A PHASE 1, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND EFFICACY OF INTRAMUSCULAR INJECTION OF HUMAN PLACENTA-DERIVED CELLS (PDA-002) IN SUBJECTS WITH PERIPHERAL ARTERIAL DISEASE AND DIABETIC FOOT ULCER

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PROTOCOL SUMMARY

Study Title

A Phase 1, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of Intramuscular Injection of Human Placenta-Derived Cells (PDA-002) in Subjects with Peripheral Arterial Disease and Diabetic Foot Ulcer.

Indication

This study will investigate the safety and efficacy of the intramuscular injection of PDA-002 in subjects with peripheral arterial disease (PAD) and diabetic foot ulcer (DFU).

Objectives

The primary objectives of the study are to assess the safety and determine the maximum tolerated dose (MTD) of PDA-002 administered intramuscularly (IM) in subjects with PAD and DFU. The secondary objective is to explore potential clinical efficacy by assessing changes in ankle-brachial index (ABI) and/or toe brachial-index (TBI). Additional assessments will include evaluating changes in Rutherford Criteria; number, extent, and size of ulcers; leg rest pain score using a visual analogue scale (VAS); incidence of hospitalization (all cause); overall survival at 24 months; and the time to first occurrence of major amputation (above the ankle) of treated leg, all-cause mortality, doubling of ulcer total surface area from baseline or de novo gangrene.

Study Design

This is a Phase 1, multicenter, open-label, dose-escalation study in subjects with PAD and DFU. The study will enroll up to 24 subjects. The study will utilize a 3 + 3 dose escalation design with 3 to 6 subjects enrolled into each of 4 dose cohorts (3×10^6 cells, 10×10^6 cells, 30×10^6 cells, and 100×10^6 cells). Initially, 3 subjects will be enrolled to receive 3×10^6 cells on Study Days 1 and 8. Progression to higher (or lower) PDA-002 dose levels will be based on the criteria found in Table 1 of Section 4.1, Study Design.

All subjects in a given dosing-cohort must complete 14 days of follow-up and the data must be reviewed by the sponsor's internal Data Monitoring Committee (DMC) and approval given to dose escalate before accrual to the next dosing cohort can begin.

Subjects who discontinue from the study prior to the Study Day 15 assessments for reasons other than a dose-limiting toxicity (DLT), (see definition of Dose-Limiting Toxicity below) will be replaced. Subjects who experience a DLT should continue to complete all protocol assessments and will not be replaced.

The pattern of enrollment outlined in Table 1 (Section 4) will continue until the maximum tolerated dose (MTD) is determined or the highest planned dose level is tested. Six subjects must be treated at a given dose level before the MTD can be declared. The MTD is defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects. At any dose level, if 2 or more subjects experience a DLT within 14 days of dosing, that cohort will have exceeded the MTD. If a previous dose level was well tolerated and no subjects experienced DLT at that level, an intermediate dose level may be defined by protocol amendment.

Subjects will undergo Screening evaluations to determine eligibility within 28 days of Study Day 1. Following Screening, subjects will be assigned to the appropriate cohort as outlined above and will receive investigational product (IP). In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest ulcer total surface area. During the treatment period subjects will receive intramuscular (IM) injections of PDA-002 on Study Days 1 and 8. No more than 1 subject may begin treatment in any 48-hour period. During the follow-up period subjects will be evaluated on Study Days 15 and 29, and Months 3, 6, 9, 12 and 24. All subjects are to receive standard of care treatment in addition to IP. An interim analysis will be performed after the last subject completes 3 months of follow-up.

Study Population

Type 1 and type 2 diabetic subjects with PAD and ischemic or neuroischemic DFU with severity of Grade 1 (full thickness only) or Grade 2 on the Wagner Grading Scale (Appendix A) greater than one month duration which has not adequately responded to conventional ulcer therapy.

Length of Study

The study consists of a 0 to 28 day screening/baseline period followed by a 7-day treatment period (Treatment on Study Days 1 and 8) plus a 24-month follow-up period.

Study Treatments

Subjects will be sequentially assigned to one of the following dose levels of PDA-002 based on entry into the study:

- Dose Level 1: 3×10^6 cells administered on Study Days 1 and 8.
- Dose Level 2: 10×10^6 cells administered on Study Days 1 and 8.
- Dose Level 3: 30×10^6 cells administered on Study Days 1 and 8.
- Dose Level 4: 100×10^6 cells administered on Study Days 1 and 8.

Overview of Efficacy Assessments

The following efficacy assessments will be performed:

1. 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. ABI and TBI will be measured during Screening, on Study Days 1 and 8 prior to administration of IP and on Study Days 15 and 29 and Months 3, 6, 9, 12, and 24.
2. The number, extent, and size of ulcers (summation of the products of the long x short axis for all ulcers measured in centimeters squared, plus ulcer depth) will be evaluated and the ulcers photographed during Screening and again on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.
3. Time to first occurrence of major amputation (above the ankle) of treated leg, doubling of ulcer total surface area from baseline, and de novo gangrene.
4. Wagner Grading Scale assessed during Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.

5. Rutherford Criteria assessed during Screening and on Study Days 1, 8, 15 and 29 and Months 3, 6, 9, 12, and 24.
6. Leg rest pain score - VAS graded from 0 (pain free) to Grade 10 (maximum pain) during Screening, on Study Days 1 and 8 prior to administration of PDA-002 and on Study Days 15 and 29 and Months 3, 6, 9, 12, and 24.
7. 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).
8. Incidence of hospitalization (all cause).

Overview of Safety Assessments

The primary endpoint is safety assessed by the frequency and severity of adverse events and DLTs and determination of the MTD defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects. To this end, the following safety assessments will be performed.

1. Adverse events (AEs) including DLTs and serious adverse events (SAEs).
2. Vital signs, height and weight and physical examinations.
3. Laboratory tests.
   a. Serum chemistry, lipid profile, fatty acids, hematology, urinalysis, and pregnancy
   b. Coagulation tests
      - Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin activation time (TAT)
      - D-dimers
      - Fibrinogen
      - Tissue factor procoagulant activity (TF-PCA)
      - Platelets
   c. Immunological and Inflammation Assessments
      - Anti-human leukocyte antigen (HLA) antibodies
      - C-reactive protein
      - Quantitative assessment of serum immunoglobulins (IgA, IgM, and IgG)
      - Vascular endothelial growth factor (VEGF)
      - Cytokines: interleukin (IL)-1β, tumor necrosis factor (TNF-α), IL-6, IL-8, IL-10, and transforming growth factor-β (TGF-β)
   d. Tryptase and Histamine
   e. Troponin I
   f. Hemoglobulin A1c
   g. Circulating endothelial cells (CECs)
   h. Urinary Cotinine

4. Assessment of injection sites.
5. Electrocardiograms (ECGs).
6. Retinal examinations.
7. Magnetic resonance imaging (MRI) or computed tomography (CT) of the chest, abdomen, and pelvis.
8. Concomitant medications and procedures.

Dose-limiting Toxicity

A DLT is defined as a Grade 2 toxicity not resolving within 14 days suspected to be related to IP or any ≥ Grade 3 toxicity suspected to be related to IP.

Stopping Rules

- Identification of 2 or more subjects within a dosing cohort with ≥ Grade 2 allergic reaction that is suspected to be related to the IP.
- Identification of 2 or more subjects within a dosing cohort experiencing an unexpected, treatment-related SAE or DLT within 14 days following the initial dose of the IP.

