening, wound care will be standardized as follows for the duration of the study/until the ulcer has completely healed:

**Surgical debridement of necrotic tissue or devitalized tissue**

The extent of debridement is based on the wound and will be determined by the Principal Investigator or his/her representative based on his/her standard of care.

**Maintenance of a clean and moist wound environment**

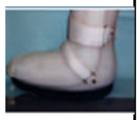
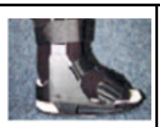
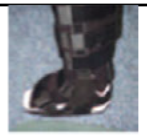
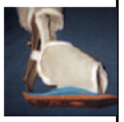
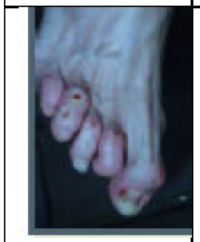
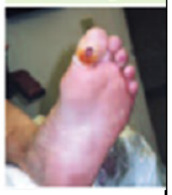
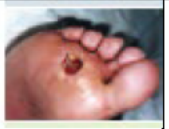
- A wound cleanser will be used to maintain a clean environment; specifically, Puracyn® Plus (Innovacyn, Inc, Rialto, CA) will be provided to the sites for use in study subjects in order to increase compliance and standardization
- A non-medicated, absorbent hydrocellular foam dressing will be used. Specifically, ALLEVYN Gentle (Smith & Nephew, London, UK) with a soft gel adhesive which minimizes trauma to the wound at dressing change will be provided to the sites for use in study subjects in order to increase compliance and standardization.

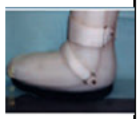
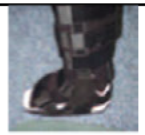
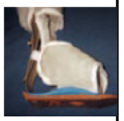
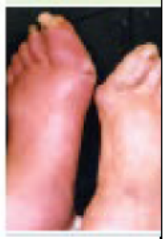
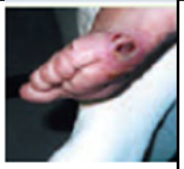
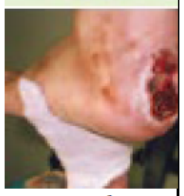
Note: in subjects with multiple ulcers on the target foot, all ulcers will be cleansed with Puracyn® Plus and dressed with ALLEVYN Gentle in order to maintain standardized care for the entire target foot.

**Use of appropriate off-loading when ambulating**

Removable footwear will be used for ulcer offloading. Choice of footwear will depend on the location of the ulcer. A boot should be considered for plantar ulcers; an off-loading postoperative shoe should be considered for all ulcers located elsewhere below the malleolus. Examples adapted from: *Consensus Recommendations on Advancing the Standard of Care for treating Neuropathic Foot Ulcers in Patients with Diabetes*, Snyder, RJ (2010)[58] are provided in Table 8.

Table 8. Removable footwear options for off-loading by ulcer location

| Ulcer location | Removable Footwear Offloading Options | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| |  CROW Boot |  Prefabricated Walker |  DH Offloading Walker |  IPOS Shoe |  Ortho Wedge |  PostOp Shoe |  Healing Sandals |  Reverse IPOS |  L'nard Splint |  PTB Brace |  MABAL Shoe |
|  Dorsal Digit | | | | | | X | | | | | |
|  Plantar Digit | X | X | X | X | X | | X | | | | X |
|  Plantar Metatarsal | X | X | X | X | X | | X | | | | X |

| Ulcer location | Removable Footwear Offloading Options | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| |  CROW Boot |  Prefabricated Walker |  DH Offloading Walker |  IPOS Shoe |  Ortho Wedge |  PostOp Shoe |  Healing Sandals |  Reverse IPOS |  L'nard Splint |  PTB Brace |  MABAL Shoe |
|  Medial Metatarsal | X | X | X | X | X | | X | | | | X |
|  Lateral Metatarsal | X | X | X | X | X | | X | | | | X |
|  Heel | X | X | X | | | | | X | X | X | X |

Adapted from: *Consensus Recommendations on Advancing the Standard of Care for treating Neuropathic Foot Ulcers in Patients with Diabetes*, Snyder, R. J. et al (2010)[58]

**Instructions for the Subject**

Subjects will be provided with the following instructions:

*Home care instructions for maintaining your wound*

The ulcer will be cared for by maintaining an optimal wound environment.

