Statistical Analysis Plan

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)**
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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 4, 2020)

February 4, 2020

VMNHU-003-SAP/E

Sponsor: **Helixmith Co., Ltd.**

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Revision: **E**

SIGNATURE PAGE

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

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LIST OF ABBREVIATIONS

ABI	Ankle Brachial Index
AE	Adverse Event
BMI	Body Mass Index
CDRC	Clinical Data Review Committee
CWIQ	Cardiff Wound Impact Questionnaire
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
HTLV	Anti-Human T-Cell Lymphotropic Virus
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
PAD	Peripheral Arterial Disease
PP	Per Protocol
PPG	Photoplethysmography
SAE	Serious AE
SOC	System Organ Class
TBD	To be determined
TBI	Toe Brachial Index
TEAE	Treatment-Emergent AE
WHODDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Helixmith Co., Ltd. (formerly ViroMed Co., Ltd.) Protocol VMNHU-003/I [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)]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report.

Study enrollment commenced under Protocol VMNHU-003/C. There were 7 subjects enrolled under protocol version C, 5 enrolled under version E, 16 enrolled under version F, and 16 enrolled under version G; no subjects were enrolled under protocol version D, H or I.

Protocol VMNHU-003/E introduced the following changes to exclusion criteria in VMNHU-003/C:

- The study ulcer decreased by 50% or more at baseline from Screening (as assessed by comparison of post-debridement photos taken at Screening and Day 0); previously only ulcers that increased by 50% or more at baseline from Screening were excluded.

- Target ulcer located on an active (hot) Charcot foot; previously any Charcot foot was excluded.

- Body mass index (BMI) > 45 kg/m^2 at Screening; previously BMI > 35 kg/m^2 was excluded.

- All steroids except inhaled or ocular steroids; previously only high dose steroids were excluded.

Since these changes to the exclusion criteria were not expected to have a meaningful influence in favor of VM202 on the efficacy and safety parameters, no inferential analyses to account for the protocol version will be conducted. Descriptive summaries of the primary efficacy endpoint and overall adverse event rates will be produced for the subjects enrolled under different versions of the protocol.

Protocol VMNHU-003/F submitted with SAP revision C introduced the following changes to the inclusion criteria:

- the upper age limit for study participants will be raised to 80 years;

- addition of ABI > 1.4 (indicative of non-compressible vessels at the ankle) as a qualifying criterion for documented PAD;

- revision of 1 criterion for documented PAD to: history of lower extremity peripheral artery disease with previous related intervention in a leg.

Protocol VMNHU-003/G introduced the following changes to the exclusion criteria:

- Removal of exclusion #2: unhealed prior amputation

- Removal of exclusion #5: more than one (1) ulcer on target foot

- Change to exclusion #22: removal of creatinine > 2.0 mg/dL as an exclusion

- Change to exclusion #23: glomerular filtration rate (GFR) $\leq$ 30 mL/min/1.73 m^2 updated to < 30 mL/min/1.73 m^2

Protocol VMNHU-003/H had no significant changes related to the SAP.

Protocol VMNHU-003/I being submitted with this SAP revision introduces the following changes:

- The definition of the intent-to-treat (ITT) population was broadened to all subjects who were randomized.

- The definition of the modified intent-to-treat (mITT) population was narrowed to include only those subjects who: 1) received any study drug injections, 2) had at least one post-baseline wound assessment, and 3) had no safety or efficacy parameter results before dosing that would have made the subject ineligible if the results had been known or disclosed at Screening

- Two per protocol (PP) populations have been defined. The former mITT population is now the first PP population (PP1), which includes all subjects in the revised mITT population who did not use the protocol-specified prohibited concomitant medications or treatments. The former PP population is now the second PP population (PP2), which includes all subjects in PP1 who: 1) met the major protocol eligibility criteria, 2) received all injections based on the randomized treatment, 3) maintained standard of care for their wounds for the duration of the study, and 4) any other additional criteria established by the CDRC before unblinding.

- The primary endpoint has been modified to include all subjects with a target wound closure by the 4-month follow-up, and no longer requires that wound closure be confirmed at two consecutive study visits at least two weeks apart.

2. ANALYSIS OBJECTIVES

- To evaluate the efficacy of VM202 in promoting ulcer healing in nonhealing foot ulcers
- To evaluate the safety of intramuscular administration of VM202 in subjects with nonhealing foot ulcers

3. STUDY DESIGN

This is a phase III, randomized, double-blind, placebo-controlled, multicenter, 7-month study designed to assess the safety and efficacy of intramuscular injections of VM202 in the calf of diabetic patients with chronic nonhealing foot ulcers and concomitant PAD. Subjects with confirmed PAD and diabetes aged $\geq$ 18 years to $\leq$ 80 years diagnosed with nonhealing foot ulcers will be screened for study eligibility after giving informed consent.