Internal Data Monitoring Committee

An internal DMC will monitor all safety information to ensure subject safety in accordance with a separate charter. The internal DMC will be comprised of members who are not involved in the day-to-day activities of the PDA-002 DFU study team. The internal DMC will recommend whether continued dosing is appropriate, whether dose escalation should proceed, whether modifications to the protocol design are necessary or whether to end dosing and/or further enrollment at either a specific dose level or for the overall study. The internal DMC will make their determinations based on available AE and clinical data. The decisions of the internal DMC will be documented in meeting minutes. The internal DMC will be convened:

- Upon completion of dosing and Day 15 assessments within each dose level cohort to review cumulative safety information and give approval to dose-escalate prior to enrollment commencing in the next higher dose cohort.
- When a study stopping rule is triggered.

The internal DMC chairman will be called if an unexpected, related SAE should occur. During any period of deliberation by the internal DMC, a temporary hold on enrollment and dosing of new subjects will be instituted until the review is completed.

The sponsor will take appropriate action based upon the recommendations of the internal DMC and this will be communicated to the Investigators. The Investigators will be responsible for notifying their Institutional Review Boards (IRBs).

Statistical Analysis:

- **Statistical Overview**

  The primary objectives of this Phase 1, multicenter, open-label, dose-escalation study are to assess the safety and determine the MTD of PDA-002 administered IM in

subjects with PDA and DFU. The secondary objectives are to assess the clinical efficacy.

Eligible subjects will be sequentially enrolled into Cohorts 1 to 4. After the last subject treated in a cohort has completed the Study Day 15 assessments and no more than 1 subject experiences a DLT, the next cohort will be opened upon recommendation from the internal DMC.

- **Sample Size**

  Based on the "3 + 3" dose escalation design, each cohort will enroll 3 to 6 subjects and the study will enroll up to a total of 24 subjects. This sample size is not determined based on formal statistical calculations, but on clinical considerations.

- **Safety Analysis**

  All subjects who receive any amount of IP will be included in the safety analyses. Descriptive statistics will be provided for adverse events, vital sign measurements, physical examination findings, clinical laboratory test results, injection site assessments, MRI or CT scan results, retinal examination results, ECG interpretations, and concomitant medications and procedures. Graphical displays will be provided where useful in the interpretation of results.

- **Efficacy Analysis**

  Descriptive statistics will be provided primarily for summaries of efficacy endpoints. No formal statistical hypothesis testing will be conducted for any of the efficacy endpoints.

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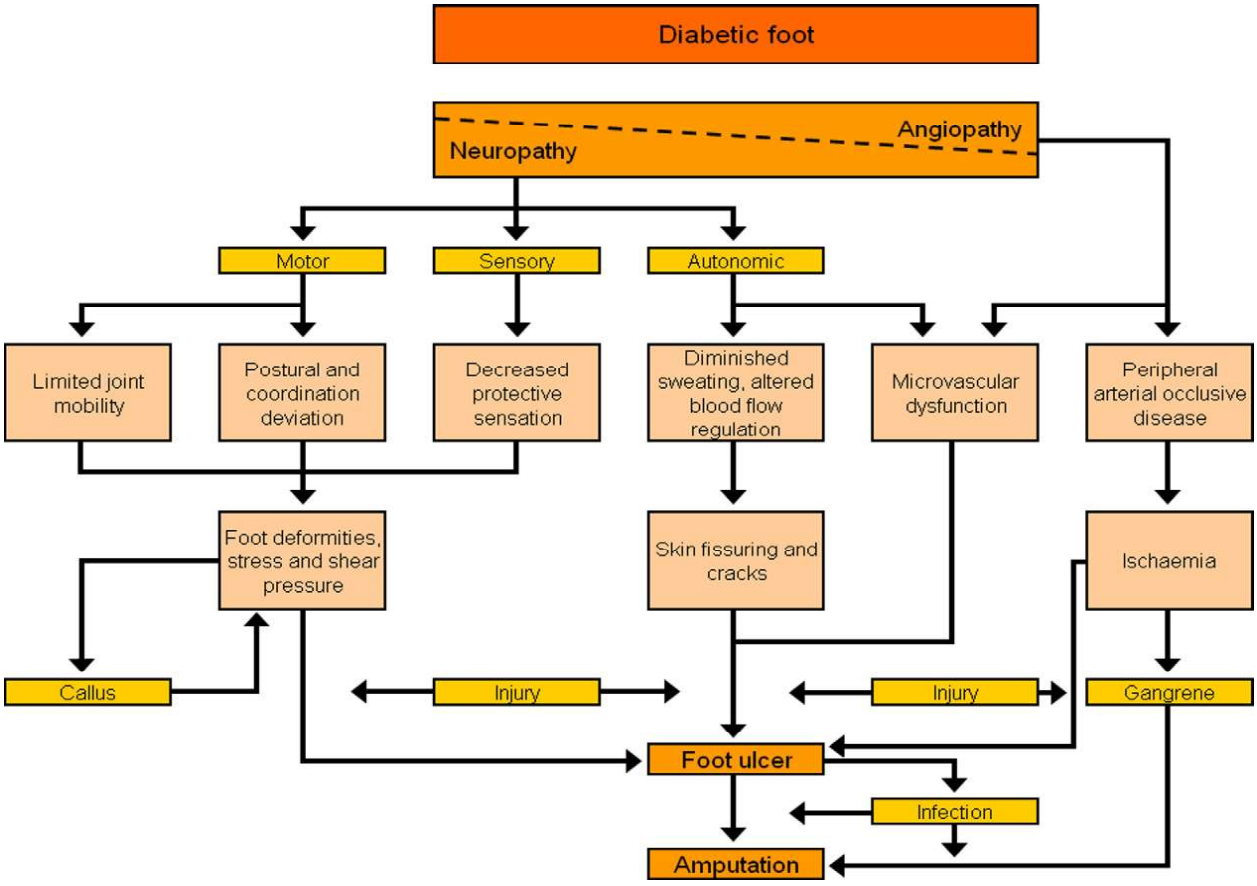
1. INTRODUCTION

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.

Patients with diabetes develop vascular disease, which can affect major vessels of the leg and the microvasculature in the foot. Large vessel disease is usually controlled with surgery and/or angioplasty. Peripheral artery disease (PAD) is common in patients with diabetes and leads to poor microcirculation and neuropathy. Poor glucose control accelerates the manifestation of PAD. Diabetic patients also develop neuropathies of the lower extremities which can lead to loss of protective sensation and reflexes. The causes of diabetic foot ulcers are mutifactorial. Ischemia, neuropathy and infection are the pathophysiological components that lead to diabetic foot complications, and constitute a triad that frequently occurs together (Lepäntalo, 2011). Infection follows tissue breakdown, which may not be noticed in a neuropathic foot. The basic schema for the diabetic foot and complications are listed below from Lepäntalo (Figure 1).

Figure 1: Pathways to Medical Complications in the Diabetic Foot



Diabetic foot ulcer is a major complication of all forms of diabetes, and occurs in about 15% of all diabetic patients. Peripheral arterial disease is usually present. 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).

Treating diabetic foot ulcers 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 non-invasive, 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 non-infected 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.

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 protein, cell and gene based therapy to promote blood vessel development may offer an alternative, promising treatment option (Hirsch, 2006; Sanchez-Alverez, 2011; Takeshita, 1994).

In summary, appropriately selected patients with diabetic foot ulcers have medical needs that can make them candidates for a Phase 1 study.

