A PHASE 2 MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO–CONTROLLED, DOSE RANGE FINDING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRAMUSCULAR INJECTION OF HUMAN PLACENTA-DERIVED CELLS (PDA-002) IN SUBJECTS WHO HAVE DIABETIC FOOT ULCER WITH AND WITHOUT PERIPHERAL ARTERIAL DISEASE

INVESTIGATIONAL PRODUCT (IP):	PDA-002
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SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Range Finding Study to Evaluate the Efficacy and Safety of Intramuscular Injection of Human Placenta-Derived Cells (PDA-002) in Subjects Who Have Diabetic Foot Ulcer (DFU) with and without Peripheral Arterial Disease (PAD).

Indication

This study will investigate the efficacy and safety of the intramuscular (IM) injection of PDA-002 in subjects who have DFU with and without PAD.

Objectives

The primary objective of the study is to evaluate the efficacy and safety of PDA-002 administered IM in subjects who have DFU with and without PAD. The secondary objective is to evaluate potential clinical efficacy of the various doses of PDA-002 in effecting changes in assessed vascular parameters including ankle-brachial index (ABI)/toe-brachial index (TBI), and transcutaneous oxygen (TcPO2) measurements.

Study Design

This is a Phase 2, randomized, multicenter, double-blind, placebo-controlled, dose range finding study in subjects who have DFU stratified into 2 parallel arms: those with and those without PAD. The study will enroll approximately 133 subjects at about 40 sites. Three dose levels of PDA-002 (3×10^6, 10×10^6 and 30×10^6 cells) versus placebo will be evaluated in a 2:2:1:2 randomization approach, with the lower number of subjects to be allocated to the highest active dose.

Subjects will undergo a Screening/Run-In /Pre-Treatment Period to determine study eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment within 28 days of Study Day 1 (Section 6.1). The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. After the Screening/Run-In/Pre-Treatment Period, subjects will be randomized to a treatment arm and will receive investigational product (IP) PDA-002 cells or placebo. Treatment assignment at baseline will be via an Interactive Voice Response System (IVRS)/or an Interactive Web Response System (IWRS) based on the presence or absence of evidence of PAD (with ABI ≥ 0.4 and ≤ 0.8 or TBI ≥ 0.30 and ≤ 0.65 or a TcPO2 $\leq$40 mmHg). The number of subjects with the above criteria of PAD is targeted to comprise approximately 50% of the study population.

In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest qualifying ulcer. During the Treatment Period subjects will receive IM injections of PDA-002 on Study Days 1 and 8. During the Follow-up Period subjects will be evaluated through 24 months. All subjects are to receive standard treatment for DFU in addition to IP or placebo throughout the study. An external Data Monitoring Committee (DMC) will be convened to review interim efficacy and safety data when approximately 25%, 50%, and 75% of subjects complete the Month 3 assessment. Study enrollment will be ongoing during these scheduled reviews. At approximately 4Q2015, an administrative interim analysis of unblinded data will be conducted

by members outside of the study team for the purpose of determining whether to allocate future resources to the program.

Study Population

Type 1 and Type 2 diabetic subjects who have DFU and an ulcer severity of Grade 1 (full thickness only) or Grade 2 on the Wagner Grading Scale (Appendix A) of greater than 1 month duration which has not adequately responded to conventional ulcer therapy. The study will include subjects with PAD (as defined as an ABI ≥ 0.4 and ≤ 0.8 or TBI ≥ 0.30 and ≤ 0.65 or a TcPO2 ≤ 40 mmHg) and those without PAD.

Length of Study

The study consists of a Screening/Run-In/Pre-Treatment Period of up to 28 days. The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. Following this, subjects will undergo a 7-day Treatment Period (Treatment on Study Days 1 and 8) plus a Follow-up Period to the end of the trial at approximately 24 months.

Study Treatments Subjects will be randomized to one of the following dose levels of PDA-002 or placebo based on entry into the study:

- PDA-002 Dose Level 1: 3×10^6 cells administered on Study Days 1 and 8
- PDA-002 Dose Level 2: 10×10^6 cells administered on Study Days 1 and 8
- PDA-002 Dose Level 3: 30×10^6 cells administered on Study Days 1 and 8
- Placebo subjects will receive the same volume of placebo administered in the same manner as the IP

Overview of Efficacy Assessments

The following efficacy assessments will be performed as outlined in the Table of Events (Table 1).

1. Complete closure of the index ulcer, defined as closure within 3 months of treatment and retaining wound closure for the subsequent 4 weeks.
2. Ulcer Closure and Complete wound closure of the index ulcer up to 6 months.
3. Ankle-brachial index and toe brachial index will be calculated by dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm.
4. The number, size of all ulcers and 50% closure of the index ulcer will be evaluated and photographed
5. Transcutaneous oxygen measurements.
6. Time to major amputation (above the ankle) of treated leg, minor amputations, to reopening of ulcer, to doubling/halving of index ulcer total surface area from baseline, de novo gangrene and foot wound infection.
7. Wagner Grading Scale.
8. Rutherford Criteria.

[redacted]

9. Leg rest pain score visual analog scale (VAS) graded from 0 (pain free) to Grade 10 (maximum pain).
10. Health quality of life assessments.
11. Immunological and Inflammation Assessments
12. Hemoglobin A1c
13. Circulating endothelial cells (CECs)
14. Vascular parameters of indocyanine green angiography (ICGA) in a subset of subjects from selected sites who have the equipment. The relevant parameters are the following: starting intensity, ingress, ingress rate, egress, egress rate and end intensity.

Overview of Safety Assessments

Safety will be assessed by the frequency and severity of adverse events (AEs). To this end, the following safety assessments will be performed as outlined in the Table of Events (Table 1).

1. Adverse events and serious adverse events (SAEs).
2. Vital signs, height and weight, body mass index (BMI), and physical examinations.
3. Clinical laboratory tests:
   a. Serum chemistry, hematology, and urinalysis
   b. Coagulation tests
      - Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin activation time (TAT)
      - D-dimers
      - Fibrinogen
      - Platelets
   c. Tryptase and Histamine
   d. Immunological and Inflammation Assessments
      - Anti-human leukocyte antigen (HLA) antibodies
4. Assessment of injection sites.
5. Twelve-lead electrocardiograms (ECGs).
6. Retinal examinations
7. Concomitant medications and procedures.
8. Overall survival at 24 months (time from PDA-002 administration to any cause of death, subjects still alive will be censored at the date of last follow-up).
9. Incidence of hospitalization (all cause).

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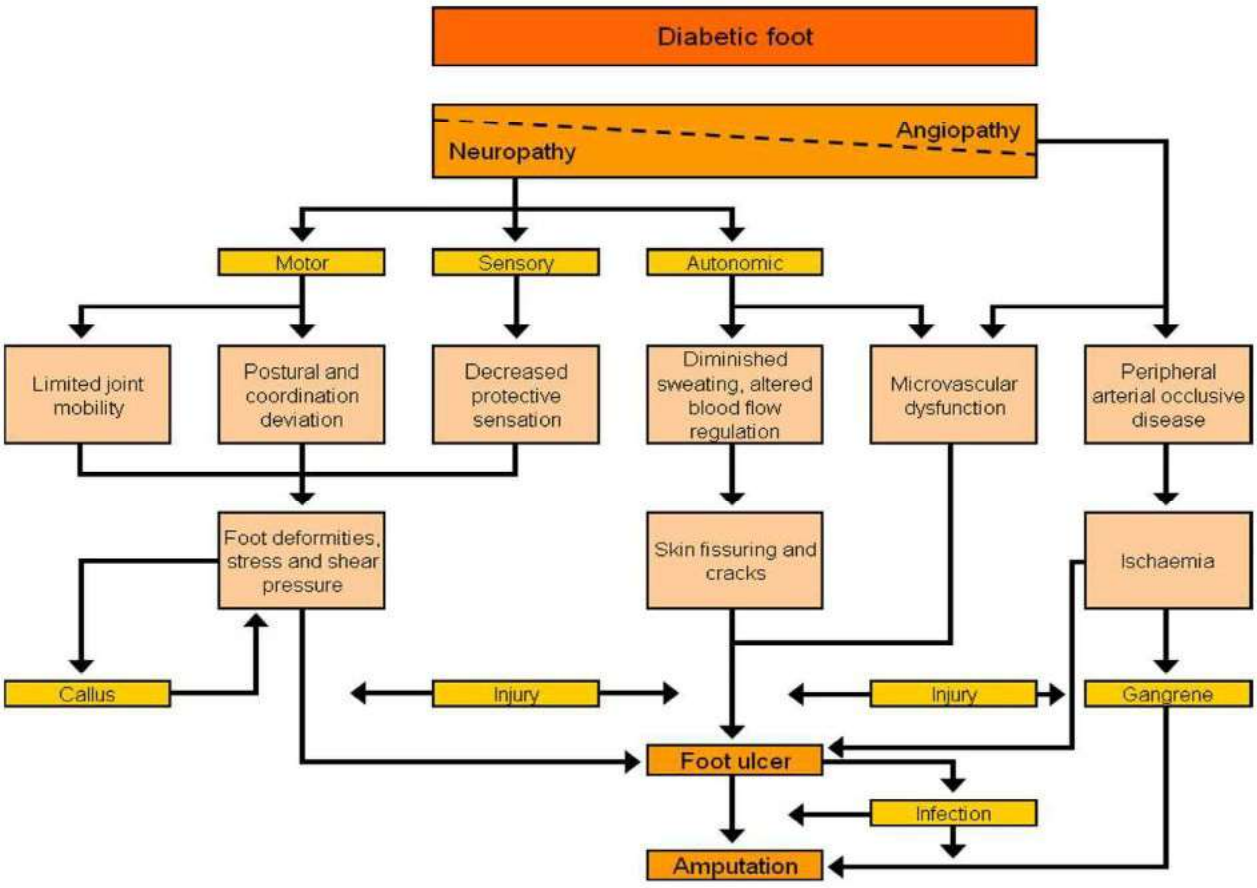
1. INTRODUCTION