At Screening, standard of care 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 moist wound environment

Three hundred patients (from up to 30 study centers) who meet the eligibility criteria will be randomized in a 2:1 ratio to one of two treatment groups: 200 patients with VM202 (16 mg) plus standard of care or 100 subjects with placebo plus standard of care, respectively. Safety will be monitored throughout the study by an independent Data Safety Monitoring Board (DSMB, Section 8.5).

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

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 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 intramuscular injections of VM202 or placebo at each injection visit.

The schedule of study visits and the clinical parameters that will be measured at the visits are summarized in Table 1 to Table 3 below.

The subjects' target ulcer will be evaluated by photograph, surface area, depth, perimeter and volume measurements. Subjects must have a non-healing ulcer on Day 0 that meets study entry inclusion criterion # 5 and does not meet exclusion criterion #6 to be eligible for study participation. 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. Measurement of the target ulcer will be performed at each follow-up visit until complete wound closure or study exit.

Further details on the study procedures and conduct are provided in the protocol.

Table 1 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 measurable)	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 Protocol Section 4.1.3

†† 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 measurable

* 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 Day60

Table 2 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 measurable)	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	✓	✓	✓	✓	✓	✓	✓	✓

†† 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 measurable

** 2 hours after injection (± 1 hour)

* Excluding weight

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

Table 3 Schedule of Laboratory Evaluation

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

4. STUDY ENDPOINTS

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with a target wound closure by the 4-month follow-up.

The statistical hypotheses for the 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 a two-sided alpha of 0.05.

4.2. Other Efficacy Endpoints

- Time to complete wound closure of foot ulcer
- Proportion of subjects with a target wound closure by 7 months
- Percent change in wound volume at 2 months (Day 60), 2.5 months (Day 74), 3 months (Day 90), 4 months (Day 120), and 7 months (Day 210)
- 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 by 2 months, 2.5 months, 3 months, 4 months, and 7 months
- Time to major amputation in the target limb
- Time to minor amputation in the target limb
- Change in target limb ABI at 4 months and 7 months
- Change in target limb TBI at 4 months and 7 months
- Change in $TcPO_2$ at 4 months and 7 months
- Change in the overall quality of life and each domain score (well-being, physical symptoms and daily living, social life) of CWIQ from Day 0 at 4 months and 7 months

4.3. Safety Outcomes

- Adverse events
- Injection site adverse events

- Vital signs
  - Blood pressure
  - Weight
  - Heart rate
  - Respiration Rate
  - Temperature
- HbA1c
- Serum Chemistry and Hematology
- Retinal fundoscopy

4.4. Pharmacokinetics

- HGF serum levels
- Number of copies of VM202 in whole blood

4.5. Planned Covariates

The primary efficacy endpoint will be analyzed by adjusting for each of the following covariates separately and all covariates simultaneously using the methods described in Section 9.4.3:

- Wound location (medial malleolus, lateral malleolus, ankle flexure, posterior ankle, dorsum of foot, sole of foot, medial aspect of foot, lateral aspect of foot, big toe, 2nd through 5th toes [collapsed]; these locations have been re-examined and were re-categorized based on the distribution and clinical considerations prior to database lock. Data will be summarized as weight bearing (plantar foot surface), and not weight-bearing (non-plantar foot surface).
- Age (≤ median and > median)
- Baseline wound area (≤ median and > median)

5. DEFINITIONS

5.1. Basic Definitions

Study Drug

Study drug for this study refers to VM202 or placebo.

5.2. Study Points of Reference

Study Day 0

The date of the first study drug administration or the date of enrollment for subjects who were not administered any dose of study drug.

Study Day

For protocol defined assessments, the number of days from the day 0 visit to a date of interest, is calculated as:

Visit day = date of interest – date of study day 0.

Note that per CDISC dataset standards, the standard study day in the datasets will actually be calculated as:

If the date of interest is >= first dose date:

Study day= date of interest- date of first dose + 1 (there is no day 0)

If the date of interest is < first dose date:

Study day= date of interest- date of first dose + 1

5.3. Study Specific Definitions

5.3.1. Definitions of Safety Outcomes

Adverse Event (AE)

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 it is considered causally related to the product.

Based on the protocol, conditions or diseases that are chronic but stable are NOT considered as AEs, nor are changes in a chronic condition or disease that are consistent with natural disease progression.