Human placenta-derived cells (PDA-002) is 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. PDA-002 is culture-expanded as a plastic-adherent, undifferentiated in vitro cell population that expresses the nominal phenotype CD34-, CD10+, CD105+ and CD200+. PDA-002 cells constitutively express moderate levels of human leukocyte antigen (HLA) Class I and undetectable levels of HLA Class II, and they do not

express the co-stimulatory molecules CD80 and CD86. PDA-002 is genetically stable, displaying a normal diploid chromosome count, normal karyotype, and exhibits normal senescence after prolonged in vitro culture.

Similar to mesenchymal stromal cells (MSCs) (Aggarwal, 2005; Nauta, 2007) in vitro studies have shown that PDA-002 is capable of immunomodulation. PDA-002 suppresses T-cell proliferation when the T-cells are activated in three different in vitro experimental systems: (1) Mixed Lymphocyte Reaction (MLR), (2) CD3 and CD28 bead-induced cross-linking reaction (BTR) and, (3) an antibody-induced T-cell reaction. In addition to suppression of T-cell proliferation, PDA-002 also modulates other cell types involved in immune and inflammatory responses such as T-cell subsets, macrophages and dendritic cells.

In vivo biodistribution and safety studies have demonstrated that PDA-002 does not proliferate in any tissues and is not associated with any observed toxicity or tumor formation in NOD-SCID (non-obese diabetic - severe combined immunodeficiency) mice.

[redacted]

The potential beneficial effects of PDA-002 on cellular components of the neurovascular system were tested using a variety of in vitro and in vivo experimental systems. The capacity of PDA-002 to elaborate angiogenic factors, induce endothelial cell survival/proliferation, induce endothelial cell migration, and induce endothelial cell tube formation, was assessed.

[redacted]

To date PDA-002 has been studied in 4 nonclinical rodent models of critical limb ischemia (CLI), 2 mouse and 2 rat studies. The data have demonstrated the efficacy of PDA-002 administered systemically and locally in these models.

To evaluate the effect of systemic versus local administration of PDA-001, a mouse HLI model was studied. Adult Balb/C mice were subjected to ligation and removal of part of the femoral artery. Local and systemic treatment with PDA-002 was given 24 to 48 hours post injury at the following dose levels: local (1×10^5, 3×10^5, and 1×10^6 cells) and systemic (1×10^6 cells). VEGF was used as the positive control. Serial blood flow measurements were evaluated up to 49 days post-treatment. The study demonstrated an effect of systemic and local administration of PDA-001 superior to VEGF. Local administration of PDA-001 at a dose level of 1×10^5 cells was as effective as higher doses with both local (3×10^5 cells, 1×10^6 cells) and systemic (1×10^6 cells) administration.

The therapeutic activity of PDA-002 cells in ischemic tissue was tested in 2 studies with the rat hind limb ischemia model. The purpose of these studies was to assess the efficacy of PDA-002 in a model of stable severe ischemia through intravenous (IV) and intramuscular (IM) administration with various dosages.

As of 31 Aug 2012, 107 subjects have been treated with PDA-001 or placebo across these studies. Sixteen subjects received only placebo in these studies. Additionally, some of the 91 PDA-001 subjects randomized to placebo treatment arm were subsequently given IV PDA-001 during the course of the study. Overall, 101 of the 107 subjects (94.4%) had AEs. The most commonly reported treatment-emergent adverse events (TEAEs) among all subjects were headache (n=28; 26.2%), pyrexia (n=24, 22.4%), nausea (n=19, 17.8%), Crohn's disease (n=18,

16.8%) urinary tract infection (n=12, 11.2%), upper respiratory tract infection (n = 12, 11.2%), and anemia (n = 11, 10.3%).

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

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of the study are to assess the safety and determine the maximum tolerated dose (MTD) of PDA-002 administered intramuscularly (IM) in subjects with peripheral arterial disease (PAD) and DFU.

2.2. Secondary Objectives

The secondary objective is to explore potential clinical efficacy by assessing changes in the ankle-brachial index (ABI) and/or toe brachial index (TBI). Additional assessments will include evaluating changes in Rutherford Criteria; number, extent and size of ulcers; leg rest pain score using a visual analogue scale (VAS); incidence of hospitalization (all cause); overall survival at 24 months; and the time to first occurrence of major amputation (above the ankle) of treated leg, all-cause mortality, doubling of ulcer total surface area from baseline or de novo gangrene.

2.3. Exploratory Objectives

The exploratory objectives are to develop novel approaches for the characterization and measurement of immune modulation and tissue repair biomarkers that could enable correlation of in vitro, nonclinical and clinical function of PDA-002 (Section 3.3).

Data from exploratory objectives may not be included in the Clinical Study Report.

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoint is determination of the MTD defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects. Safety will be assessed by the frequency and severity of adverse events. To this end, the following safety assessments will be performed.

1. AEs including DLTs and serious adverse events (SAEs).
2. Vital signs, height and weight, and physical examinations.
3. Laboratory tests.
    a. Serum chemistry, lipid profile, fatty acids, hematology, urinalysis and pregnancy
    b. Coagulation tests
        - Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin activation time (TAT)
        - D-dimers
        - Fibrinogen
        - Tissue factor procoagulant activity (TF-PCA)
        - Platelets
    c. Immunologic/Inflammation Assessments
        - Anti-HLA antibodies
        - C-reactive protein
        - Quantitative assessment of serum immunoglobulins (IgA, IgM, and IgG)
        - Vascular endothelial growth factor (VEGF)
        - Cytokines: interleukin (IL)-1β, tumor necrosis factor (TNF-α), IL-6, IL-8, IL-10, and transforming growth factor-β (TGF-β)
    d. Tryptase and Histamine
    e. Troponin I
    f. Hemoglobulin A1c
    g. Circulating endothelial cells (CECs)
    h. Urinary Cotinine
4. Assessment of injection sites.
5. Electrocardiograms (ECGs).
6. Retinal examinations.
7. Magnetic resonance imaging (MRI) or computed tomography (CT) of the chest, abdomen, and pelvis.
8. Concomitant medications and procedures.

3.2. Secondary Endpoints

The secondary endpoints are to explore clinical efficacy and include:

1. 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. ABI and TBI will be measured during Screening, on Study Days 1 and 8 prior to administration of IP and on Study Days 15 and 29 and Months 3, 6, 9, 12 and 24.
2. The number, extent, and size of ulcers (summation of the products of the long x short axis for all ulcers measured in centimeters squared, plus ulcer depth) will be evaluated and photographs of ulcers taken during Screening and again on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24 (Appendix E, Appendix F).
3. Time to major amputation (above the ankle) of treated leg, doubling of ulcer total surface area from baseline and de novo gangrene.
4. Wagner Grading Scale (Appendix A) assessed during Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.
5. Rutherford Criteria (Appendix B) assessed during Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.
6. Leg rest pain score - visual analogue scale (VAS) (Appendix D) graded from 0 (pain free) to Grade 10 (maximum pain) during Screening, on Study Days 1 and 8 prior to administration of PDA-002 and on Study Days 15 and 29 and Months 3, 6, 9, 12, and 24.
7. 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).
8. Incidence of hospitalization (all cause).

3.3. Exploratory Endpoint

Serum samples and peripheral blood mononuclear cells (PBMC) may be collected at Screening and Study Days 1, 8, 15, and 29, and Months 3 and 6 for potential new biomarkers predictive of efficacy as well as characterization of the DFU population response to treatment. Specific goals include: contribution to evaluation of safety and efficacy, evidence for repair and regeneration activity, and identification of universal pharmacodynamic biomarkers for PDA-002. Analysis of biological fluids and PBMCs will include the examination of research biomarkers as well as vascular and standard inflammatory markers. The analyses will be performed via polymerase chain reaction (PCR)-based evaluation of levels of messenger ribonucleic acid (mRNA), as well as proteomics-based assessment of protein levels in response to treatment. The analyses will not include any genetic testing of subjects.