Diabetes mellitus is a disease in which hyperglycemia damages the nerves, kidneys, eyes, and blood vessels over time. The estimated incidence of diabetes in the United States (US) exceeds 1.9 million new cases annually, with an overall prevalence of over 25 million people or 8.3% of the US population (Centers for Disease Control and Prevention, 2011). Type 2 diabetes (adult onset or non-insulin dependent diabetes) is by far the most common form, occurring in about 95% of patients diagnosed with diabetes.

Diabetic foot ulcer is a major complication of all forms of diabetes, and occurs in about 15% of all diabetic patients. Medical problems related to foot ulcers commonly develop in people with diabetes and can quickly become serious and/or life-threatening, as they frequently become infected and are a major cause of hospital admissions (Bassi, 2012; Dang, 2003; Pinzur, 2005). In the 1983-90 National Hospital Discharge Summary (NHDS) data (Harris, 1995), 6% of hospital discharge records that listed diabetes also listed a lower extremity ulcer condition, and chronic ulcers were listed on 2.7% of records. Clinical epidemiologic studies suggest that foot ulcers precede about 85% of lower extremity amputations (Harris, 1995; Palumbo, 1995; Reiber, 1999). Nearly 80,000 lower extremity amputations are performed on diabetics each year (Margolis, 2011). The basic schema for the diabetic foot and complications are listed below from Lepäntalo (Lepäntalo, 2011) (Figure 1).

Figure 1: Pathways to Medical Complications in the Diabetic Foot



Treating DFUs includes awareness of the complexity that underlies the pathophysiology and the need to take a multifactorial approach (Lepäntalo, 2011) as recommended by the International Working Group. These recommendations are as follows:

- Patients in need of revascularization to improve perfusion and achieve healing should be identified by an extensive clinical examination and noninvasive, vascular testing.
- Intensive management of diabetes, including glycemic control and limitation of platelet aggregation, treatment of hypertension and dyslipidemia.
- Antibiotic therapy is necessary for virtually all infected wounds, but it is not beneficial for noninfected ulcers and is insufficient without appropriate wound care.
- Surgical intervention (local debridement of callus and necrotic tissue) for moderate or severe infections is likely to decrease the risk of major amputation.
- Dressings; adequate nutrition; pressure relief in the areas of the foot that are most subject to weight bearing.
- Surgical correction of a predisposing deformity may be needed.

Patients who have DFU with PAD have a limited ability to heal a foot ulcer compared to patients without PAD. Bakker et al. reported that in patients with DFU, limb perfusion as measured by a patient's ankle blood pressure, toe pressure, and limb transcutaneous oxygen pressure predicted the likelihood that a patient's ulcer would heal (Bakker, 2012). Similarly, in an observational study of a cohort of patients with PAD and limb ulcer, Marston et al. reported an ulcer healing rate of approximately 10% at 3 months in the overall cohort (Marston, 2006). In this cohort, 70% of patients had diabetes and 83% of patients had an ulcer present on the foot. This rate of healing was lower than the observed rates of ulcer healing in patients with DFU without substantial PAD treated with topical therapies (approximately 20% to 40%) at 3 months (Apligraf PI, Dermagraft PI).

Treatment challenges emerge and become narrowed in DFU patients when they are resistant to conservative treatment methods, not responsive to concomitant medication therapy, and where by-pass surgery and percutaneous revascularization are not options because of the widespread distribution of the vascular obstruction. Lower extremity peripheral vascular disease (PVD) is one of the most important causes for pain, nonhealing ulceration, gangrene, and amputation in individuals with or without diabetes (Gibbons, 2003). For such patients, therapeutic angiogenesis using cell based therapy to promote blood vessel development may offer an alternative, promising treatment option (Hirsch, 2006; Sanchez-Alverez, 2011; Takeshita, 1994).

Human placenta-derived cells (PDA-002) are characterized as a cellular immune modulating agent with therapeutic potential. PDA-002 is a mesenchymal-like cell population derived from normal, full-term human placental tissue. [redacted]

Similar to mesenchymal stromal cells (MSCs) (Aggarwal, 2005; Nauta, 2007) in vitro studies have shown that PDA-002 is capable of immunomodulation. [redacted]

[redacted]

As PDA-002 can potentially have a therapeutic effect in patients with DFU by potentially modulating the immune system, or inducting angiogenesis, the early phase clinical program is designed to evaluate the treatment effect of patients who have DFU with and without PAD.

[redacted]

Study PDA-002-DFU-002 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose range finding study. The study will enroll approximately 133 subjects in four treatment groups (3×10^6 cells, 10×10^6 cells, 30×10^6 cells, or placebo). The primary objective of the study is to assess the efficacy and safety of PDA-002 administered IM in subjects who have DFU with and without PAD. The secondary objective is to explore potential clinical efficacy by assessing changes in vascular parameters such as ABI and/or TBI, and TcPO2. Secondary endpoints include evaluating changes in Rutherford Criteria; number and size of ulcers; leg rest pain score using a VAS; time to healing, overall survival at 24 months; and the time to first occurrence of major amputation (above the ankle) of treated leg, all-cause mortality, doubling/halving of index ulcer total surface area from baseline, de novo gangrene and foot wound infection. Health related outcomes and quality of life assessments will also be conducted. Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the IP.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

[redacted]

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the efficacy and safety of PDA-002 administered intramuscularly (IM) in subjects who have DFU with and without PAD.

2.2. Secondary Objectives

The secondary objective is to explore potential clinical efficacy of the various doses of PDA-002 in effecting changes in assessed vascular parameters including ABI/TBI, and TcPO2 measurements.

2.3. Exploratory Objectives

[redacted]

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

The primary efficacy endpoint is to evaluate complete wound closure of the index ulcer, defined as closure within 3 months after dosing [Visit 8] and retaining wound closure for the subsequent 4 weeks in subjects who have DFU with and without PAD.

The primary safety endpoint is to evaluate the frequency and severity of AEs. To this end, the following safety assessments will be performed as outlined in the Table of Events (Table 1).

1. Number and frequency of AEs and SAEs.
2. Vital signs, height and weight, and physical examinations.
3. Clinical laboratory tests:
   a. Serum chemistry, hematology, and urinalysis
   b. Coagulation tests
      - Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin activation time (TAT)
      - D-dimers
      - Fibrinogen
      - Platelets
   c. Tryptase and Histamine
   d. Immunological and Inflammation Assessments
      - Anti-human leukocyte antigen (HLA) antibodies
4. Assessment of injection sites.
5. Twelve-lead ECGs.
6. Retinal examinations.
7. Concomitant medications and procedures.
8. Overall survival at 24 months (time from PDA-002 administration to any cause of death, subjects still alive will be censored at the date of last follow-up).
9. Incidence of hospitalization (all cause).

[redacted]

3.2. Secondary Endpoint(s)

Secondary endpoints will include evaluating clinical, vascular assessment parameters, health related measures (quality of life [QoL] assessments) ulcer and neuropathy assessments in subjects who have DFU with and without PAD. Additionally, the number of wound closures, time to healing and healing of contra-lateral ulcers will be assessed as outlined in the Table of Events (Table 1).

1. Time to ulcer closure and complete wound closure of the index ulcer up to 6 months.
2. ABI and TBI will be calculated by dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm.
3. The number, size of all ulcers and 50% closure of the index ulcer will be evaluated and photographed.
4. Transcutaneous oxygen measurements (Appendix F).
5. Time to major amputation (above the ankle) of treated leg, minor amputations, to re-opening of ulcer, to doubling / halving of index ulcer total surface area from baseline, de novo gangrene and foot wound infection.
6. Wagner Grading Scale (Appendix A).
7. Rutherford Criteria (Appendix B).
8. Leg rest pain score-visual analog scale (VAS) graded from 0 (pain free) to Grade 10 (maximum pain) (Appendix D).
9. 36-item Short Form Health Survey (SF-36).
10. Diabetic Foot Ulcer Scale Short Form (DFS-SF) index ulcer (Appendix G).
11. Neuropathy Assessment by Michigan Neuropathy Screening Instrument (screening) and Patient Global Impression of Change in Neuropathy (PGICN).
12. EuroQOL-5D- health utility index assessment (EQ-5D).