Serious AE (SAE)

Any untoward medical occurrence which results in death; is a life-threatening experience; requires hospitalization (admission to hospital with a stay > 24 hours) or prolongation of an existing hospitalization which is not specifically required by the protocol or is elective; results in permanent impairment of a body function or permanent damage to a body structure; or requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

5.3.2. Definitions of Efficacy Endpoints

Complete Wound Closure

Defined as skin 100% re-epithelization without drainage or dressing at any time during the study. Complete wound closure will be assessed by the investigator at the sites and 100% reconciled with the ARANZ data, when possible. The primary analysis will be based on the eCRF page "Photography and Measurement of Ulcer in Target Leg".

Wound Volume, Wound Perimeter, Wound Area, and Wound Depth

The target wound's volume, perimeter, area, and depth will be measured using ARANZ Silhouette products at baseline and every scheduled post-baseline visit until wound closure.

Formation of New Foot Ulcer

Defined as a newly formed non-healing or poorly healing full-thickness wound, below the ankle on the target foot; these will be identified solely based the AE data provided by the site. The AE verbatim term will be scanned for the text "ULCER" and for "LEFT" vs. "RIGHT". The side will be matched with the target limb side from the eCRF and, if no information on site is present, it will be assumed that the new ulcer is on the target limb.

Major amputation

Defined as an amputation of the lower extremity above the ankle; these will be identified based on a blinded review of the AE data. The affected leg identified in the verbatim term on the AE electronic case report form (eCRF) and target foot noted on Physical Exam eCRF will be used to determine if the major amputation was in the target limb. These amputations will be noted in the clinical study report (CSR).

Minor amputation

Defined as an amputation of a foot or any parts of a foot such as toes; these will be identified based on a blinded review of the AE data. The affected leg identified in the verbatim term on the AE eCRF and target foot noted on Physical Exam eCRF will be used to determine if the minor amputation was in the target limb. These amputations will be noted in the CSR.

Cardiff Wound Impact Questionnaire (CWIQ)

The CWIQ is a patient-reported outcome measure designed to assess the impact of leg and diabetic foot ulcers on patient health-related quality of life (HRQoL). There are 3 domains/subscales:

- well-being (7 items, graded on a 5-point scale [1 = strongly disagree to 5 = strongly agree])
- physical symptoms and daily living (24 items, graded on a 5-point scale [1 = not at all to 5 = always])

- social life (14 items, graded on a 5-point scale [1 = not at all/not applicable to 5 = very])

The first and third subscales measure both the experience of the given concerns/symptoms and the stress they caused the patient; this duplication was not present in the referenced development and validation report cited below. In addition, there are Overall Quality of Life questions (2 items graded on a 11-point scale [0 = my quality of life is the worst possible or not at all satisfied to 10 = my quality of life is the best possible or very satisfied]).

Individual items are scored based on the CWIQ scoring instructions and summed for each domain and the Overall Quality of Life items. The tool is scored in such a way that a high score represents a 'good' HRQoL and a low score represent a 'poor' HRQoL. With the exception of one item in the well-being domain ("I am confident that the wound(s) I have will heal"), all items are scored 5-1 within the subscales reading from left to right on the questionnaire.

Reference:
Price P, Harding K. Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. Int Wound J 2004;1:10-17.

5.4. Derived Variables

Baseline Value

The last non-missing value prior to first dose of study drug. If a subject does not receive any study drug, baseline is the latest recorded measurement on or before the randomization date.

Change from Baseline Value

Change from baseline value is the arithmetic difference between a value of interest and a baseline value: Change from baseline value = (value of interest – baseline value).

Percent Change from Baseline Value

The ratio of the arithmetic difference between a value of interest and the baseline value to the baseline value multiplied by 100: (Change from Baseline / Baseline) × 100.

Time to Complete Wound Closure

Time to complete wound closure is the time interval (in days) from Day 0 to the date of the first visit date within the allowed visit window where wound closure is so indicated by the investigator. If a subject has not experienced complete wound closure, the subject will be considered censored at the subject's end of study date.

Time to a major amputation in the target limb

Time to a major amputation in the target limb is the time interval (in days) from Day 0 to the earliest date of a reported AE of an amputation of the lower extremity above the ankle of the target limb.

Time to a minor amputation in the target limb

Time to a minor amputation in the target limb is the time interval (in days) from Day 0 to the earliest date of a reported AE of an amputation of a foot or any parts of a foot such as toes on the target limb.

Absolute Differentials

If not provided by the individual study center labs, values for the absolute differentials (i.e., neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be calculated by multiplying the WBC count by the corresponding percent differential in the total WBC count. Results should be rounded to the nearest hundred for units equivalent to $10^3/\mu L$.

Percent Differentials

If not provided by the individual study center labs, values for the percent differential (i.e., neutrophils, lymphocytes, monocytes, eosinophils, and basophils) will be calculated by dividing the corresponding absolute differential count by the total WBC count. Results should be rounded to the tenth of a percentage point.