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 1, multicenter, open-label, dose-escalation study in subjects with PAD and DFU. The study will enroll up to 24 subjects. The study will utilize a 3 + 3 dose escalation design with 3 to 6 subjects enrolled into each of 4 dose cohorts. Subjects will be assigned to a dose cohort based on the order of entry into the study.

Four PDA-002 dose levels are planned in this study:

Dose Level 1: 3×10^6 cells administered on Study Days 1 and 8.

Dose Level 2: 10×10^6 cells administered on Study Days 1 and 8.

Dose Level 3: 30×10^6 cells administered on Study Days 1 and 8.

Dose Level 4: 100×10^6 cells administered on Study Days 1 and 8.

Initially, 3 subjects will begin dosing at the 3×10^6 cells dose level. Progression to higher (or lower) PDA-002 dose levels will be based on the following criteria:

Table 1: Dose Escalation Scheme

Number of Dose-limiting Toxicities	Action Regarding Study Drug
If 0 out of 3 subjects experience a DLT during the first 14 days of follow-up (Day 15) at a given dose level:	Enroll 3 subjects at the next highest dose level (If at the 100×10^6 cells dose level, 3 additional subjects will be enrolled).
If 1 out of 3 subjects experience a DLT during the first 14 days of follow-up (Day 15) at a given dose level:	Enroll 3 additional subjects at the current dose level
If ≥ 2 out of 3 subjects experience a DLT at a given dose level:	Enroll 3 subjects at the next lowest dose level[a]
If 3 additional subjects are enrolled at a given dose level:	
If 1 subject out of 6 subjects experiences a DLT during the first 14 days of follow-up (Day 15) at a given dose level:	Enroll 3 subjects at the next highest dose level (except if at the highest dose level of 100×10^6 cells).
If ≥ 2 subjects out of 6 subjects experience a DLT during the first 14 days of follow-up (Day 15) at a given dose level:	Enroll 3 subjects at the next lowest dose level

Abbreviations: DLT = Dose-limiting toxicities; MTD= Maximum tolerated dose.
[a] If dose level 1 (3×10^6 cells) exceeds the MTD, a PDA-002 dose level of 1×10^6 cells will be evaluated.

All subjects in a given dosing-cohort must complete 14 days of follow-up and the data reviewed by an internal Data Monitoring Committee (DMC), as detailed in Section 6.4) and approval given to dose escalate before accrual to the next dosing cohort can begin.

Subjects who discontinue from the study prior to the Study Day 15 assessments for reasons other than a dose-limiting toxicity (DLT) will be replaced. Subjects who experience a DLT should continue to complete all protocol assessments and will not be replaced.

The pattern of enrollment outlined in Table 1 will continue until the MTD is determined or the highest planned dose level is tested. Six subjects must be treated at a given dose level before the MTD can be declared. The MTD is defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects. At any dose level, if 2 or more subjects experience a DLT within 14 days of dosing, that cohort will have exceeded the MTD. If a previous dose level was well tolerated and no subjects experienced DLT at that level, an intermediate dose level may be defined by protocol amendment.

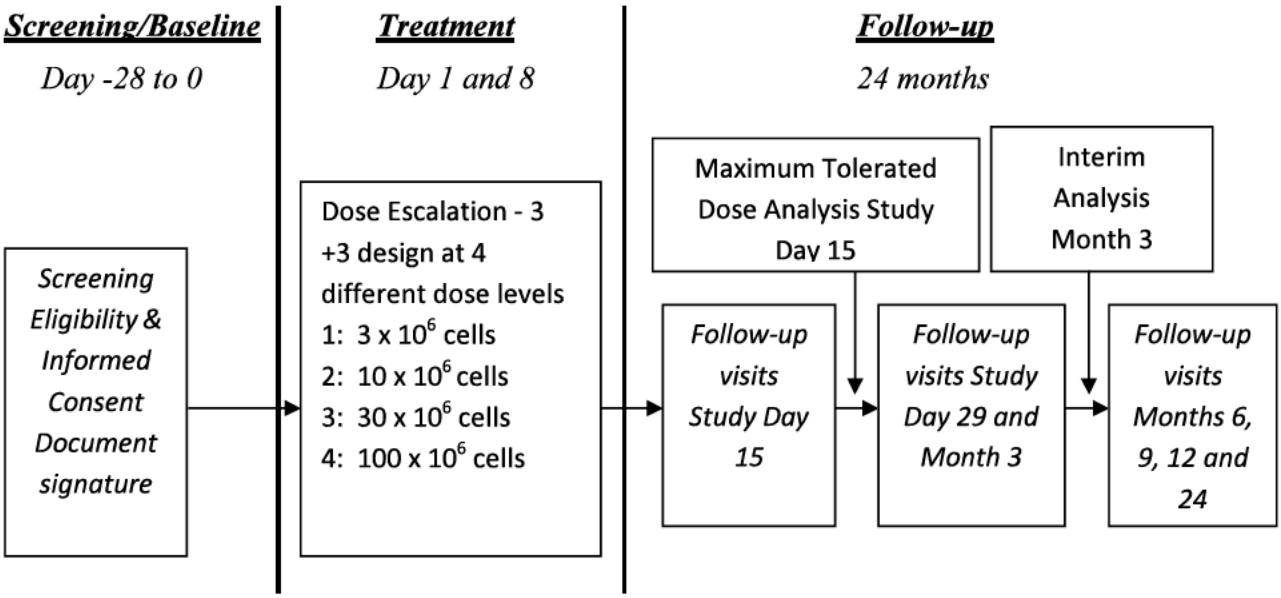
Subjects will undergo screening evaluations to determine eligibility within 28 days of Study Day 1. Following Screening, subjects will be assigned to the appropriate cohort as outlined above and will receive IP. In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest ulcer total surface area. During the treatment period, subjects will receive intramuscular (IM) injections of PDA-002 on Study Days 1 and 8. No more than 1 subject may begin treatment in any 48-hour period. During the follow-up period subjects will be evaluated on Study Days 15 and 29, and Months 3, 6, 9, 12, and 24. All subjects are to receive standard of care treatment in addition to IP. An interim analysis will be performed after the last subject completes 3 months of follow-up.

All subjects who receive any dose of PDA-002 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, Table 2, Table of Events for the scheduled visits and assessments.

Primary safety assessments, including AE reporting, physical examinations, vital sign measurements, ECG, injection site assessments, MRI or CT scan results, retinal examination results, concomitant medications, and clinical laboratory evaluations will be performed at scheduled visits throughout the study.

Efficacy analyses will include assessment of changes in the ABI and/or TBI. Additional assessments include evaluation of changes in Rutherford Criteria, number; extent and size of ulcers; leg rest pain score using a VAS, incidence of hospitalization (all cause); overall survival at 24 months; and the time to first occurrence of major amputation (above the ankle) of treated leg, all-cause mortality, doubling of ulcer total surface area from baseline, or de novo gangrene (see Section 3).