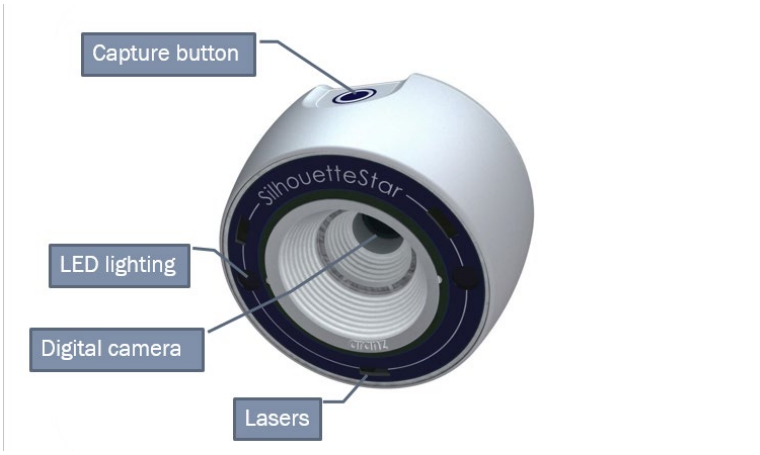
1. Wash your hands thoroughly and apply gloves.
2. Remove the old dressing and gently cleanse the wound with saline water.
3. Gently pat the ulcer and surrounding skin from the center of the wound outward with dry gauze.
4. Try to avoid disrupting the tissue or causing bleeding of the wound.
5. Be sure to completely dry the area around the wound after cleansing the wound or washing the foot. Note: No antimicrobial soap or products should be used to cleanse the wound or the foot. Do not use any lotions, gels, or ointments on the wound.
6. Apply the assigned primary and secondary dressings to the wound.
7. Apply your sock and the appropriate offloading device.

# Appendix 5. Target Ulcer Documentation

SilhouetteStar + SilhouetteConnect system (ARANZ Medical, Christchurch, New Zealand) will be used to capture photographs, and measure the target ulcer.

- The SilhouetteStar is a 3D camera that connects to a Windows computer using a USB cable.
- SilhouetteConnect is software installed on a Windows computer that controls the SilhouetteStar camera.

Silhouette contains a 3-megapixel camera that is always in focus, with its own lighting system that provides consistent ambient background lighting, and a single button (for image capture). Users are able to repeatedly obtain high quality and consistent images from visit to visit using a device that may be the easiest-to-use digital camera available.




Silhouette is a family of products for imaging, measuring and documenting wounds. Silhouette is designed to improve workflow in wound assessment, allowing a user to quickly image and accurately analyze a wound using a portable, non-contact device, with all measurements saved directly into an electronic database designed specifically for wounds and other external surface features. All measurements are made without touching the patient, eliminating patient discomfort and reducing risk of infection.

Key features of SilhouetteStar + SilhouetteConnect include:

- Multiple tools in one – wound imaging, measurement and documentation
- Repeatable and accurate measurements
- Accurate measurement of surface area, length, width, perimeter, maximum depth, average depth, and volume
- Non-contact measurements
- The ability to track wound healing over time
- Quick and easy to use

The third component in the Silhouette Product Suite is SilhouetteCentral.™

SilhouetteCentral enables central storage for the collection of high-quality data of each target ulcer (including images and measurements) for all clinical sites through transmission of data through the internet. Furthermore, SilhouetteCentral:

- Enables review by personnel from remote location
- Facilitates export of data for analyses
- Capable of automatic report generation and report distribution

*Measurements – Accuracy and Repeatability*

Studies have shown that the inter- and intra-rater repeatability of measurements of wound surface area made using Silhouette are superior to those made using acetate tracings, the current clinical standard for such measurements.[a]

A study of SilhouetteStar + SilhouetteConnect[b] shown that the inter-rater and intra-rater variability were less than 1% for both area and perimeter, and less than 2% for average depth and volume on wound models. This indicates that repeated measurements over time, even by different users, will detect small differences as a wound changes in size.