6. SAMPLE SIZE CALCULATION

Based on prior VM202 studies, the percentage of subjects achieving complete wound closure by the 4-month follow-up (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 4 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 specified in Section 4.1.

Table 4 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%.

7. ANALYSIS POPULATIONS

7.1. Intent-to-Treat (ITT) Population

The ITT population includes all subjects who are randomized. Subjects in the ITT population will be analyzed according to the randomized assignment, regardless of the actual treatment received. All baseline characteristics will be summarized based on the ITT population. The primary analyses of the primary efficacy endpoint will be based on the ITT population.

7.2. Safety Population

The safety population will contain all subjects who are randomized and receive at least one study drug injection. Subjects will be grouped according to their actual treatment received, not according to their randomization assignment. Subjects treated with any VM202 will be grouped in the VM202 group; subjects never treated with any VM202 will be grouped in the placebo group. All safety summaries will be based on the safety population.

7.3. Modified Intent-to-Treat (mITT) Population

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

- 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 treatment, not the actual treatment received. The mITT population will be used in the sensitivity analyses for the primary efficacy endpoint.

7.4. Per Protocol (PP) Populations

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

- Have not used the protocol-specified prohibited concomitant medications such as COX-2 inhibitor drug(s) or non-specific COX-1/COX-2 inhibiting 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.

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.

7.5. Subgroup Analysis Subsets

The primary and exploratory efficacy endpoints will be evaluated as described in Section 9.4.2 for the following subgroup subsets; except where noted, these subsets are based on the categories of the covariates described in Section 4.5.

- Wound location (weight-bearing [sole of the foot], and not weight-bearing [all other locations])
- Age (≤ median and > median)
- Baseline wound area (≤ median and > median)

These subgroups will be re-examined and may be recategorized or eliminated (if only two categories) due to small sample size (if there are < 10% of subjects within each subgroup) before unblinding for analysis.

The treatment by subgroup interaction will be examined and tested as described in Section 9.4.2. The subgroup analyses will be exploratory in nature and will be conducted in the ITT population.

8. DATA HANDLING

8.1. General Principles of Data Handling

Data screening will be conducted in a blinded fashion periodically during the conduct of the study. The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. Any questionable values or situations will be reported to the CDRC for blinded review and confirmation.

Except as noted below, the data source for all safety and efficacy endpoints will be the study's Electronic Data Capture database (DATATRAK). Extracts from the Interactive Web Response System used for randomization will be the data source for the randomized treatment. The actual treatment received will be determined from the randomized treatment with adjustments based

on externally noted protocol/procedural deviations. All wound measurement data will come from the ARANZ Medical study-specific database, and pharmacokinetic data (HGF serum levels and copies of VM202 in whole blood) will be provided by [redacted], Inc.

8.2. Visit Windows

Data at each scheduled follow-up visit will be analyzed according to the nominal visit identified on the data record. In case of multiple different visits identified with the same nominal visit, the visit with the visit date closest to the target days of each protocol-specified visit schedule (Table 5) will be used for the efficacy analyses of exploratory endpoints assessed at specific months. For visits with the same distance to the target days, the later nominal visit record will be used. Data from the other visits (if any) will be provided in data listings.

Table 5 Target Day and Month Descriptor

	1ST INJECTION	2ND INJECTION	3RD INJECTION	4TH INJECTION	DAY 60	DAY 74	DAY 90	DAY 120	DAY 210
TARGET DAY	0	14	28	42	60	74	90	120	210
FOLLOW-UP MONTH	-	-	-	-	2	2.5	3	4	7

Data from 'weekly wound assessment and dressing change', 'confirmation of ulcer healing', 'early withdrawal', and any unscheduled study visits will be used in addition to the scheduled target day visits to determine efficacy endpoints that are the response rate by a given follow-up visit (e.g., the primary efficacy endpoint) or a time to event endpoint (e.g., time to complete wound closure).

8.3. Unmasking of Randomization Codes

For the final data analyses, the randomization code will be unmasked to the project team after all the data queries related to the efficacy and safety outcomes have been resolved and the corresponding data revisions have been completed in the database.

The randomization code for individual safety data will be unmasked to the DSMB members and the team that will prepare the unblinded summary tables for the DSMB meetings. However, in order to prevent bias, the unblinded detailed safety data summaries and listings will not be shared with the sponsor management team, the CDRC, the study sites, or the team that is monitoring the clinical data collection.

The randomization code will be unmasked to the team that will prepare the interim futility analysis described in Section 10. These unmasked primary efficacy results and the conditional power will be shared with unblinded Regulatory and Clinical advisors (to be named) and may be shared with the sponsor management team. However, in order to prevent bias, the unmasked interim results will not be shared with the CDRC, the study sites, or the team that is monitoring the clinical data collection.