Figure 2: Overall Study Design



4.2. Study Design Rationale

This is the first study that will evaluate the safety and potential efficacy of IM injection of PDA-002 in type 1 and type 2 diabetic subjects with PAD and DFU. 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. Debridement of necrotic tissue and callus is always indicated in the treatment of DFU and is allowed in this study. Patients with infections need to be treated and have the infection resolved prior to continuation of medical management (Frykberg, 2006). There is a current medical need for treatments that could restore blood flow to the lower extremities and therefore aid in the healing of diabetic foot ulcers. Current results from the rat hind limb ischemia model show that stem cells isolated from human placenta (formulated for IM injection as PDA-002) have potential clinical use in tissue repair through increasing angiogenesis and promoting muscle regeneration (see Investigator's Brochure, Section 3.1.2.1.2). Furthermore, these PDA-002 cells implanted in a mouse model of chronic hind limb ischemia improved blood perfusion and limb functional recovery.

The use of a 3+3 dose escalating tolerability algorithm with strict DLT criteria will allow detection of significant toxicity in this first trial with PDA-002 given by IM injection. With regard to route of administration, IM administration of the cells is expected to reduce the potential risk of vascular complications seen with direct IV administration of the PDA-001cells. After IM administration in animal models, there was no evidence of distribution to the vascular compartment and PDA-002 cells were detected only at the site of administration and draining lymph nodes. Care will be taken to avoid systemic injection of cells. It is unlikely that detectable numbers of PDA-002 cells will enter the systemic circulation.

To further reduce the risk of vascular complications, this study is including subjects with PAD (with ankle-brachial index > 0.6 and ≤ 0.9 or toe-brachial index > 0.35 and ≤ 0.7) and DFU. Men and women with an ankle-brachial index of > 0.6 have lower 10-year-total mortality,

cardiovascular mortality, and major coronary event rates than subjects with an ankle-brachial index < 0.6 (Chronic Limb Ischemia [CLI]) (Fowkes, 2008). Subjects can have stable angina (Canadian Cardiovascular Society [CCS] Class I-II angina), but must not have a history of malignant ventricular arrhythmia, CCS Class III-IV angina pectoris, myocardial infarction/PCI (percutaneous coronary intervention)/CABG (coronary artery bypass graft) in the preceding 6 months, have planned coronary revascularization in the next 3 months, or transient ischemic attack/cerebrovascular accident in the preceding 6 months. Subjects may not have New York Heart Association [NYHA] Stage III or IV congestive heart failure or uncontrolled hypercoagulation, diabetes or blood pressure (see Section 7).

The dose levels for this study are based, in part upon the pre-clinical in vitro and in vivo data. Intramuscular administration of PDA-002 cells to rats at doses up to 12 x 10^6/rat were well tolerated. There were no deaths, adverse clinical observations, or histopathologic findings related to cell dosing in tissues examined. The presence of human DNA was detected only on Day 1 and only at the injection site. PDA-002 cells at doses as low as 1000 and 3000 cells were active in improving blood flow in mouse and rat HLI models, respectively. The dose levels planned for this study will range from 3 x 10^6 to 100 x 10^6 cells (less than 25% of the highest equivalent dose tested in rats). All dose levels of PDA-002 are expected to be well tolerated based on the in vitro and ex vivo data. This study will not have adequate numbers of patients to determine benefit unless dramatic responses are observed. The objectives of this study are to define an MTD(primary) for further study in Phase 2, and asses safety and tolerability as well as initiating exploration of potential efficacy, mechanisms of action and potential predictive biomarkers for PDA-002.

4.3. Study Duration

The study consists of a 0 to 28 day screening/baseline period followed by a 7-day treatment period (treatment on Study Days 1 and 8) plus a 24-month follow-up period.

5. TABLE OF EVENTS

Table 2 Table of Events

Table 2: Table of Events (Continued)

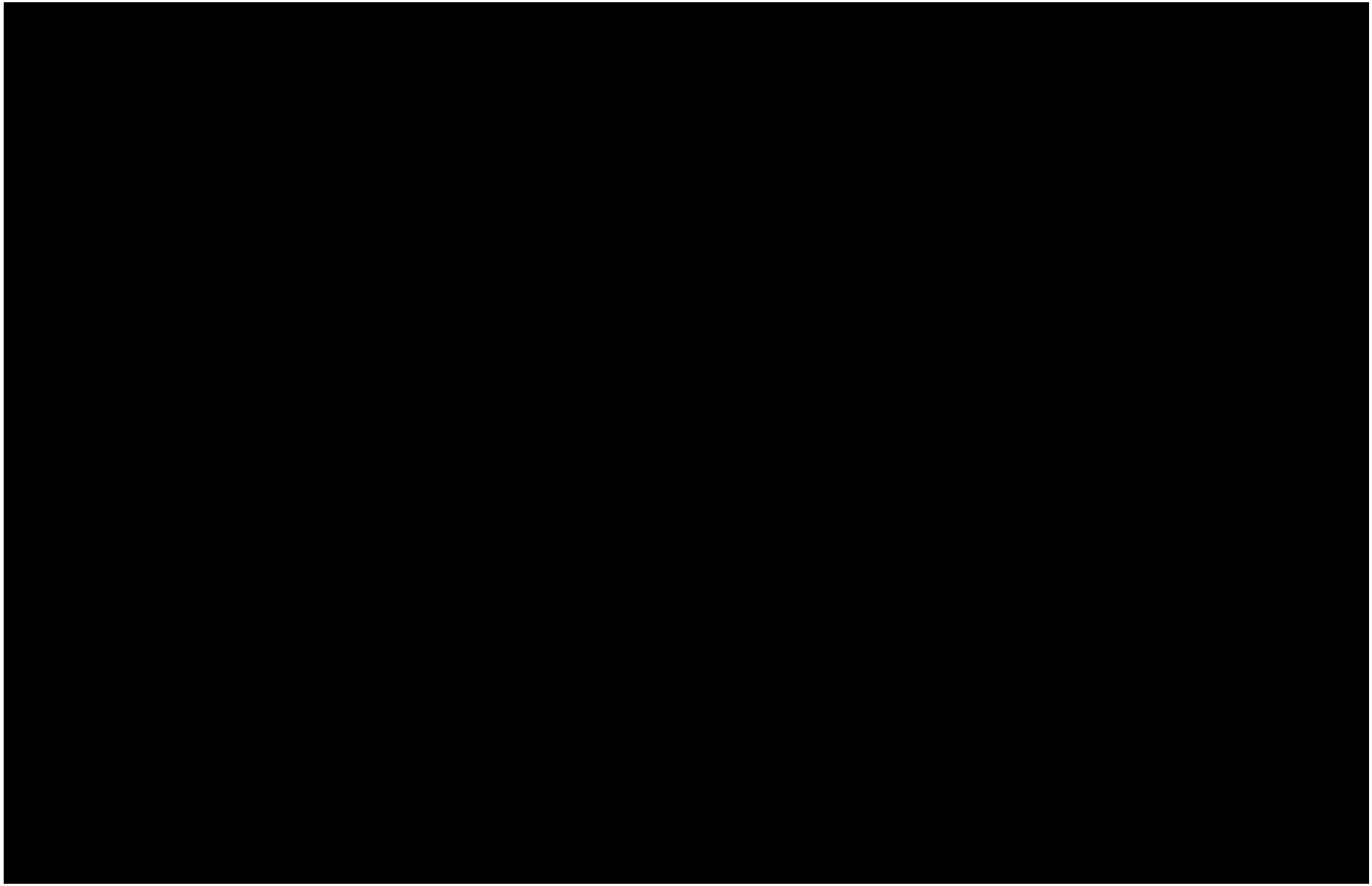


Table 2: Table of Events (Continued)

Table 2: Table of Events (Continued)

6. PROCEDURES

The study is divided into 3 periods: Screening/baseline, Treatment and Follow-up with associated evaluations and procedures that must be performed at specific timepoints. The Screening/Baseline Period is defined as the 28 days before administration of IP, during which subjects are evaluated for eligibility. The Treatment Period consists of Study Days 1 and 8 when the IP is administered. The Follow-up Period begins after Study Day 8 and is completed at Month 24. An interim analysis of safety and efficacy will be performed after the last subject in the study completes 3 months of follow-up. All subjects should be followed for the full 24 months regardless of clinical response.