3.3. Exploratory Endpoint(s)

[redacted]

[redacted]

[redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, randomized, multicenter, double-blind, placebo-controlled, dose range finding study in subjects who have DFU stratified into 2 arms: those with and those without PAD. The study will enroll approximately 133 subjects at about 40 sites. Three dose levels of PDA-002 (3×10^6, 10×10^6 and 30×10^6 cells) versus placebo will be evaluated in a 2:2:1:2 randomization approach, with the lower number of subjects to be allocated to the highest active dose.

Subjects will undergo a Screening/Run-In/Pre-Treatment Period to determine study eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment within 28 days of Study Day 1 (Section 6.1). The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. After the Screening/Run-In/Pre-Treatment Period, subjects will be randomized to a treatment arm and will receive IP or placebo. Treatment assignment at baseline will be via an Interactive Voice Response System (IVRS)/or an Interactive Web Response System (IWRS) based on evidence of PAD (with ABI ≥ 0.4 and ≤ 0.8 or TBI ≥ 0.30 and ≤ 0.65 or a TcPO2 value ≤ 40 mmHg). The number of subjects with a diagnosis of PAD is targeted to comprise approximately 50% of the study population.

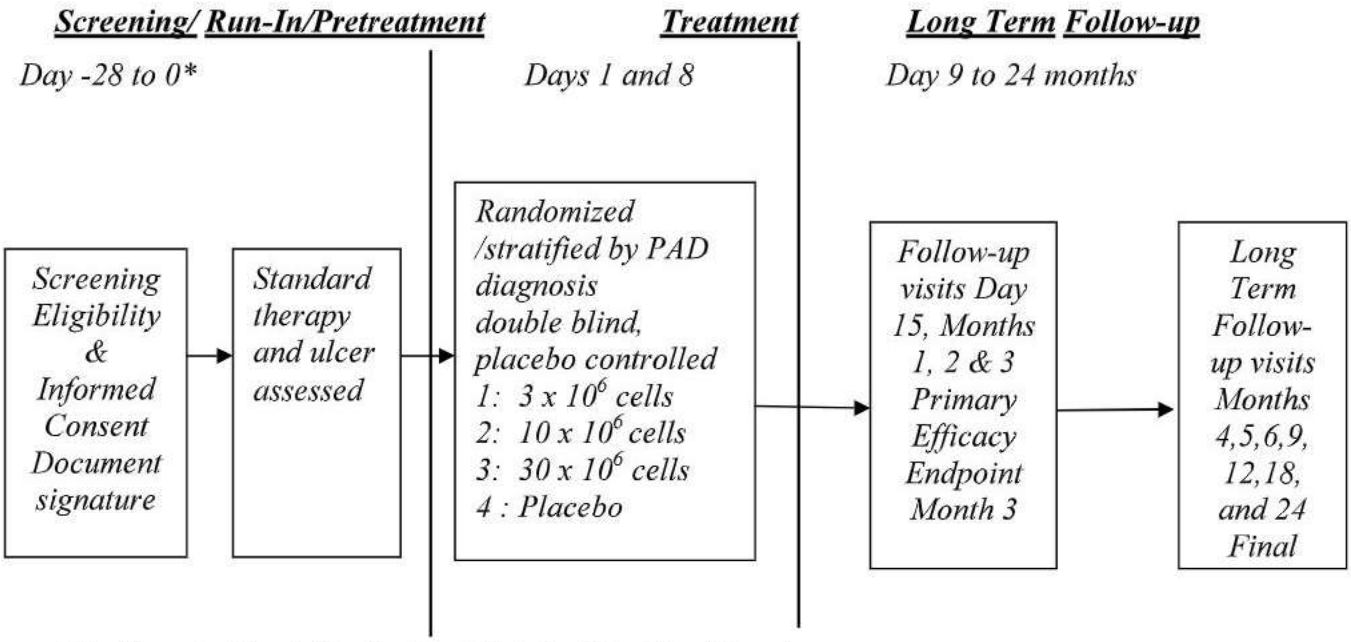
In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest qualifying ulcer. During the Treatment Period, subjects will receive IM injections of PDA-002 on Study Days 1 and 8. During the Follow-up Period subjects will be evaluated as indicated in the Table of Events (Table 1). All subjects are to receive standard treatment for DFU in addition to IP or placebo throughout the study. All subjects who receive any dose of PDA-002 or placebo will participate in the 24-month Follow-up Period. Refer to Figure 2 in this section for the overall study visit design and (Section 5) for the scheduled visits and assessments.

The primary efficacy assessment will evaluate complete wound closure of the index ulcer, defined as ulcer closure within 3 months after dosing [Visit 8] and retaining wound closure for the subsequent 4 weeks in subjects who have DFU with and without PAD treated with PDA-002.

Primary safety assessments include the frequency and severity of adverse events and the safety assessments in the Table of Events (Table 1).

Additional secondary efficacy assessments include evaluation of changes in ABI/TBI, Wagner Grading Scale, Rutherford Criteria, number, and size of ulcers; leg rest pain score using a VAS, and TcPO2 measurements (Section 6.2.5).

Figure 2: Overall Study Design



* The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks.

4.2. Study Design Rationale

This study will evaluate the efficacy and safety of IM injection of PDA-002 in Type 1 and 2 diabetic subjects who have DFU with and without PAD. There are limited options available for DFU subjects when conservative treatment methods and vascular surgery have not and/or are not expected to provide benefit. [redacted]

The dose levels and schedule for this study are based upon the Phase 1 study PDA-002-DFU-001. [redacted] The schedule was based

[redacted]

4.3. Study Duration

Subjects will undergo a Screening/Run-In/Pre-Treatment Period visits to determine study eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment within 28 days of Study Day 1 (Section 6.1). The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. After the Screening/Run-In/Pre-Treatment Period visits, subjects will be randomized to a treatment arm and will receive IP or placebo. Treatment assignment at baseline will be via an Interactive Voice Response System (IVRS)/or an Interactive Web Response System (IWRS) based on the presence or absence of evidence of PAD (with ABI $\geq$ 0.4 and $\leq$ 0.8 or TBI $\geq$ 0.30 and $\leq$ 0.65 or a TcPO2 value $\leq$ 40 mmHg). The number of subjects with a diagnosis of PAD is targeted to comprise approximately 50% of the study population.

The Treatment Period is a 7-day period (treatment on Study Days 1 and 8). Following the Treatment Period, subjects will enter a Follow-up Period. The trial will last approximately 24 months.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary, exploratory, and safety analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

[redacted]

5. TABLE OF EVENTS

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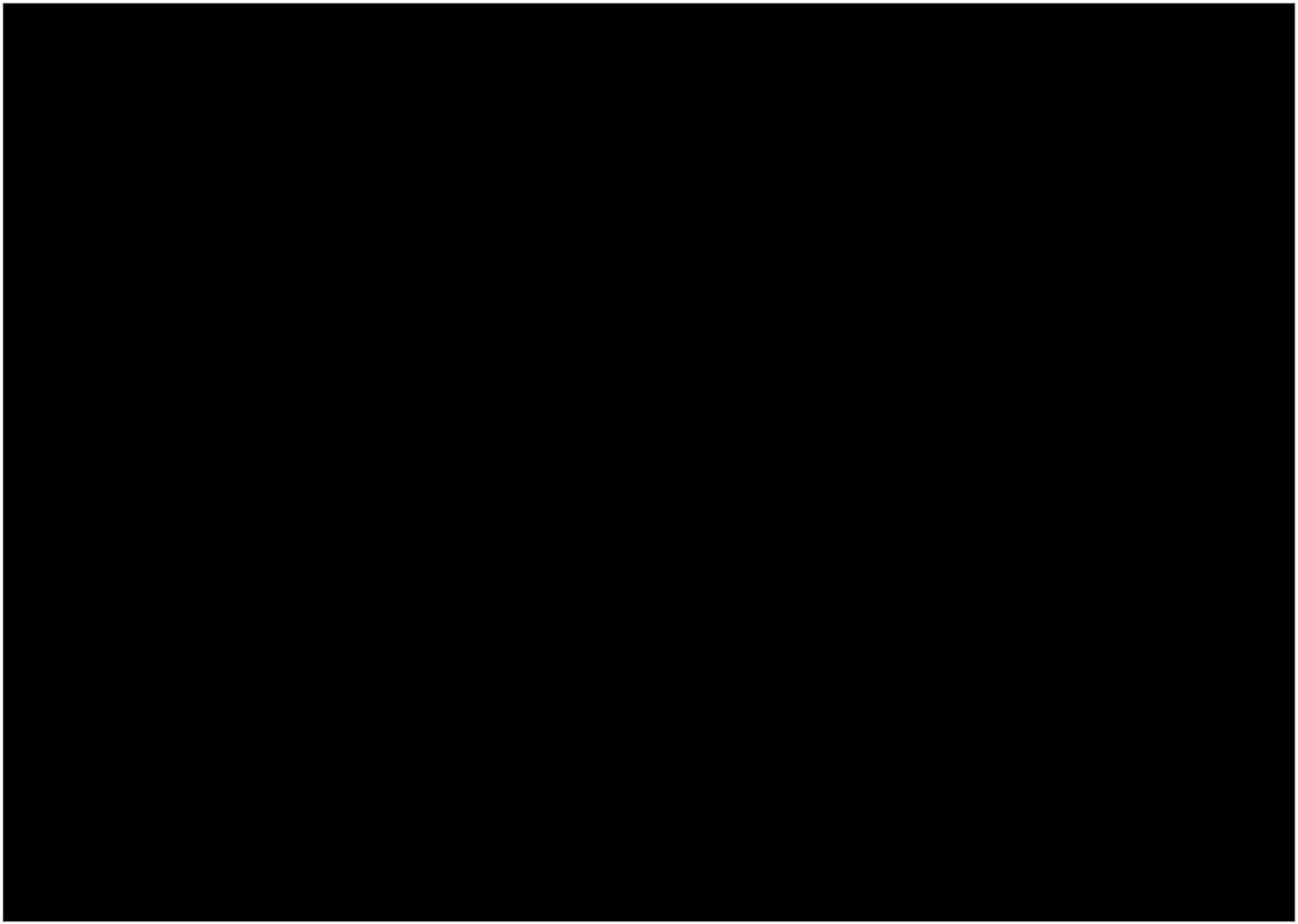