8.4. Multiplicity Adjustment

No multiplicity adjustment will be performed since the study has one primary efficacy endpoint with one primary population and analysis method. Sensitivity analyses for the primary efficacy endpoint are supportive and analyses for other efficacy endpoints are exploratory.

8.5. Data Safety Monitoring Board

An independent DSMB will periodically review a limited set of unblinded safety 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 the study sponsor regarding the safety of 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 reviews. The DSMB may be asked to review and provide guidance regarding protocol deviations that may affect the determination of the PP populations. Further details of DSMB responsibilities are included in the DSMB Charter.

8.6. Handling of Missing and Incomplete Data

Subjects may have missing specific data points for a variety of reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or a clinical parameter not measured at a particular point in time. The general procedures outlined below describe how missing data are handled.

8.6.1. Missing Values for the CWIQ

No imputation for missing item scores within the CWIQ Overall Quality of Life will be performed; if a Quality of Life question (item) is unanswered at a subject's visit then the Overall Quality of Life score will be missing for that visit. Missing individual item scores within the three CWIQ domains may be imputed using the average score across the non-missing items within the domain at a subject's visit provided that the proportion of missing items scores within that domain is less than 25%; otherwise the domain score at that visit is missing. Thus, at least 11 of 14 items in the social life domain, 6 of 7 items in the well-being domain, and 19 of 24 items in the physical symptoms and daily living domain must be non-missing to avoid having a missing corresponding domain score.

8.6.2. Missing / Unknown Values of Covariates

For categorical covariates, the missing / unknown values will be combined with the category with the most subjects if the missing / unknown rate is $\leq 2\%$ of the pooled data and will be classified into a separate category if the missing / unknown rate is $\geq 2\%$ of the pooled data. If the covariate is also used as a subgrouping variable, the imputed values of the subgrouping variable will not be used for subgroup categorization.

8.6.3. Missing Dates and Times

If a start or stop date for an adverse event or a concomitant medication is completely missing, it will not be imputed. If that date is partially missing, imputed dates specified in Table 6 will be used to derive the duration of the adverse event or the duration of the medication use. If the start or stop date for an adverse event is not missing but the corresponding time is partially or completely missing, imputed times specified in Table 7 will be used to derive the duration of the adverse event. For adverse event attribution relative to a specific injection, a missing start date and time should default to the date and time of the immediately documented prior injection. Missing years will not be estimated under any conditions.

Table 6 Imputation Rules for Partial Adverse Event or Concomitant Medication Start and Stop Dates

	MISSING	IMPUTATION	EXCEPTION
Start Date	Day	01	Default to Study Day 0 (day of first injection procedure) if an event starts in the same year and month as Study Day 0
	Day/Month	01JAN	Default to Study Day 0 if an event starts in the same year as Day 0
Stop Date	Day	Last day of the month	Default to the End of Study Date if the imputed event stop date is after the End of Study Date or before start day of the event
	Day/Month	31DEC	

Table 7 Imputation Rules for Partial or Missing Adverse Event Start and Stop Times

	MISSING	IMPUTATION	EXCEPTION
Start Time	Minute	00	Default to time of first injection if an event starts on Study Day 0
	Hour: Minute	00:00	
Stop Time	Minute	59	(none)
	Hour: Minute	23:59	Default to 23:59 on the End of Study Date if the imputed event stop date is after the End of Study Date or before start day of the event

9. STATISTICAL METHODS

9.1. General Principles of Data Analyses

The primary analyses of the efficacy endpoints (Sections 9.4.1.1, 9.4.4) will be based on the ITT population. Additional sensitivity analyses for the primary efficacy endpoint, utilizing other populations and/or different ways of handling missing data, will be performed to further assess the effects of the treatment (Section 9.4.1.2). Supportive subgroup and covariate-adjusted analyses of the primary efficacy endpoint in the ITT population are described in Sections 9.4.2 and 9.4.3, respectively. Analyses of the safety outcomes (Section 9.5) will be based on the safety population.

The statistical analyses will be reported using summary tables, figures and listings. Continuous variables will be summarized with means, standard deviations, medians, minimums, maximums, and number of non-missing observations for each treatment group. Other selected percentiles, such as the 25th percentile and 75th percentile, may be presented for parameters that are not normally distributed or are suspected of exhibiting that tendency. Categorical variables will be summarized by counts and the percentage of subjects in corresponding categories. All data collected, including for subjects screened but not randomized, will be included in data listings.

All inferential statistical analyses will be performed with a two-sided confidence level of 95% or a two-sided significance level of 0.05.

All analyses and tabulations will be performed using SAS® Version 9.3 or higher on a PC platform.