All subjects are to receive standard of care for DFU in addition to IP.

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

6.1. Study Entry, Screening and Baseline 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.

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 more detailed medical history to identify patients at high risk of developing new tumors or having prior tumors recur will be done. A physical examination, including collection of vital signs, height and weight, 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 will be assessed. An MRI or CT of the chest, abdomen and pelvis, an ECG, and a retinal examination will also be completed.

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, hematology, urinalysis, lipids and fatty acid analysis,

CECs, immunological and inflammation assessments, hemoglobin A1c, pregnancy test (only in females of childbearing potential), urinary cotinine, troponin I, coagulation assessments, and exploratory biomarkers will be collected. If the subject meets all the study eligibility criteria (Section 7), the subject will be assigned to a cohort as outlined in Section 4.1 and scheduled for dosing with IP.

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.

6.2. 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 ulcer total surface area. 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 for serum chemistry, hematology, troponin I, lipids and fatty acid analysis, immunological/inflammation assessments, hemoglobin A1c (Study Day 1 only), tryptase, histamine, CECs, exploratory biomarkers, and coagulation assessments should be drawn on the day of treatment prior to dosing with the IP. A urinalysis, a urine pregnancy test in females of child bearing potential, and a urinary cotinine test should also be performed prior to dosing with IP. Assessment of Rutherford Criteria, Wagner Grading Scale for foot lesions, measurement/assessment and photographs of ulcers, and determination of ABI, TBI, and leg rest pain score (VAS), should be performed on Study Days 1 and 8.

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) will be administered as described in Section 8.2. Vital signs (including heart rate, respiration, resting systolic and diastolic blood pressure, body temperature, and pulse oximetry) will be monitored prior to starting the injections and every 15 minutes for a minimum of 2 hours after completion of the injections. Blood samples for tryptase and histamine, coagulation assessments, CECs, and exploratory biomarkers will be collected approximately 2 hours after the injections have been completed. The injections must be completed within 4 hours of IP thaw time. Injection sites will be assessed. See Section 6.4.4 regarding injection site reactions.

6.3. Efficacy Procedures

6.3.1. Rutherford Criteria

Limbs will be assessed using the Rutherford Criteria (Rutherford Classification of Chronic Limb Ischemia, Appendix B) during Screening, on Study Days 1, 8, 15, and 29, Months 3, 6, 9, 12, and 24, and at early termination. 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.

6.3.2. Ulcer Assessment

Ulcers will be graded using the Wagner Grading Scale (Appendix A) and will also be assessed using the E-Z graph system Appendix E). In addition, photographs will be taken of the ulcers

(Appendix F). The number, extent, and size of ulcers, including summation of the products of the long x short axis for all ulcers measured in centimeters squared plus the ulcer depth will be captured. Ulcer healing is defined as skin closure without drainage or need for dressing. Limbs will also be assessed for gangrene. Ulcers will be assessed at Screening, on Study Days 1, 8, 15, and 29, Months 3, 6, 9, 12, and 24, and at early termination. Information for ulcers assessed at non-scheduled visits will also be collected.

6.3.3. 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 during Screening, on Study Days 1 and 8 prior to administration of PDA-002, on Study Days 15 and 29, Months 3, 6, 9, 12, and 24, and at early termination.

6.3.4. Pain

Leg rest pain score will be assessed using a visual analog scale (VAS) (Appendix D) during Screening, on Study Days 1 and 8 prior to administration of PDA-002, on Study Days 15 and 29, Months 3, 6, 9, 12, and 24, and at early termination.

6.3.5. Other Clinical Assessments

Subjects will be accessed for amputation status and need for hospitalization. Major amputation is defined as that occurring above the ankle. 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).

6.4. Safety

Safety will be assessed by an ongoing review of clinical laboratory tests (hematology, serum chemistry, lipids, fatty acids, coagulation, troponin I, pregnancy, urinalysis, immunological/inflammation), physical examination results, vital sign measurements, 12-lead electrocardiogram (ECG), evaluations by MRI or CT scans of the chest, abdomen and pelvis, retinal exams, use of concomitant medications/procedures, and the incidence and severity of injection site and injection-related reactions (including tryptase and histamine) and treatment-emergent AEs.

6.4.1. Dose-Limiting Toxicity

A DLT is defined as a Grade 2 toxicity not resolving within 14 days suspected to be related to the IP or any toxicity ≥ Grade 3 suspected to be related to the IP.

In the event that 2 separate subjects within a dosing cohort experience a DLT, the events will be forwarded to the internal DMC for review and confirmation as to whether or not the MTD has been exceeded. If the MTD is confirmed by the internal DMC, no further IP administration will occur within that dose level or at any higher dose level. An intermediate dose may be defined by protocol amendment.

6.4.2. Internal Data Monitoring Committee

An internal DMC will monitor all safety information to ensure subject safety in accordance with a separate charter. The internal DMC will be comprised of members who are not involved in the day-to-day activities of the PDA-002 DFU study team. The internal DMC will recommend whether continued dosing is appropriate, whether dose-escalation can occur, whether modifications to the protocol design are necessary or whether to end dosing and/or further enrollment at either a specific dose level or for the overall study. The internal DMC will make determinations on study continuation and modifications based on available AE and clinical data. The decisions of the internal DMC will be documented in meeting minutes.

The internal DMC will be convened:

- Upon completion of dosing and Study Day 15 assessments within each dose level to review cumulative safety information and give approval to dose escalate prior to enrollment commencing in the next higher dose cohort.
- When a study stopping rule is triggered (see Section 6.4.3).

The internal DMC chairman will be called if an unexpected, related SAE should occur. During any period of deliberation by the internal DMC, a temporary hold on enrollment of new subjects will be instituted until the review is completed.

The sponsor will take appropriate action based upon the internal DMC recommendation and this will be communicated to the Investigators. The Investigators will be responsible for notifying their IRBs. The internal DMC will evaluate on an ongoing basis all available safety data, in particular all serious adverse events (SAEs) and their potential relationship to PDA-002. The internal 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 internal DMC will be spelled out in the internal DMC charter.

6.4.3. Stopping Rules

- Identification of 2 or more subjects within a dosing cohort with ≥ Grade 2 allergic reaction that is suspected to be related to the IP.
- Identification of 2 or more subjects within a dosing cohort experiencing an unexpected, treatment-related SAE or DLT within 14 days following the initial dose of the IP.

6.4.4. 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.

6.4.5. 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 routine physical examination will be performed at all visits. Routine physical examination to include vital signs and 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.

All abnormal findings at baseline will be recorded as medical history. Any physical examination finding that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an AE and should be recorded and monitored as such.

Vital Signs

Vital sign measurements include:

- Temperature (°C)
- Pulse (beat/minute)
- Pulse oximetry (%) only on Study Days 1 and 8
- Respiration (breaths/minute)
- Resting systolic and diastolic blood pressure (mmHg)
- Height (cm) (At Screening only or when possible)
- 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, and pulse oximetry) will be monitored prior to starting the injections and every 15 minutes for a minimum of 2 hours after completion of the injections.

Any clinically significant finding during Screening will be recorded as medical history. Any vital sign value that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value will be considered an AE and be recorded and monitored as such.