Table 1: Table of Events (Continued)

[redacted]

Table 1: Table of Events (Continued)

[redacted]

Table 1: Table of Events (Continued)

[redacted]

6. PROCEDURES

The study is divided into 3 periods: Screening/Run-In/Pre-Treatment Period, Treatment and Follow-up with associated evaluations and procedures that must be performed at specific time points. The Screening/Run-In/Pre-Treatment Period is defined as the 28 days before administration of the IP during which subjects are evaluated for eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment (Section 9.1). The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. The Treatment Period consists of Study Days 1 and 8 when the IP is administered. The Follow-up Period begins after dosing on Study Day 8 and is completed at Month 24.

The schedule of study procedures is shown in the Table of Events (Table 1) and the Study Design Schema (Figure 2). A description of specific study procedures is provided in the following subsections.

6.1. Study Entry, Screening, Run-In Period, Pretreatment Visit and Treatment Period

Explain Study and Obtain Written Informed Consent

Before or at Visit 1, the Investigator or designee will explain the study to the subject, answer all of his or her questions and obtain written informed consent and Health Insurance Portability Accountability Act (HIPAA) authorization before performing any study-related procedures. Procedures conducted as part of standard of care performed prior to signing of the informed consent must be documented in the eCRF.

A copy of the informed consent will be given to the subject.

Demographic and Medical History Including Baseline Signs and Symptoms

Demographics and medical history will be obtained by the Investigator or designee during Screening. Demographics will include date of birth, gender, ethnicity, and race. Medical history should include history relevant to the study indication, psychiatric history, current medical conditions, height and weight information on all prior therapies related to the study indication, and any allergic conditions. A physical examination, including collection of vital signs and ECG, will be performed. Baseline signs and symptoms will be recorded as medical history. Prior therapies should include all medications (including contraceptive measures and over-the-counter products) and therapies used within 30 days prior to the Screening Visit. Rutherford Criteria, Wagner Grading Scale for foot lesions, measurement/assessment and photography of ulcers, ABI and TBI, and leg rest pain score using a VAS, and TcPO2 content will be assessed.

Review Inclusion/Exclusion Criteria Including Concomitant Medications

Prior to treatment with IP all subjects will be screened for study eligibility. Any concomitant medications the subject is currently taking will be recorded and assessed for eligibility (Section 9). Samples for serum chemistry, serum glucose screening, hematology, urinalysis, CECs, hemoglobin A1c, serum pregnancy test (only in females of childbearing potential [FCBP]), coagulation assessments, and exploratory biomarkers will be collected. If the subject meets all the study eligibility criteria (Section 7), the subject will be randomly assigned to

receive either active treatment (PDA-002) at one of 3 doses or placebo which will be communicated to the site pharmacist or delegated site staff who will remain unblinded.

If the subject does not meet all of the study eligibility criteria, the subject will be considered a screen failure and will be discontinued and replaced.

Screening/Run-In/Pre-Treatment Visit

The Screening/Run-In/Pre-Treatment Period visit consists of 28 days before administration of the IP during which subjects are evaluated for eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment (Section 9.1). The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. During these visits, an assessment of study eligibility will be performed as outlined in the Table of Events (Table 1). During this time all subjects will receive standard treatment for their ulcer including pressure offloading, wound care and debridement and will continue with this treatment throughout the study.

For offloading, all subjects will be required to reduce pressure and stress on the index ulcer if the ulcer is located on the plantar aspect of the foot using a Removable Cast Walker specific for the management of diabetic ulcers, (ie, Bledsoe CAM Diabetic Boot or Ossur DH Offloading Walker, or similar as appropriate to what the site has available). The Investigator will assure that each subject is undergoing offloading at least 4 weeks after initial ulcer closure.

For wound care and debridement, subjects will receive appropriate wound care including dressings and other treatments deemed necessary by the Investigator. Debridement will be performed as necessary at the discretion of the Investigator and will not be considered an adverse event.

During the Screening/Run-In/Pre-Treatment Period, the size of the index ulcer will be evaluated for eligibility prior to Treatment. Subjects with an index ulcer that has decreased or increased in size by $\geq 30\%$ as assessed by wound photography during the Pre-Treatment visit will be excluded from the study.

Treatment

Subjects will be treated with IP administered IM on Study Days 1 and 8. In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest qualifying ulcer. Prior to dosing with the IP, subjects will undergo a physical examination, including weight and vital signs, an ECG, and a review of concomitant medications and procedures. Blood samples should be drawn on the day of treatment prior to dosing with the IP as indicated in the Table of Events (Table 1). A urine pregnancy test in FCBP, should also be performed as indicated in the Table of Events (Table 1) prior to dosing with IP. Assessment of Rutherford Criteria, Wagner Grading Scale for foot lesions, measurement/assessment and photographs of ulcers, and leg rest pain score (VAS), should be performed as outlined in the Table of Events (Table 1). Determination of ABI, TBI, and TcPO2 measurements should be performed as outlined in the Table of Events (Table 1).

Investigational product will be thawed and diluted as per the pharmacy manual. Thawing of the IP should not begin until it is confirmed that the subject meets all eligibility criteria. The injections of IP (PDA-002 or placebo) will be administered as described in Section 8.2. Vital signs (including heart rate, respiration, resting systolic and diastolic blood pressure, body temperature will be monitored prior to starting the injections and at 1 and 2 hours after completion of the injections. Blood samples for tryptase and histamine, coagulation

assessments, CECs and exploratory biomarkers will be collected. Biomarkers will be collected before IP injection. Injection sites will be assessed. See Section 6.3.2 regarding injection site reactions.

6.2. Efficacy Procedures

6.2.1. Rutherford Criteria

Limbs will be assessed using the Clinical Description of the Rutherford Criteria (Rutherford Classification of Chronic Limb Ischemia) (Appendix B) during Screening, and at the Month 3 and Month 6 visits. Subjects who improve by at least one numeric category will be defined as improved, while subjects who fail to improve or deteriorate by at least one category will be defined as non-responsive.

6.2.2. Ulcer Assessment

The measurement of the index ulcer is to be evaluated and measured after debridement (if necessary) at the visits outlined in the Table of Events (Table 1). The index and all ulcers including bilateral ulcers will be graded using the Wagner Grading Scale and will be photographed (Appendix A). An assessment of the ulcer and photographs of closed index ulcers will also be taken 4 weeks after ulcer closure to confirm complete wound closure. Ulcer closure is defined as skin closure of the index ulcer without drainage or need for dressing. Complete wound closure is defined as closure of the index ulcer and retaining wound closure for the subsequent 4 weeks. Limbs will also be assessed for gangrene. Information for ulcers assessed at non-scheduled visits will also be collected. The procedure for obtaining and processing images will be described in a separate manual provided by the manufacturer and distributed to the sites.

6.2.3. Ankle-Brachial Index and Toe-Brachial Index

The ABI and TBI should be obtained bilaterally by measuring both the posterior tibial and dorsalis pedis arteries for the ABI and the first or second toe digital artery for the TBI dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm. ABI and TBI will be assessed as indicated in the Table of Events (Table 1).

6.2.4. Pain

Leg rest pain score will be assessed using a visual analog scale VAS (Appendix D) during as indicated in the Table of Events (Table 1).

6.2.5. Transcutaneous Oxygen Measurements

Transcutaneous oxygen measurements (TcPO2 measurements) will be performed as indicated in the Table of Events (Table 1) at Screening, at Month 3 and Month 6 and at early termination. The area measured with TcPO2 should be free of edema and thickened skin. Simultaneous measurements of TcPO2 values will be obtained at the chest and at the dorsum of both feet. The laboratory room temperature will be maintained at approximately 25°C. All subjects will be acclimatized for a minimum of 10 minutes before commencing the study. The device should be calibrated according to the manufacturer's guidelines. The measurements will be simultaneously performed bilaterally on the lower extremities, by a vascular technologist or a designated trained

[redacted]

staff member with the subject resting in supine position during one session, applying one electrode at the dorsum of the foot and one reference at the thorax (Appendix F). The reported values represent averages of the measurements assessed by the observer. The process by which the TcPO2 data is obtained and stored is defined in a separate core lab manual (de Meijer, 2008).