Studies on large skin features[c] (for example areas of erythema) have also shown that Silhouette can accurately measure surface area of lesions ranging from 150 $cm^2$ to 900 $cm^2$. In this study both the repeatability associated with the three raters and intra-rater variability for each of the three raters were less than 2%.

*Training*

Each site will be trained in the use of the SilhouetteStar + SilhouetteConnect system prior to enrollment of any subjects into the study.

[a] Nixon MA, Davey BLK, Fright WR, McCallum BC, Kieser D, Comparison Between Two Methods of Wound Measurement on Wound Models: Acetate Tracing and a Hand-Held, Electronic Wound Measurement Device, Symposium on Advanced Wound Care (SAWC) April 2009, Dallas, Texas, Oral Presentation.

[b] Nixon MA, Rivett TR, Robinson BR, Assessment of Accuracy and Repeatability on Wound Models of a New Hand-Held, Electronic Wound Measurement Device, Symposium on Advanced Wound Care (SAWC) Spring, April 2012, Atlanta, Georgia, Poster Presentation.

[c] Nixon MA, Goodwin SR, Davey BLK, Accuracy and Repeatability of Area Measurements on Large Areas of Erythema using an Electronic Wound Measurement Device, Symposium on Advanced Wound Care (SAWC) Spring, April 2011, Dallas, Texas, Poster Presentation.

# Appendix 6. ABI, TBI and Toe Pressure

Ankle-Brachial Index (ABI) and Toe Brachial Index (TBI) will be determined at Screening, on Day 0, Day 120 (4 months) and Day 210 (7 months) in the target limb. Toe pressure will be determined at Screening in the target limb.

**Definitions**

- Dorsalis pedis (DP) — pulse located at approximately the mid-anterior aspect of the ankle joint.
- Posterior tibial artery (PT) — pulse located just posterior to the medial malleolus of the ankle joint.
- ABI — the ABI for each limb is defined as the ratio between the higher of the two pedal systolic blood pressure measurements (dorsalis pedis and posterior tibialis) on a leg and the higher of the two systolic brachial pressure measurements (right or left brachial).

  Right ABI = Highest pressure in **right** foot/highest systolic pressure in **both** arms

  Left ABI = Highest pressure in **left** foot/highest systolic pressure in **both** arms

- TBI — The TBI is calculated as the ratio of the systolic blood pressure of the first toe on each side divided by the higher of the systolic blood pressures of the two arms.

  Right TBI = **right** toe systolic pressure/highest systolic pressure in **both** arms

  Left TBI = **left** toe systolic pressure/highest systolic pressure in **both** arms

**Equipment needed:**

- Doppler
- Ultrasound gel
- Blood pressure cuff

**Performing a Resting ABI**

1. Resting ABI measurements must be taken after the subject has rested for at least 10 minutes in the supine position. All ABI measurements must be made using a continuous wave 5-10 MHz Doppler probe.
2. Use the appropriate cuff for the limb you are assessing—a standard cuff for the upper limbs and an ankle cuff for the lower limbs. If an ankle cuff is not available, choose the appropriate size cuff for the upper and lower limbs. It may be necessary to use 2 different cuff sizes.
3. Resting ABI pressures should be obtained in a horseshoe shape starting with right arm and finishing with the left arm.
4. Use a generous amount of gel.
5. Adjust the probe, before inflating the cuff, until you find the strongest (loudest), clearest pulse sound.
6. Keep hand and Doppler probe stabilized (i.e., on bed, subject, etc.).