Contraception

Females of child bearing potential (FCBP)* must use adequate contraception for the duration of their participation in the study including all Follow-Up Periods (up to 24 months postdose). 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.

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 of the study and the Follow-Up Period (up to 24 months postdose).

Retinal Examination

Retinal examinations conducted by an ophthalmologist or optometrist will be performed during Screening and 6 and 12 months after treatment.

Electrocardiogram

A 12-lead ECG will be obtained during Screening, and on Study Days 1, 8, and 15, and at early termination. At Screening, 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 readings are to be done in triplicate. The ECG will be reviewed by the Investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the Investigator. The following will be recorded on the electronic case report form (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 recorded and monitored.

Diagnostic Imaging

An MRI scan of the chest, abdomen and pelvis will be performed at baseline, and 12 and 24 months post dose. If a specific contraindication exists for an MRI, then a CT scan may be performed instead. The same method of assessment and the same technique used at baseline should be used during follow-up evaluations.

* 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).

Clinical Laboratory Tests

Samples for serum chemistry, hematology, urinalysis, troponin I, hemoglobin A1c, urinary cotinine, lipid and fatty acid analysis, coagulation, CECs, exploratory biomarker samples, and immunological/inflammation assessments will be taken at the times indicated on the Time and Events Schedule (Table 2) 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 and will include the following:

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

Hematology

Hematology tests will be performed at all visits 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 all visits and will include the following:

- 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

Lipid Profile

A lipid profile will be performed at Screening and Study Days 1, 8, 15, and 29 and will include the following:

- Total Cholesterol
- Low Density Lipoprotein (LDL)
- High Density Lipoprotein (HDL)
- Very Low Density Lipoprotein (VLDL)
- Triglycerides

Fatty Acids

Fatty acids assessment will be assessed at Screening and Study Days 1, 8, 15, and 29 and will include the following:

- Alpha-linolenic Fatty Acid
- Arachidate Fatty Acid
- Oleic Fatty Acid
- Linoleic Fatty Acid
- Stearic Fatty Acid

Immunological/Inflammation Assessments

Immunological/inflammation assessment will include the following testing:

- Anti-HLA antibodies: Screening, Study Days 1, 8, 15, 29, Month 3, and at early termination.
- C-reactive protein: Screening, Study Days 1, 8, 15, and 29, and at Months 3 and 6.
- Quantitative assessment of serum immunoglobulins (IgA, IgM, and IgG): Screening, Study Days 1, 8, 15, 29, Month 3, and at early termination.

- VEGF: Screening, Study Days 1, 8, 15, and 29, Months 3 and 6, and at early termination.
- Cytokines IL-1β, TNF-α, IL-6, IL-8, IL-10, and TGF-β: Screening, Study Days 1, 8, 15, and 29, Months 3 and 6, and at early termination.

Troponin I

Troponin I will be measured during Screening, Study Days 1 and 8 prior to treatment, and 15.

Hemoglobin A1c

Hemoglobin A1c will be measured during Screening, Study Day 1 and Months 3, 6, 9, 12, and 24.

Urinary Cotinine

Urine samples will be collected and sent to the central laboratory to measure cotinine levels during Screening, on Study Days 1, 8 prior to treatment, 15, and Month 3.

Coagulation Tests

Coagulation tests including assessment of PT/PTT, TAT, D-dimers, fibrinogen, TF-PCA and platelets will be assessed at Screening, on Study Days 1 and 8 prior to dosing with IP, approximately 2 hours post dose on Study 1 and 8 and also on Study Days 15 and 29.

Tryptase and Histamine

Tryptase and histamine levels will be assessed on the day of treatment prior to dosing with IP and approximately 2 hours postdose on Study Days 1 and 8.

Circulating Endothelial Cells

Circulating endothelial cells (CECs) will be measured at Screening, on Study Days 1 and 8 prior to dosing with IP, approximately 2 hours post dose on Study 1 and 8 and also on Study Days 15 and 29.

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Up to 24 subjects will be enrolled at approximately 14 study centers in the US.

7.2. Inclusion Criteria

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

1. Males and females, 18 to 80 years of age 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 2.
5. Ischemic or neuro-ischemic 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.
6. Peripheral arterial disease with ankle-brachial index > 0.5 and ≤ 0.9 or toe-brachial index > 0.35 and ≤ 0.7.
7. No planned revascularization or amputation over the next 3 months after Screening visit, in the opinion of the Investigator.
8. Screening should not begin until at least 14 days after a failed reperfusion intervention and at least 30 days after a successful mechanical intervention but longer wait times may be employed at the discretion of the investigator.
9. Subject can have stable angina, (Canadian Cardiovascular Society (CCS) Class I-II angina (Appendix H).
10. Subjects should be receiving appropriate medical therapy for hypertension and diabetes.
11. 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.
12. 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.

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. Subjects whom, in the judgment of the Investigator, are at elevated risk for the development of a malignancy. This judgment may be based on family history, history of industrial exposures, smoking history or other cancer risk factors.
5. Known to be positive for human immunodeficiency virus.
6. Pregnant or lactating females.
7. Subjects with a body mass index > 40 at Screening.
8. AST or ALT > 2.5 x the upper limit of normal (ULN) at Screening.
9. Estimated Glomerular Filtration Rate (eGFR) <45mL/min/1.73 m^2 at Screening calculated using the Modification of Diet in Renal Disease Study equation (Levey, 2006) or history of eGFR decline > 15 mL/min/1.73 m^2 in the past year.
10. Alkaline phosphatase > 2.5 x the ULN at Screening.
11. Bilirubin level > 2 mg/dL (unless subject has known Gilbert's disease) at Screening.
12. Untreated chronic infection or treatment of any infection with systemic antibiotics, including the ulcer site, within 4 weeks prior to dosing with IP.
13. Known osteomyelitis.
14. Ulcer that has decreased or increased in size by ≥ 50% during the screening period.
15. 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).
16. Poorly controlled diabetes mellitus (hemoglobin A1c > 10%).
17. Untreated proliferative retinopathy.
18. History of malignant ventricular arrhythmia, CCS Class III-IV angina pectoris, myocardial infarction/PCI (percutaneous coronary intervention)/CABG (coronary artery bypass graft) in the preceding 6 months, pending coronary revascularization in the following 3 months, transient ischemic attack/cerebrovascular accident in the preceding 6 months, and/or New York Heart Association [NYHA] Stage III or IV congestive heart failure (Appendix C).
19. Abnormal ECG: new right bundle branch block (BBB) ≥ 120 msec in the preceding 3 months.
20. Uncontrolled hypercoagulation.
21. Life expectancy less than 2 years due to concomitant illnesses.
22. In the opinion of the Investigator, the subject is unsuitable for cellular therapy.

23. History of malignancy within 5 years 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.
24. History of hypersensitivity to any of the components of the product formulation (including bovine or porcine products, dextran 40, and dimethyl sulfoxide [DMSO]).
25. Disorders or allergies precluding the use of radiographic contrast or renal insufficiency severe enough to contraindicate the use of radiographic contrast.
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 gene or cell therapy.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product

PDA-002 is a novel product being developed specifically for local injectable delivery applications of PDA-001 cells. PDA-001 is Celgene Cellular Therapeutics' (CCT) original product and has been used in clinical studies for Crohn's disease, sarcoidosis, multiple sclerosis, rheumatoid arthritis, and stroke indications that require systemic administration. PDA-001 and PDA-002 have the same drug substance process (production of cells), but different drug product process (formulation and cryopreservation) and properties.