9.2. Subject Enrollment and Disposition

Subject disposition will be summarized for all the randomized subjects, including the number and percentage (based on the total number of subjects randomized) of subjects in each of the following categories:

- Early Termination based on the ITT population
- Safety, ITT, mITT, and PP populations

Major protocol deviations for subjects not in the PP populations will be listed.

9.3. Demographics and Baseline Characteristics

The following outcomes will be summarized by the standard methods for continuous and categorical variables described in Section 9.1.

The demographics include the following parameters:

- Age at informed consent
- Sex
- Race
- Ethnicity

The baseline characteristics include the following:

- Wound location
- Baseline wound volume
- Baseline ABI
- Baseline TBI
- Toe pressure categorized by assessment method (Doppler, PPG)

- $TcPO_2$ (collected at a subset of study centers)
- Baseline BMI
- Baseline HbA1c
- Vital signs: blood pressure, weight, BMI, heart rate, respiration rate, temperature
- Medical history categorized by MedDRA system organ class (SOC)
- 12-lead EKG Interpretation: Normal, Abnormal NCS, Abnormal CS
- Urine pregnancy test: Positive, Negative, and Not Applicable

These parameters will be summarized by treatment group for the ITT population and included in data listings. Other collected baseline characteristics will be listed only.

9.4. Efficacy Endpoint Analyses

9.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with a target wound closure by the 4-month follow-up (responder). The responder rate will be compared between the two treatment groups (VM202 and placebo).

9.4.1.1. Primary Analysis of the Primary Efficacy Endpoint

The primary analysis for the responder rate will be based on the ITT population.

Fisher's exact test will be used to compare the responder rate between the treatment groups. The 95% confidence interval of the responder rate of each treatment group will be derived using the binomial distribution and the 95% confidence interval of the responder rate difference will be calculated.

Subjects whose status of wound closure cannot be assessed at 4 months (e.g., due to earlier discontinuation from the study), will be considered non-responders.

9.4.1.2. Sensitivity Analyses of the Primary Efficacy Endpoint

To further evaluate and demonstrate the robustness of the results for the primary efficacy outcome, the following supportive sensitivity analyses will be conducted.

9.4.1.2.1. Odds ratio from a logistic regression model

A logistic regression with treatment as the main effect (using placebo as the reference category) will be used for comparing the primary efficacy endpoint between the treatment groups. The odds ratio and corresponding 2-sided 95% Wald confidence interval will be provided.

The analyses above will be performed based on the ITT population.

9.4.1.2.2. Analysis in other analysis populations

Fisher's exact test for the primary efficacy endpoint will be performed on the mITT and PP populations as defined in Sections 7.3 and 7.4, respectively. The estimated responder rates and the corresponding exact 95% confidence interval based on binomial distribution will be calculated for each treatment group. The exact 95% confidence interval of the responder rate difference will also be obtained.

9.4.2. Subgroup Analyses of the Primary Efficacy Endpoint

For each subgrouping variable identified in Section 7.5 meeting the minimum group size requirement (the subgroup is included if there are ≥ 10% of subjects within that subgroup), the available data for primary efficacy endpoint will be summarized by treatment group for the ITT population. Fisher's exact test will be performed within each such subgroup.

The Cochran–Mantel–Haenszel test will be performed to compare the responder rates between the treatment groups adjusted for the subgrouping variable. Additionally, the possible treatment-by-subgroup interaction will be tested for each subgrouping variable as follows:

- The Breslow-Day test will be performed for each subgrouping variables. If the p-value of the Breslow-Day test is ≥ 0.05, the treatment-by-subgroup interaction is not significant.

- If the interaction effect is statistically significant (i.e., p-value < 0.05), then the Gail and Simon[1] test will be used to test for the qualitative interaction at a significance level of 0.05 and provided as an aid for interpretation.

9.4.3. Analysis of Covariates

The logistic regression model with treatment and all covariates listed in Section 4.5 will be used to obtain the 2-sided 95% confidence intervals for the covariate-adjusted estimate of the treatment effect for the primary efficacy endpoint.

9.4.4. Other Efficacy Endpoints

All the exploratory efficacy analyses will be based on the available data in the ITT population.

9.4.4.1. Time to complete wound closure of foot ulcer

The log-rank test will be used to compare the distributions of the time to complete wound closure (event) between the treatment groups. Kaplan-Meier estimates of the survival function for each treatment group will be graphically displayed. Kaplan-Meier estimates of quartiles

1 Gail, MH, and Simon, R., Testing for qualitative interactions between treatment effects and patient subsets. Biometrics, 1985;41: 361-372.

(25th, median, and 75th percentiles) with 2-sided 95% confidence interval will be calculated if estimable.