7. Watch the Doppler probe while inflating the cuff; not the sphygmomanometer. This will ensure that the probe is not inadvertently moved, thereby losing the pulse.
8. Inflate the cuff about 20 mmHg above the last audible pulse sound.
9. Turn attention to the sphygmomanometer and deflate the cuff slowly (about 2 mmHg per second). Record the reading of the first sound you hear that you are confident is a pulse sound.
10. Wait twenty seconds, with the cuff completely deflated. Repeat steps 4 through 9 to obtain a second pressure at each vessel. Use the average of the two measurements to define a single pressure for each vessel. If individual pressures for a vessel are ≥ 10 mmHg different from each other, repeat the process until the difference between the pair of systolic pressures is < 10 mmHg.

**Performing a Resting TBI**

1. Resting TBI measurements must be taken after the subject has rested for at least 10 minutes in the supine position.
2. Resting TBI pressures should be obtained in a horseshoe shape starting with right arm and finishing with the left arm (brachial pressures should be obtained even if previously obtained for ABI measurements).
3. Use arm cuff appropriate to the size of the arm being tested.
4. Position cuff so the middle of the bladder is over brachial vessel & wrap cuff tight enough so that no more than two fingers can be inserted between the cuff and the arm.
5. Use an adequate amount of gel.
6. Use Doppler (not a stethoscope).
7. Search for strongest pulse, prior to inflating the cuff (do not use first sound heard).
8. Keep hand and Doppler stabilized (i.e., on bed, subject, etc.).
9. Watch Doppler hand while inflating cuff.
10. Inflate approximately 20mm above last heard pulse.
11. Deflate cuff slowly, approximately 2mm every second.
12. Record the reading of the first sound you hear that you are relatively certain is a pulse sound.
13. Deflate cuff and wait at least 20 seconds.
14. Repeat steps 1 through 13 on the same vessel. Use the average of the two measurements to define a single pressure for that vessel.
15. If the first and second readings are 10mm or more different from each other, discard both readings and restart the assessment of the pressure of this vessel.

**Toe Pressure (using a photoplethysmography [PPG]):**

1. Apply double-sided clear tape over the pad of the big toe
2. Use a toe cuff
3. Ensure any ulcers present are protected. Position the cuff comfortably snug around the base of the big toe
4. Affix the PPG probe to the pad of the toe where the double-sided tape was applied
5. Ensure the subject's toes are warm to the touch prior to obtaining the pressure
6. Set the PPG machine waveform motion to run at 5 mm per second and allow the readout to stabilize
7. Ensure the printed waveform fits well within the printed readout
8. Inflate the cuff approximately 20 mmHg above last viewed reading
9. Watch both the waveform motion on the PPG and the sphygmomanometer while deflating the cuff
10. Deflate the cuff slowly, approximately 2 mmHg every second
11. Identify the return of the systolic pressure (first viewed waveform motion)
12. Deflate cuff and wait at least 20 seconds before obtaining the next pressure
13. Repeat above steps on the same vessel for a second measurement
14. The average of the two pressures in the affected limb will be assessed against the inclusion criteria.

**Toe Pressure (using a 5-10 MHz Doppler probe):**

1. Use a toe cuff
2. Ensure any ulcers present are protected. Position the cuff comfortably snug around the base of the big toe
3. Ensure the subject's toes are warm to the touch prior to obtaining the pressure
4. Search for strongest pulse, prior to inflating the cuff (do not use first sound heard)
5. Keep hand and Doppler stabilized (i.e., on bed, subject etc.)
6. Watch Doppler hand while inflating cuff
7. Inflate the cuff approximately 20 mmHg above last heard pulse
8. Deflate the cuff slowly, approximately 2 mmHg every second
9. Appropriately identify the return of the systolic pulse (first sound that you hear that you are relatively certain is a pulse sound)
10. Deflate cuff and wait at least 20 seconds before obtaining the next pressure
11. Repeat above steps on the same vessel for a second measurement
12. The average of the two pressures in the affected limb will be assessed against the inclusion criteria.

# Appendix 7. Test Article Administration

1. ***Test article preparation***

***VM202*** - VM202 is supplied in a sterile glass vial containing [redacted] study product. Before administration, it will be reconstituted [redacted] for a final VM202 concentration of 0.5 mg / mL. Each reconstituted vial is only to be used for one subject. For subjects randomized to the VM202 arm of the study, the final doses of VM202 will be divided evenly between the Day 0, Day 14, Day 28 and Day 42 administration. Each individual injection will be 0.5 mL. All injections administered by IM injections. The VM202 group will receive 16 injections of VM202 in the calf ipsilateral to the target ulcer at all four injection visits.