6.2.6. The 36 Item Short Form Health Survey Assessment

All subjects will be evaluated for health related quality of life (HRQOL) using the SF-36 as indicated in the Table of Events (Table 1).

6.2.7. Diabetic Foot Ulcer Assessment Scale

All subjects will be evaluated using the 29-item DFS-SF. Assessment will be performed as indicated in the Table of Events (Table 1) (Appendix G).

6.2.8. Neuropathy Assessment

All subjects will be assessed for diabetic neuropathy using the Michigan Neuropathy Screening Instrument at Screening. Patient Global Impression of Change in Neuropathy (PGICN) will be assessed as indicated in the Table of Events (Table 1).

6.2.9. Health Utility Index Assessment

All subjects will be evaluated for Health Utility Index using the 5-question EuroQOL 5D Health Utility Index (EQ-5D) scale as indicated in the Table of Events (Table 1).

6.2.10. Retinal Assessment

All subjects will be evaluated for diabetic retinopathy as indicated in the Table of Events (Table 1) using the International Clinical Diabetic Retinopathy Disease Severity Scale and rated numerically from 0 (no abnormalities) to 4 (proliferative diabetic retinopathy) (Appendix H).

6.2.11. Other Clinical Assessments

Subjects will be assessed for amputation status and need for hospitalization. Assessments will be performed as indicated in the Table of Events (Table 1).

Major amputation is defined as that occurring above the ankle. Minor amputations will also be recorded. The reason for amputation will be assessed and documented (pain, gangrene, disease progression, local infection, systemic infection, failure to heal, osteomyelitis, other) on the electronic case report form (eCRF).

6.2.12. Indocyanine Green Angiography

Indocyanine green angiography (ICGA) allows for the collection of quantitative and qualitative data to assess skin perfusion using a charge coupled camera, a laser, and intravenous contrast. The area around the index ulcer will be assessed using ICGA during Screening, Month 3 and Month 6 (Table 1). The relevant parameters are the following: starting intensity, ingress, ingress rate, egress, egress rate and end intensity.

The procedure and collection of data will be as described in the manufacturer's manual.

Note: This procedure will be performed only at selected sites that have the equipment.

6.3. Safety

Safety will be assessed by an ongoing review of clinical laboratory tests (hematology, serum chemistry, coagulation, urinalysis, physical examination results, vital sign measurements, 12-lead ECG, height, weight, use of concomitant medications/procedures, and the incidence and severity of injection site and injection-related reactions (including tryptase and histamine), non-emergent and treatment-emergent AEs.

6.3.1. External Data Monitoring Committee

An external DMC will monitor all safety information to ensure subject safety in accordance with a separate charter. In addition, the external DMC will have access to efficacy data in order to assess the overall benefit risk for subjects participating in the study. The external DMC will be comprised of members who are not involved in the day-to-day activities of the PDA-002 DFU study team. Data review packets will be forwarded to the DMC members for review approximately seven (7) days prior to each scheduled DMC teleconference/meeting. Data will be current through approximately fourteen (14) days prior to each scheduled DMC teleconference/meeting.

The external DMC will be convened to review interim efficacy and safety data when approximately 25%, 50% and 75% percent of subjects complete the Month 3 assessment. Study enrollment would be ongoing during these scheduled reviews.

The external DMC chairman will be notified if an AE of medical interest should occur and will determine if a full DMC would need to be convened. During any period of deliberation by the external DMC on an AE of medical interest, a temporary hold on enrollment of new subjects will be instituted. The AEs of medical interest that would trigger this process are:

- Identification of 1 or more subjects within a dosing treatment arm with ≥ Grade 3 allergic reaction that is suspected to be related to the IP.
- Identification of 1 or more subjects experiencing an unexpected, treatment-related SAE within 14 days following the initial dose of the IP (Suspected Unexpected Serious Adverse Reaction [SUSARS]).
- Identification of 1 or more subjects with a new malignancy.

The sponsor will take appropriate action based upon the external DMC recommendation and this will be communicated to the Investigators. The Investigators will be responsible for notifying their Independent Review Boards (IRBs). The external DMC will evaluate on an ongoing basis all available safety data, in particular all SAEs and their potential relationship to PDA-002. The external DMC may recommend modifications to enrollment or to the study design in order to ensure subject safety. Further explanation of the roles and responsibilities of the external DMC will be outlined in the external DMC charter.

6.3.2. Injection-Related Reactions

An injection-related reaction is any sign or symptom experienced by a subject during the injections or any event occurring within 24 hours of the IP administration. The duration and severity of injection-related reactions will be collected and recorded on the eCRF.

Any allergic reaction ≥ Grade 3 and associated with the IP is to be reported as a SAE.

6.3.3. Other Safety Assessments

Adverse Events and Concomitant Medications

Adverse events and concomitant medication use will be collected from the time of the signing of the informed consent until Month 24.

Physical Examination

A full physical exam including examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, extremities, and neurological function particularly sensory and motor function of the affected leg will be performed during the Screening/Run-In Period, End of Study Visit 15 (Month 24) and Early Termination. At all other assessments, physical examinations should only be directed to evaluate reported Adverse Events (Table 1).

All abnormal findings at baseline will be recorded as medical history.

Vital Signs

Vital sign measurements include:

- Temperature (°C)
- Pulse (beat/minute)
- Respiration (breaths/minute)
- Resting systolic and diastolic blood pressure (mmHg)
- Height (cm) (At Screening only)
- Weight (kg)

Before pulse and blood pressure are measured, the subject must be resting for at least 5 minutes (the same position and arm should be used each time vital signs are measured for a given subject).

On the day of IP administration, vital signs (including heart rate, respiration, blood pressure, body temperature) will be monitored prior to starting the injections and at 1 and 2 hours after completion of the injections (Table 1).

Contraception

Females of childbearing potential[1] must use adequate contraception for the duration of their participation in the study (which includes 28 days prior to starting IP, during the study therapy including dose interruptions and the Follow-up Period or for 28 days after discontinuation of study therapy). Adequate contraception is defined as the simultaneous use of two of the following forms of contraception methods: oral, injectable or implantable hormonal contraception; tubal ligation; intrauterine device (IUD); barrier contraceptive with spermicide; or a vasectomized partner (Table 1).

[1] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).Tubal ligation is not sufficient for non-child bearing potential.

[redacted]

Males (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in sexual activity with FCBP for the duration their participation in the study.

Retinal Examination

Retinal examinations conducted by an ophthalmologist or optometrist will be performed during as indicated in the Table of Events (Table 1) and scored using the retinal scoring scale (Appendix H).

Electrocardiogram

A 12-lead ECG will be obtained as indicated in the Table of Events (Table 1). If a 12-lead ECG was done as part of the subject's previous routine care before signing the informed consent document and completed within 28 days before the administration of IP it does not need to be repeated. The subject should be relaxed and must be in a supine position at least 5 minutes before recording an ECG. The ECG will be reviewed by a qualified physician (paper or electronic tracing) and will be available for comparison with subsequent ECGs. The following will be recorded on the eCRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QT_cB (Bazett's formula) and/or QT_cF (Fredericia's formula) Interval (msec)
- Heart Rate (BPM)
- RR Interval (msec)

Any ECG finding that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an AE and recorded and monitored.

Clinical Laboratory Tests

Samples for serum chemistry, hematology, urinalysis, hemoglobin A1c, coagulation, CECs, exploratory biomarker samples, will be taken at the times indicated in the Table of Events (Table 1) and will be evaluated by a central laboratory. Refer to the Laboratory Manual for detailed information on the collection, storage, and shipment of blood and urine samples.

Serum Chemistry

Serum chemistry will be assessed at all visits as indicated in the Table of Events (Table 1) and will include the following:

- Calcium
- Chloride
- Potassium
- Sodium
- Total Bilirubin
- Indirect Bilirubin
- Direct Bilirubin
- Glucose

- Phosphorus
- Uric acid
- Alanine Aminotransferase (ALT; SGPT)
- Aspartate Aminotransferase (AST; SGOT)
- Creatinine
- Blood Urea Nitrogen (BUN)
- Bicarbonate or Carbon Dioxide
- Lactic Dehydrogenase (LDH)
- Alkaline Phosphatase (ALK)
- Total Protein
- Albumin

Hematology

Hematology tests will be performed at all visits as indicated in the Table of Events (Table 1) and will include the following:

- Hemoglobin
- Red Blood Cell (RBC) Count
- Absolute Neutrophil Count (ANC)
- Hematocrit
- Platelet Count
- White Blood Cell (WBC) Count and Differential Count

Urinalysis

Urinalysis will be performed at visits indicated in the Table of Events (Table 1) and will include the following:

Urine albumin and creatinine are to be collected with the morning void

- Protein
- Ketones
- pH
- Microscopic (if gross findings are positive, then a microscopic examination, including WBCs/high power field (HPF) and RBCs/HPF, will be performed).
- Leukocyte Esterase
- Glucose
- Blood (hemoglobin)
- Specific Gravity
- Bilirubin
- Urinary Albumin
- Creatinine

Immunological/Inflammation Assessments

Immunological/inflammation assessment will include the following testing:

- Anti-HLA antibodies as indicated in the Table of Events (Table 1).