The log-rank test and Kaplan-Meier methods above will be performed for this endpoint for each subgroup identified in Section 7.5 meeting the minimum group size requirement. Differences between the time-to-event distributions of the treatment groups will be compared adjusting for the subgrouping variable using the log-rank test with the subgrouping variable added as a stratification factor in the modeling.

9.4.4.2. Proportion of subjects with a wound closure by 7 months.

The proportion of subjects with wound closure by the 7-month follow-up will be calculated for each treatment group. The 95% confidence intervals of the proportion will be provided based on the binomial distribution and the exact 95% confidence intervals of the proportion difference will also be obtained. Fisher's exact test will be used to compare the proportions between two treatment groups.

The subgroup analyses described in Section 9.4.2 will also be performed for this exploratory endpoint.

9.4.4.3. Percent change in wound volume at 2, 2.5, 3, 4, and 7 months

The percent change in wound volume at 2, 2.5, 3, 4, and 7 months from baseline will be summarized for each treatment group and compared between the treatment groups using a linear mixed-effects model for repeated measures[2]. The model will include treatment, visit, and treatment-by-visit interaction as the main fixed effects, and baseline wound volume as a covariate using an unstructured variance-covariance matrix. The point estimates for the least-squares mean of the treatment difference (VM202 – Placebo) at each visit and the corresponding 95% confidence interval and p-value will be summarized. Other variance-covariance structures may be substituted if convergence problems arise using corrected Akaike's information criterion (AICC) to pick from among the following structures: compound symmetry (CS), autoregressive ("AR(1)"), variance components (VC), and Toeplitz (TOEP).

The repeated measures analysis above will be performed for this endpoint for each subgroup identified in Section 7.5 meeting the minimum group size requirement. Differences between treatment groups will be compared adjusting for the subgrouping variable using the repeated measures with the subgrouping variable added as a fixed effect in the modeling.

9.4.4.4. Percent change in wound perimeter, area and depth at 2, 2.5, 3, 4, and 7 months

The analyses on the percent change in wound perimeter, area and depth at 2, 2.5, 3, 4, and 7 months from baseline will be based on statistical methods described in Section 9.4.4.3 with the corresponding baseline wound measurement as the covariate.

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2 Vonesh, EF and Chinchilli, VM (1996), Linear and Nonlinear Models for the Analysis of Repeated Measurements, New York: Marcel-Dekker.

9.4.4.5. Proportion of subjects with formation of new ulcers on the target foot by 2, 2.5, 3, 4, and 7 months

The proportion of subjects with new ulcers formed by the 2-, 2.5-, 3-, 4-, and 7- month follow-up visits will be calculated for each treatment group. The 95% confidence intervals of the proportion will be provided based on the binomial distribution and the exact 95% confidence intervals of the proportion difference will also be obtained. Fisher's exact test will be used to compare the proportion between the treatment groups at each time point.

The subgroup analyses described in Section 9.4.2 will be performed for these exploratory endpoints.

9.4.4.6. Time to a major amputation in the target limb

The log-rank test and Kaplan-Meier methods described in Section 9.4.4.1 will be used for comparing the time to a major amputation between the treatment groups. Similar subgroup analyses will also be performed as described in Section 9.4.4.1.

9.4.4.7. Time to a minor amputation in the target limb

The log-rank test and Kaplan-Meier methods described in Section 9.4.4.1 will be used for comparing the time to a minor amputation between the treatment groups. Similar subgroup analyses will also be performed as described in Section 9.4.4.1.

9.4.4.8. Change in target limb ABI at 4 and 7 months

Change in ABI at 4 and 7 months will be analyzed in a manner similar to the repeated measurement models described in Section 9.4.4.23 with the baseline ABI values as the covariate.

9.4.4.9. Change in target limb TBI at 4 and 7 months

Change in TBI at 4 and 7 months will be analyzed in a manner similar to the repeated measurement models described in Section 9.4.4.23 with the baseline TBI values as the covariate. An additional fixed factor for the method of toe pressure assessment used (Doppler vs PPG) will be added to the models. TBI results for a subject will be omitted from the analysis if the same method was not used for all his/her toe pressure assessments.

9.4.4.10. Change in each domain score of CWIQ at 4 months and 7 months

Descriptive statistics of each CWIQ domain score and overall Quality of Life scores will be summarized by treatment group at each visit (baseline, 4 months, and 7 months). Change in each CWIQ score at 4 and 7 months will be analyzed in a manner similar to the repeated measurement models described in Section 9.4.4.23 with the baseline score as the covariate.

9.5. Safety Analyses

No formal statistical testing will be conducted for the safety analyses. The following sections summarize the descriptive analysis presented for these safety endpoints. All subjects in the safety population will be included in these analyses, with subjects grouped by the actual treatment received. All summaries will be derived based on available data at scheduled visits; safety data at unscheduled visits will only be included in data listings. No imputation will be performed for missing values.