***Placebo*** - Subjects assigned to the placebo arm will receive VM202 vehicle injections. The placebo group will receive 16 injections of VM202 vehicle in the calf ipsilateral to the target ulcer at all four injection visits. Visually, VM202 vehicle is indistinguishable from reconstituted VM202.

Table 9. Single dose preparation and delivery for Day 0, Day 14, Day 28 and Day 42 Visits

| Treatment Arm | Number of Vials at each visit | Number of injections† | Total Volume to be Injected |
|---|---|---|---|
| **VM202**<br>4 mg / visit - total dose: 16 mg | 2 Vials VM202, reconstituted with WFI | 16 of VM202 | 8 mL |
| **Placebo – VM202 vehicle** | 2 Vials of VM202 Vehicle | 16 of placebo | 8 mL |

†Injection volume for each individual injection = 0.5 mL

2. ***Test material administration*** – Subjects will receive injections of VM202 or placebo on Day 0, Day 14, Day 28 and Day 42. A fine needle (e.g., 27 gauge, 1.25") suitable for IM injections will be used. **The ipsilateral calf to the target ulcer will be treated with 16 injections at each visit.** Distribute injection sites evenly over the calf muscle, carefully avoiding fascia.

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

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

## Appendix 8. The Cardiff Wound Impact Questionnaire (CWIQ)

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

# Cardiff Wound Impact Schedule

The following questionnaire is concerned with the effects that your wound has on your daily life. Please answer the questions carefully by placing a tick in the box which most closely reflects how you feel; it should take about ten minutes to complete.

If you are unsure about how to answer a question, please tick the answer which is closest to how you feel. All answers are confidential.

# Personal Details

**Subject Initials** ☐☐☐ **Subject Number** ☐☐☐☐

**Gender** M F (Please circle)

**Date of Birth** D D M M M Y Y

**Assessment Date** D D M M M Y Y

**Assessment** 1st 2nd 3rd 4th 5th (Please circle)

**Next Assessment Due** D D M M M Y Y

**Wound status** Healed ☐ Not Healed ☐

**Do you live on your own?** Yes ☐ No ☐

**How often do you see your family and friends?**

Once a day ☐ Once a month ☐

Once a week ☐ Less than once a month ☐

# Well-being

## To what extent do you agree/disagree with the following statements?

| | Strongly Disagree | Disagree | Not Sure | Agree | Strongly Agree |
|---|---|---|---|---|---|
| I feel anxious about my wound(s) | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel frustrated at the time it is taking for the wound(s) to heal | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am confident that the wound(s) I have will heal | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry that I may get another wound in the future | ☐ | ☐ | ☐ | ☐ | ☐ |
| The appearance of the wound site is upsetting | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel anxious about bumping the wound site | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry about the impact of the wound(s) on my family/friends | ☐ | ☐ | ☐ | ☐ | ☐ |

# Physical Symptoms and Daily Living

## Have you <u>experienced</u> any of the following during the past week?

| | Not at all/ Not applicable | Seldom | Sometimes | Frequently | Always |
|---|---|---|---|---|---|
| Disturbed sleep | ☐ | ☐ | ☐ | ☐ | ☐ |
| Difficulty in bathing | ☐ | ☐ | ☐ | ☐ | ☐ |
| Immobility around the home | ☐ | ☐ | ☐ | ☐ | ☐ |
| Immobility outside the home | ☐ | ☐ | ☐ | ☐ | ☐ |
| Leakage from the wound | ☐ | ☐ | ☐ | ☐ | ☐ |
| Pain from the wound site | ☐ | ☐ | ☐ | ☐ | ☐ |
| Discomfort from the bandaging/dressing | ☐ | ☐ | ☐ | ☐ | ☐ |
| Unpleasant odour or smell from the wound | ☐ | ☐ | ☐ | ☐ | ☐ |
| Problems with everyday tasks (eg shopping) | ☐ | ☐ | ☐ | ☐ | ☐ |
| Difficulty in finding appropriate footwear | ☐ | ☐ | ☐ | ☐ | ☐ |
| Problems with the amount of time needed to care for the wound site | ☐ | ☐ | ☐ | ☐ | ☐ |

| | | | | | |
|---|---|---|---|---|---|
| Financial difficulties as a result of the wound | ☐ | ☐ | ☐ | ☐ | ☐ |