Hemoglobin A1c

Hemoglobin A1c will be measured as indicated in the Table of Events (Table 1).

Coagulation Tests

Coagulation tests including assessment of PT/PTT, TAT, D-dimers, fibrinogen, and platelets will be assessed as indicated in the Table of Events (Table 1).

Tryptase and Histamine

Tryptase and histamine levels will be assessed as indicated in the Table of Events (Table 1).

Circulating Endothelial Cells, and Exploratory Biomarkers

Circulating endothelial cells (CECs) and exploratory biomarkers will be measured as indicated in the Table of Events (Table 1).

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 133 subjects will be enrolled at about 40 study centers.

7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Males and females, at least 18 years of age or older at the time of signing the informed consent document.
2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures are conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Diabetes mellitus Type 1 or Type 2.
5. Diabetic foot ulcer with severity of Grade 1 (full thickness only) or Grade 2 on the Wagner Grading Scale (Appendix A) of greater than one month duration which has not adequately responded to conventional ulcer therapy with a size of at least of 1cm^2 except if present on the toe. The maximum lesion size range in the index ulcer is $\leq$ 10 cm^2. The measurement of the index ulcer is to be evaluated and measured after debridement (if necessary) at the Screening Visit. If located on the plantar aspect of the foot, the index ulcer must be able to be adequately offloaded in the assessment of the investigator.
6. No planned revascularization or amputation over the next 3 months after Screening visit, in the opinion of the Investigator.
7. Screening should not begin until at least 14 days after a failed reperfusion intervention and at least 30 days after a successful reperfusion intervention.
8. Subjects should be receiving appropriate medical therapy for hypertension and diabetes any other chronic medical conditions for which they require ongoing care.
9. A female of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to treatment with study therapy. In addition, sexually active FCBP must agree to use 2 of the following adequate forms of contraception methods simultaneously such as: oral, injectable, or implantable hormonal contraception; tubal ligation; IUD; barrier contraceptive with spermicide or vasectomized partner for the duration of the study and the Follow-up Period.
10. Males (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in reproductive sexual activity with FCBP for the duration of the study and the Follow-up Period (Section 6.3.3).

7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he or she were to participate in the study.
3. Any condition that confounds the ability to interpret data from the study.
4. Pregnant or lactating females.
5. Subjects with a body mass index > 45 kg/m^2 at Screening.
6. AST (SGOT) or ALT (SGPT) > 2.5 x the upper limit of normal (ULN) at Screening.
7. Patient on renal dialysis for abnormal kidney function.
8. An ABI < 0.4 and or TBI < 0.3 in the leg with the index ulcer.
9. Alkaline phosphatase > 2.5 x the ULN at Screening.
10. Bilirubin level > 2 mg/dL (unless subject has known Gilbert's disease) at Screening.
11. Untreated chronic infection or treatment of any infection with systemic antibiotics, including the ulcer site, must be free of antibiotics within 1 week prior to dosing with IP.
12. Active osteomyelitis, infection, or cellulites at or adjacent to the index ulcer. Patients with a history of being treated for an osteomyelitis without a surgical resection.
13. Index ulcer that has decreased or increased in size by ≥ 30% during the Screening/Run-In/ Pre-Treatment Period.
14. Active Charcot Neuroarthropathy in the foot with the index ulcer
15. Pain at rest due to limb ischemia.
16. Uncontrolled hypertension (defined as diastolic blood pressure > 100 mmHg or systolic blood pressure > 180 mmHg during Screening at 2 independent measurements taken while subject is sitting and resting for at least 5 minutes).
17. Poorly controlled diabetes mellitus (hemoglobin A1c > 12% or a screening serum glucose of ≥ 300mg/dl).
18. Untreated proliferative retinopathy.
19. History of malignant ventricular arrhythmia, CCS Class III-IV angina pectoris [Canadian Cardiovascular Society Angina Grading Scale](Appendix I), myocardial infarction/ percutaneous coronary intervention (PCI) / coronary artery bypass graft (CABG) in the preceding 6 months prior to signing the informed consent form (ICF), pending coronary revascularization in the following 3 months, transient ischemic attack/cerebrovascular accident in the preceding 6 months, prior to signing the ICF, and/or New York Heart Association [NYHA] Stage III or IV congestive heart failure (Appendix C).
20. Abnormal ECG: new right bundle branch block (BBB) ≥ 120 msec in the preceding 3 months prior to signing the ICF.

21. Uncontrolled hypercoagulation syndrome.
22. Life expectancy less than at 2 years at the time of signing the ICF due to concomitant illnesses.
23. In the opinion of the Investigator, the subject is unsuitable for cellular therapy.
24. History of malignancy within 5 years prior to signing the ICF except basal cell or squamous cell carcinoma of the skin or remote history of cancer now considered cured or positive Pap smear with subsequent negative follow-up.
25. History of hypersensitivity to any of the components of the product formulation (including bovine or porcine products, dextran 40, and dimethyl sulfoxide [DMSO]).
26. Subject has received an investigational agent —an agent or device not approved by the US Food and Drug Administration (FDA) for marketed use in any indication— within 90 days (or 5 half-lives, whichever is longer) prior to treatment with study therapy or planned participation in another therapeutic study prior to the completion of this study.
27. Subject has received previous investigational gene or cell therapy.

[redacted]

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product(s)

PDA-002 is characterized as a cellular angiogenic and immune modulating agent with therapeutic potential. The product contains a mesenchymal-like cell population derived from normal, full-term human placental tissue. [redacted]

8.2. Treatment Administration and Schedule

Investigational product (IP) will be administered on Study Days 1 and 8. [redacted]

[redacted]

Note: For this study, all ≥ Grade 3 allergic reactions associated with the use of IP must be reported to Celgene Cellular Therapeutics(CCT) as an SAE within 24 hours of the Investigator's knowledge of the event.

8.3. Method of Treatment Assignment

[redacted]

8.4. Packaging and Labeling

[redacted]

[redacted]

[redacted]

8.5. Investigational Product Accountability and Disposal

[redacted]

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to the investigative site during the course of the study.

If any IP is lost or damaged, its disposition should be documented in the source documents. The sponsor will provide instructions to the Investigator(s) for the return or destruction of unused IP and IP supplies at the end of the study.

PDA-002 is regulated by the US FDA as a human cellular product. The FDA (21 Code of Federal Regulations [CFR] 1271.290) requires that a record-keeping system be used to track human cellular and tissue-based products from the donor to the consignee and vice versa, or any other final disposition (for example, shipment was lost or the integrity of the unit was compromised). In accordance with this regulation, CCT has established a tracking system for PDA-002.

For each unit of PDA-002 that is administered, it is important to maintain records sufficient to permit prompt identification of the recipient. At no time will the identification of the donor be known by the subjects in the clinical study.

[redacted]

[redacted]

[redacted]

8.6. Investigational Product Compliance

Accurate recording of all IP administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

8.7. Blinding

With the exception of individuals noted below, all study site personnel, subjects, and sponsor personnel and their designees involved with the study, including the sponsor medical monitor, will remain blinded to treatment assignment until the last subject has completed Month 6 (Visit 11), and the database has been locked. At that time the sponsor and their designees will be unblinded. Study site personnel and subjects will remain blinded during the course of the study.

[redacted]

[redacted]

9. CONCOMITANT MEDICATIONS AND PROCEDURES

All medications (prescription and non-prescription), treatments and therapies taken from 30 days prior to Visit 1 (the Screening/Run-In Visit) until Month 24 must be recorded on the appropriate page of the eCRF.

9.1. Required Standard of Care for Subjects who have DFU With and Without PAD

All subjects are to receive standard medical care for the treatment of chronic DFU and its complications unless contraindicated throughout the study.

Standard medical care for DFU includes pressure offloading, wound care and debridement.

Subjects should be receiving adequate medical therapy for control of hypertension, diabetes, and any other chronic medical conditions for which they require ongoing care.

For offloading, all subjects will be required to reduce pressure and stress on plantar ulcers of the index foot using Removable Cast Walker specific for the management of diabetic ulcers. For example the Bledsoe CAM Diabetic Boot or Ossur DH Offloading Walker, or similar device as appropriate to what the site has available. The use of a custom Ankle Foot Orthosis instead of a DH Walker or CAM walker is permitted. The investigator will assure that each subject is undergoing offloading treatment.

For wound care and debridement, subjects will receive appropriate wound care including dressings and other treatments deemed necessary by the Investigator. Debridement will be performed as necessary at the discretion of the Investigator and will be noted in the eCRF but will not be considered an adverse event.

An effort should be made to maintain the subject's standard medical care until Month 6 [Visit 11] unless changes are necessary to ensure the best care for the subject.