9.5.1. Study Drug Exposure

Study drug exposure (number of injections and total volume administered) will be summarized by treatment group for Day 0, Day 14, Day 28, and Day 42 using descriptive statistics for continuous variables.

9.5.2. Injection Site Adverse Events

The number and percentage of subjects with an injection site AE, by type (injection site reaction, ulceration, allergic reaction/hypersensitivity) and overall, will be summarized by treatment group at each weekly 'wound assessment and dressing change' visit and for the pre- and post-injection assessments on scheduled injection visit days (i.e., Days 0, 14, 28, and 42). The denominator for these percentages will be based on the number in the risk set following a given injection, which is the number of subjects who received that specific injection. The number and percentage of subjects for each grade within a given type of injection site AE will be summarized by treatment group at each assessment time point.

9.5.3. Adverse Events

Adverse events will be collected once subjects meet all the study eligibility criteria and are randomized and administered study drug. However, all adverse event summaries will be restricted to Treatment-Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after first dosing and those pre-existing conditions that worsened during the study. If the start time for an AE that occurs on the first date of dosing is unknown, then the event will be assumed to be a TEAE. If the start date of an AE is unknown, the event will be assumed to be a TEAE.

The number of subjects experiencing a particular event, the percentage of subjects experiencing the event, and the total number of events will be presented. The following summaries will be created:

- Overall summary of TEAEs, which includes the subject incidence of TEAEs and total number of unique TEAEs from each of the following AE summaries without regard to MedDRA system organ class or preferred term
- TEAE by SOC and preferred term
- TEAE by SOC and preferred term by injection number. Subjects and events are attributed to a given injection only if the event start date (subject to the missing date and

time imputation rules of Section 8.6.3) occurs on or after the date and time of that injection and not before the next injection.

- TEAE by SOC, preferred term and protocol version

- TEAE by SOC, preferred term and maximum severity. At the across-SOC and preferred term levels of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events; severity within an SOC is not summarized. AEs with missing severity will be considered severe for this summary.

- TEAE by SOC, preferred term and closest relationship to study treatment (Related/Not Related). At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered 'related' for this summary; events classified as 'possibly', 'probably' or 'definitely' will be considered 'related'.

A listing of treatment-emergent SAEs (if any) will be provided, and if more than one occurs within any given preferred term, a summary of treatment-emergent SAEs by SOC and preferred term will be created.

9.5.4. Vital Signs

Vital signs and change from baseline will be summarized descriptively at each visit by treatment group. Note that weights were not collected at the weekly 'wound assessment and dressing change' visits nor at the 'confirmation of ulcer healing' visit for subjects enrolled under protocol version D or later; weights collected at such visits from subjects enrolled prior to protocol version D will be included in listings only.

9.5.5. HbA1c, Serum Chemistry and Hematology

Shift tables (i.e., normal or abnormal at baseline versus normal or abnormal at follow-up in a 2-by-2 contingency table) based on the normal range will be provided to assess changes in laboratory values from baseline to follow-up results for each scheduled follow-up visit. Additionally, shift tables of severity (low, normal, high) at baseline vs low, normal and high at each scheduled follow-up visit will also be summarized for hematology and chemistry parameters. Low and high severities are with respect to the lower and upper limits of normal, respectively, while normal is within normal limits. The counts and percentage of subjects with each of the 4 possible "shift" outcomes will be calculated by treatment group.

Individual laboratory parameter values and changes from baseline will be summarized descriptively by treatment group at each scheduled follow-up visit.

Laboratory values and their center-specific normal ranges will be listed and summarized using SI units. For the WBC differentials, only the absolute values will be summarized; percent differentials, if provided by the study center, will be listed only.

9.5.6. Prior and Concomitant Medications

Prior medications are those medications taken within 60 days of the first injection of study drug. Concomitant medications are those medications taken on or after the day of the initial dose of study drug. All prior and concomitant medications will be assigned preferred drug names using WHODDE. Prior and concomitant medications of interest will be determined by the CDRC and will be used to define the per-protocol populations.

9.5.7. Retinal Fundoscopy

Retinal fundoscopy findings in each eye (presence or absence of proliferative retinopathy, other finding) at screening and the 7-month follow-up and any changes from the baseline at follow-up will be summarized descriptively by treatment group.

9.5.8. Pharmacokinetics

HGF serum levels and the number of copies of VM202 in whole blood will be analyzed by an independent lab designated by the study sponsor. Data will be listed only.

10. INTERIM ANALYSIS

Due to the early stopping of the study, the protocol-specified interim analysis will not be conducted.