# Physical Symptoms and Daily Living

## How <u>stressful</u> has this experience been for you?

| | Not at all/ Not applicable | Slightly | Moderately | Quite a bit | Very |
|---|---|---|---|---|---|
| Disturbed sleep | ☐ | ☐ | ☐ | ☐ | ☐ |
| Difficulty in bathing | ☐ | ☐ | ☐ | ☐ | ☐ |
| Immobility around the home | ☐ | ☐ | ☐ | ☐ | ☐ |
| Immobility outside the home | ☐ | ☐ | ☐ | ☐ | ☐ |
| Leakage from the wound | ☐ | ☐ | ☐ | ☐ | ☐ |
| Pain from the wound site | ☐ | ☐ | ☐ | ☐ | ☐ |
| Discomfort from the bandaging/dressing | ☐ | ☐ | ☐ | ☐ | ☐ |
| Unpleasant odour or smell from the wound | ☐ | ☐ | ☐ | ☐ | ☐ |
| Problems with everyday tasks (eg shopping) | ☐ | ☐ | ☐ | ☐ | ☐ |
| Difficulty in finding appropriate footwear | ☐ | ☐ | ☐ | ☐ | ☐ |
| Problems with the amount of time needed to care for | ☐ | ☐ | ☐ | ☐ | ☐ |

| | | | | | |
|---|---|---|---|---|---|
| the wound site | | | | | |
| Financial difficulties as a result of the wound | ☐ | ☐ | ☐ | ☐ | ☐ |

# Social Life

**Have you <u>experienced</u> any of the following during the past week?**

| | Not at all/ Not applicable | Slightly | Moderately | Quite a bit | Very |
|---|---|---|---|---|---|
| Difficulty getting out and about | ☐ | ☐ | ☐ | ☐ | ☐ |
| Relying more on others | ☐ | ☐ | ☐ | ☐ | ☐ |
| Your family/friends being over protective | ☐ | ☐ | ☐ | ☐ | ☐ |
| Unable to enjoy your usual social life (eg hobbies) | ☐ | ☐ | ☐ | ☐ | ☐ |
| Limited contact with family/friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| Not going out for fear of bumping your wound site | ☐ | ☐ | ☐ | ☐ | ☐ |
| Wanting to withdraw from people | ☐ | ☐ | ☐ | ☐ | ☐ |

# Social Life

## How <u>stressful</u> has this experience been for you?

| | Not at all/ Not applicable | Slightly | Moderately | Quite a bit | Very |
|---|---|---|---|---|---|
| Difficulty getting out and about | ☐ | ☐ | ☐ | ☐ | ☐ |
| Relying more on others | ☐ | ☐ | ☐ | ☐ | ☐ |
| Your family/friends being over protective | ☐ | ☐ | ☐ | ☐ | ☐ |
| Unable to enjoy your usual social life (eg hobbies) | ☐ | ☐ | ☐ | ☐ | ☐ |
| Limited contact with family/friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| Not going out for fear of bumping your wound site | ☐ | ☐ | ☐ | ☐ | ☐ |
| Wanting to withdraw from people | ☐ | ☐ | ☐ | ☐ | ☐ |

# Overall Quality of Life

## How would you rate your overall quality of life during the past week?

Please circle a number below (Score = number as circled)

**How good is your quality of life?**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| My quality of life is the worst possible | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | My quality of life is the best possible |

**How satisfied are you with your overall quality of life?**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Not at all satisfied | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Very satisfied |

**Overall Comment(s)**