9.2. Prohibited Concomitant Medications and Procedures

Concomitant medications in this study including any investigational agent and any wound coverings consisting of cells, (such as Apligraf, Dermagraft), other ECM (extra cellular matrix) treatments, decellularized membrane preparations or growth factors used in the treatment of DFU are prohibited until Month 6 [Visit 11]. The use of these treatments is allowed for non-index ulcers.

[redacted]

10. STATISTICAL ANALYSES

10.1. Overview

The primary objective of this Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose range finding study is to assess the efficacy and safety of PDA-002 versus placebo administered IM in subjects who have DFU with and without PAD.

Eligible subjects will be enrolled into four treatment arms as described in Section 8.2. A statistical plan is outlined in this section. A detailed Statistical Analysis Plan (SAP) will be provided in a separate document.

10.2. Study Population Definitions

The following analysis populations are planned for this study:

- Safety Population – all subjects who receive any amount of IP.
- Efficacy Evaluable (EE) Population – all subjects who receive any amount of IP, and have a baseline and at least one postbaseline efficacy assessment at Day 15 [Visit 5].

10.3. Sample Size and Power Considerations

Assuming a response rate of 10% in the control group, the sample size was chosen to detect with at least 90% power a response rate of greater or equal to 40% in the combined treatment groups, assuming no differential effect due to the baseline ABI, TBI and TcPO2 levels. With a sample size of n=38 in the control group and n=95 in the treatment groups. The power is 94%. The power in the comparison of the control group and one of the lower active treatment dose groups (n=38) (either 3 x 10^6 cells versus control or 10 x 10^6 cells versus control), assuming no differential effect due to the baseline ABI, TBI and TcPO2 levels is 82% without adjusting for multiple analyses.

10.4. Background and Demographic Characteristics

Baseline and demographic characteristic will be summarized by treatment arm. Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

Efficacy analyses will be conducted using the EE population as defined in Section 10.2. Formal statistical analyses of the primary endpoint of complete wound closure of the index ulcer in subjects who have DFU with and without PAD and combined will be performed using models that incorporate baseline PAD status information as a covariate, and evaluate the effect of the stratification variable. Ulcer closure is defined as skin closure of the index ulcer without drainage or need for dressing. Complete wound closure is defined as index ulcer closure within 3 months after dosing [Visit 8] and retaining wound closure for the subsequent 4 weeks.

Descriptive statistics will also be provided for changes in Rutherford Criteria, number and size of ulcers, ABI, TBI, leg rest pain score (VAS), TcPO2 measurements and incidence of hospitalization at all visits. Similarly, the occurrence of new ulcers, the increase or decrease in size of the index ulcer or existing ulcers in the index limb (doubling or halving), time to closure of the index ulcer, duration of closure of the index ulcer, time to gangrene, and time to amputation will be tabulated.

The details of these analyses will be presented in the SAP.

10.7. Safety Analysis

The Safety analyses will be conducted using the Safety Population as defined in Section 10.2. Adverse events, vital sign measurements, physical examination findings, clinical laboratory test results, injection site assessments, retinal examination results, ECG interpretations, concomitant medications and procedures will be tabulated and summarized as appropriate.

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 whenever possible.

The frequency of AEs will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by NCI CTCAE grade. Adverse events leading to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, study-drug-related events, and SAEs will be tabulated and listed separately. By-subject listings of all AEs, SAEs, discontinuations due to AEs, and deaths will be provided.

Clinical laboratory data will be summarized. Laboratory data will be graded according to NCI CTCAE version 4.03 criteria wherever possible. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by screening status.

Vital signs, ECG, and retinal examination data will be summarized by cross-tabulations presenting normal and abnormal values.

Graphical displays will be provided where useful in the interpretation of results.

10.8. Interim Analyses

At approximately 4Q2015, an administrative interim analysis of unblinded efficacy and safety data will be conducted by members outside of the study team. The purpose of the analysis is to

[redacted]

determine whether to allocate future resources to the program. The members outside of the study team who will be unblinded to the study results will consist of a clinical research physician, a statistician, and non-research members of senior management. The results of this analysis will not be distributed outside of this group and this group will not disclose the results to members of the study team. Specific positions attached to these roles and the details of the firewall between this group and the study team will be described in a separate charter or plan. The conduct and execution of this study will not be modified as a result of this interim analysis. The details for this analysis will be covered in the interim analysis SAP.

An additional analysis will be conducted when all subjects would have completed their Month 6 visit.

10.9. Other Topics

Descriptive statistics will be provided for collected biomarker data and parameters collected from the ICGA procedure (see Section 6.2.12). Exploratory analyses such as scatter plots or Cox proportional hazards model will be used to assess the association between the biomarker and clinical efficacy or safety endpoints.

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until the last study visit and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

[redacted]

AEs that are not defined in the CTCAE should be evaluated for severity / intensity according to the following scale:

Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required

Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3. Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6. Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until the last study visit) and any SAE made known to the Investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

11.5.1. Safety Queries

[redacted]

11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to PDA-002 based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse event(s)
- Lack of efficacy
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Pregnancy
- Recovery
- Non-compliance with IP
- Study terminated by sponsor
- Physician decision
- Screen failure
- Technical problems
- Disease relapse
- Failure to meet randomization criteria
- Site terminated by sponsor
- Completed
- Other

The reason for discontinuation should be recorded in the eCRF and in the source documents. The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. However, the investigator is not required to contact a medical monitor to discuss discontinuation or unblinding as the investigator has the ability to discontinue or rapidly unblind subjects.

Subjects who discontinue will have laboratory assessments performed as specified in the Early Termination Column in the Table of Events (Table 1) using the Unscheduled Visit Kit, in addition to an ECG. Those who discontinue prior to Month 3 (Visit 8) will also have an Exploratory Biomarker Sample Collection.

13. EMERGENCY PROCEDURES

13.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on call Celgene/Contract Research organization (CRO) Medical Monitor, who will then contact you promptly.

Note: The back-up 24 hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

13.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study unless in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, the Investigator or authorized person should open the randomization envelope/peel apart the 2-part label; use an emergency unblinding personal identification number (PIN) and call IVRS for unblinded dose information, etc. However, every effort should be made to contact the Clinical Research Physician/Medical Monitor prior to breaking the blind. Contact or attempted contact with the Clinical Research Physician/Medical Monitor as well as the reason for breaking the blind must be documented in the source documents.

[redacted]

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. [redacted]

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

[redacted]

[redacted]

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

14.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

[redacted]

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

14.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;

- Failure to adhere to the study protocol.

[redacted]

15. DATA HANDLING AND RECORDKEEPING

15.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

15.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of eCRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;

[redacted]

- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study. No single center publication will be permitted until the overall study has been published.

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[redacted]

19. APPENDICES

Appendix A: Wagner Grading Scale

Wagner Ulcer Classification System

Grade 0: No open lesions; may have deformity or cellulitis

Grade 1: Superficial diabetic ulcer (partial or full-thickness)

Grade 2: Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis

Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis

Grade 4: Gangrene localized to portion of forefoot or heel

Grade 5: Extensive gangrenous involvement of the entire foot

Source: Frykberg, 2002.

[redacted]

Appendix B: Rutherford Classification of Chronic Limb Ischemia

Table A1: Rutherford Classification of Chronic Limb Ischemia

Grade	Category	Clinical Description	Objective Criteria
0	0	Asymptomatic—no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise[a]; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise[a] **and** AP after exercise < 50 mmHg
II[b]	4	Ischemic rest pain	Resting AP < 40 mmHg, flat or barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
III[b]	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
	6	Major tissue loss—extending above TM level, functional foot no longer salvageable	Same as Category 5

Abbreviations: AP = ankle pressure; PVR = pulse volume recording; TM = transmetatarsal; TP = toe pressure.
[a] Five minutes at 2 mph on a 12% incline.
[b] Grades II and III, categories 4, 5, and 6, are embraced by the term chronic critical ischemia.
Source: Rutherford, 1997.

Appendix C: New York Heart Association (NYHA) Classification

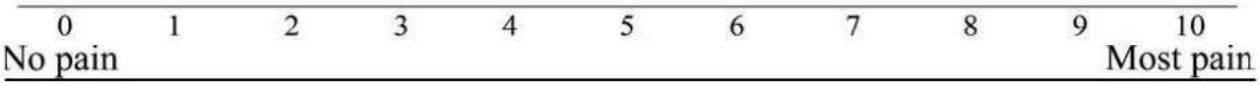
Table A2: New York Heart Association Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association NYHA Classification – The stages of heart failure. Heart Failure Society of America. http://www.abouthf.org/questions_stages.htm. Accessed 28 Sep 2012.

Appendix D: Visual Analog Scale Pain

Numeric Pain Scale



Source: Johnson, 2005.

Appendix E: Thawing Protocol

[redacted]

[redacted]

[redacted]

[redacted]

Appendix F: Transcutaneous Oxygen Measurements Guidelines

Pre TcPO2 Testing

1. Inform the patient about the procedure
2. Ensure the following is in the patient file
   - General patient consent form

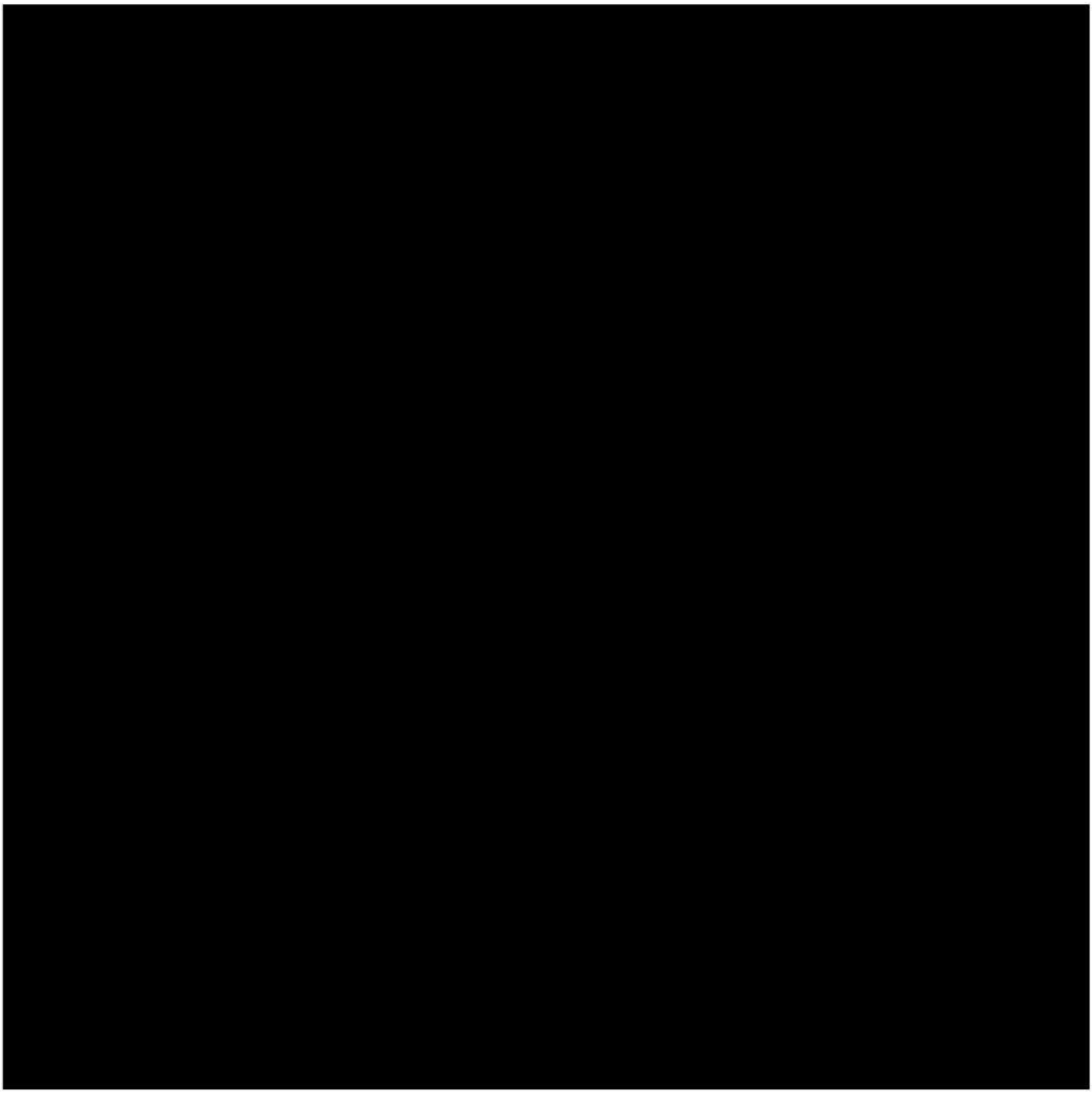
Monitor Set Up

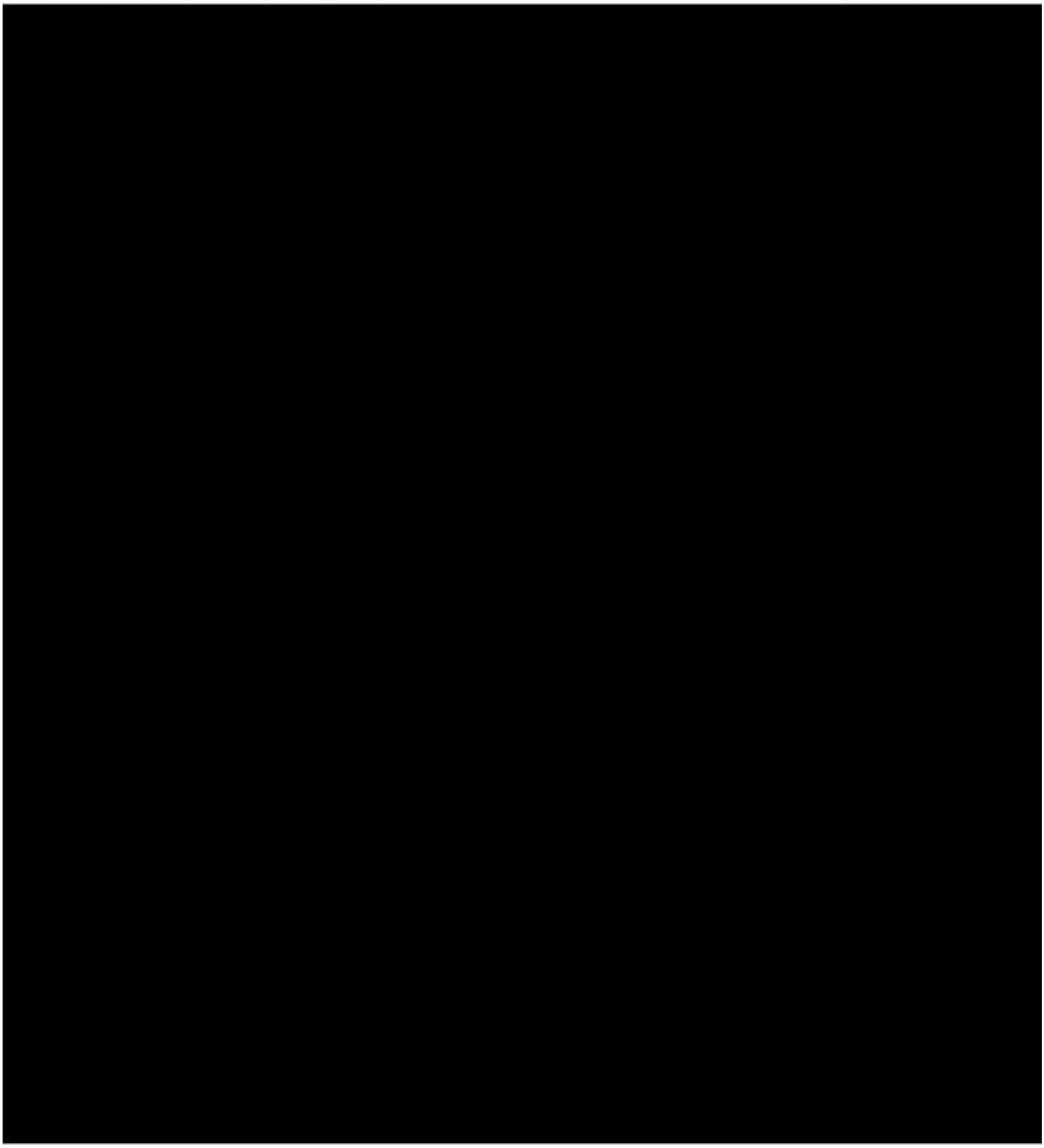
3. Follow manufacturer's instructions for monitor set up.

Appendix G: Diabetic Foot Ulcer Scale Short Form (DFS-SF)

[redacted]

[redacted]





Appendix H: International Clinical Diabetic Retinopathy Disease Severity Scale

AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe NPDR
Severe nonproliferative diabetic retinopathy	Any of the following: • More than 20 intraretinal hemorrhages in each of four quadrants • Definite venous beading in two or more quadrants • Prominent IRMA in one or more quadrants **And** no signs of proliferative retinopathy
Proliferative diabetic retinopathy	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy.

[redacted]

Appendix I: Canadian Cardiovascular Society Angina Grading Scale

Clinical Findings	Features	Grade
no limitation of ordinary activity	Ordinary physical activity (such as walking or climbing stairs) does not cause angina. Angina may occur with strenuous rapid or prolonged exertion at work or recreation.	I
slight limitation of ordinary activity.	Angina may occur with • walking or climbing stairs rapidly; • walking uphill; • walking or stair climbing after meals or in the cold in the wind or under emotional stress; • walking more than 2 blocks on the level at a normal pace and in normal conditions • climbing more than 1 flight of ordinary stairs at a normal pace and in normal conditions	II
marked limitation of ordinary physical activity	Angina may occur after • walking 1-2 blocks on the level or • climbing 1 flight of stairs in normal conditions at a normal pace	III
unable to carry on any physical activity without discomfort	Angina may be present at rest.	IV

Source: Campeau, 1976.