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. The cells are culture-expanded in vitro as a plastic-adherent, undifferentiated, cell population that expresses the nominal phenotype CD34-, CD10+, CD105+, and CD200+. The cells constitutively express moderate levels of HLA Class I and undetectable levels of HLA Class II.

[redacted]

8.2. Treatment Administration and Schedule

PDA-002 will be provided in 5-mL units at a concentration of 20 million cells/mL and will be diluted with normal saline to achieve the desired concentration based on dose level. Product thawing, dilution, and infusion will be performed according to sponsor provided instructions.

Investigational product will be administered on Study Days 1 and 8. No more than 1 subject may begin treatment in any 48-hour period. T[redacted]

[redacted]

Subjects will receive IP administered as fifteen 0.33 mL injections (approximately 5 mL total) in the treatment leg. The target region is suggested to be below the knee and above the ankle. Injections are suggested to be at least 1 cm apart horizontally and laterally and at a depth of approximately 1 to 4 cm. It is suggested that they be administered in a pattern of 3 x 5 injections around the leg and injections should not be near a blood vessel.

PDA-002 is not intended for IV administration. When the injection is given, the syringe should be aspirated to avoid inadvertent venous administration. If any blood is aspirated into the

syringe, the needle is to be pulled out a little, and the syringe reaspirated. If no blood is seen, the IP may be injected.

Vital signs (including heart rate, respiration, blood pressure, body temperature, and pulse oximetry) will be monitored prior to starting the injections and every 15 minutes for a minimum of 2 hours after completion of the injections. Blood samples for tryptase and histamine, coagulation assessments, CECs, and exploratory biomarkers will be collected approximately 2 hours after the injections have been completed.

Physician support must be available onsite. The investigational centers must also offer appropriate supplemental services that support clinical care to ensure that the protocol specified monitoring will be followed.

Administration Instructions. Under aseptic conditions, PDA-002 will be injected IM, below the knee, at 15 sites on the affected limb on Study Days 1 and 8. The injection volume will be 0.33 mL. A 1.0 mL syringe with a 22-gauge 1.5-inch long needle will be used to inject the IP.

[redacted]

Please refer to the Study Manual for more detailed instructions and a recommended injection grid.

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

8.2.1. Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from further treatment with the IP and/or from the study:

- Adverse event(s)
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation
- Inclusion/exclusion criteria not met

The reason for discontinuation should be recorded in the eCRF and in the source documents.

Patients who discontinue will have laboratory assessments performed as specified in the Early Termination Column in the Table of Events (Table 2) using the Unscheduled Visit Kit in addition to an ECG. Those who discontinue prior to Visit 7 will also have Exploratory Biomarker Sample Collection.

8.3. Method of Treatment Assignment

Eligible subjects will be assigned to a cohort based on the order in which they enter the study according to the dose escalation scheme (Section 4.1).

The pharmacist/designee at the study site will prepare the appropriate IP and deliver it to the personnel performing the injections. **Pharmacists should consult the pharmacy manual for detailed instructions on the preparation and handling of PDA-002 for this study**

8.4. Packaging and Labeling

The syringe rack label, affixed subsequently to thawing/dilution and prior to administration, will provide expiry, volume, and handling instructions.

8.5. Investigational Product Accountability and Disposal

PDA-002 is regulated by the United States 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.

Celgene will instruct the Investigator on the return, disposal and/or destruction of investigational product and/or medical device materials if applicable.

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.

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.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

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

9.1. Permitted Concomitant Medications and Procedures

All subjects are to receive standard medical care for the treatment of chronic DFU and its complications unless contraindicated. An effort should be made to maintain the patient's standard medical care for at least the first 12 Weeks following the initiation of dosing unless changes are necessary to ensure the best care for the patient.

9.2. Prohibited Concomitant Medications and Procedures

There are no prohibited concomitant medications in this study except for investigational agents.

9.3. Required Concomitant Medications and Procedures

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

10. STATISTICAL ANALYSES

10.1. Overview

The primary objectives of this Phase 1, multi-center, open-label, dose-escalation study are to assess the safety and determine the maximum tolerated dose of PDA-002 administered IM in subjects with PAD and DFU. The secondary objectives are to assess the clinical efficacy.

Eligible subjects will be sequentially enrolled into Cohorts 1 to 4 as described in Sections 8.2 and 8.3. 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 post-baseline efficacy assessment.

10.3. Sample Size and Power Considerations

Based on the "3 + 3" dose escalation design, each cohort will enroll 3 to 6 subjects and the study will enroll up to a total of 24 subjects. This sample size is not determined based on formal statistical calculations, but on clinical considerations.

10.4. Background and Demographic Characteristics

Baseline and demographic characteristic will be summarized by cohort and 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 cohort and treatment arm. 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 Efficacy Evaluable (EE) population as defined in Section 10.2. Descriptive statistics will be provided primarily for summaries of efficacy endpoints. No formal statistical comparisons are planned due to the small sample size and the exploratory nature of the study.

Descriptive statistics will also be provided for changes in Rutherford Criteria, number, extent and size of ulcers, ABI, TBI, leg rest pain score (VAS), and incidence of hospitalization.

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, MRI/CT scan results, retinal examination results, ECG interpretations, concomitant medications and procedures will be tabulated and summarized by cohort, 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.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

The frequency of adverse events 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 serious adverse events will be tabulated and listed separately. By-subject listings of all adverse events, serious adverse events, 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, retinal examination and MRI/CT scan 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 Analysis

An interim analysis will be performed after the last subject in the study has completed Visit 5 (Month 3) and all relevant study data have been processed and integrated into the analysis database. A comprehensive Statistical Analysis Plan (SAP) will be developed for this study that prospectively describes all planned analyses and the analysis populations for this study. The SAP will be approved before the database is locked and the analyses completed.

In addition, an internal DMC will monitor all safety information and recommend whether continued dosing is appropriate, whether dose escalation should proceed, whether modifications to the protocol design are necessary or whether to end dosing and/or further enrollment as described in detail in Section 6.4.2.

10.9. Other Topics

Descriptive statistics will be provided for collected biomarker data (see Section 3.3). Exploratory analyses such as scatter plots or Cox proportional hazards model will be used to assess the association between biomarker and clinical efficacy or safety endpoint.

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 below), 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.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. In the event of overdose or exaggerated response, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for PDA-002 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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 other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 24 months after the last dose of 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.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- 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 version of the NCI CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the NCI 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:	The temporal relationship of the adverse event to IP administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	The temporal relationship of the adverse event to IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

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 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 (death due to another cause) 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.

11.4. Pregnancy

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 24 months 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 or therapeutic 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 to 24 months after the last dose of IP), and those made known to the Investigator at anytime thereafter that are suspected of being related to IP. Serious Adverse Events occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries 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 will 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/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

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg. missing causality assessment) may be handled by phone.

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.

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 Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form / Completion Guidelines or to the Pregnancy Report Form / Completion Guidelines.

12. DISCONTINUATIONS

Subjects who discontinue from the study prior to the Study Day 15 assessments for reasons other than a dose-limiting toxicity (DLT) (see definition of Dose-Limiting Toxicity below) will be replaced. Subjects who experience a DLT should continue to complete all protocol assessments and will not be replaced.

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

- Adverse Event(s)
- Withdrawal of consent
- Death
- Lost to follow up
- Protocol violation
- Inclusion/exclusion criteria not met

The reason for discontinuation should be recorded in the eCRF and in the source documents.

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).

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

This is an open-label study; therefore, IP will be identified on the package labeling.

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 E6and 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. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

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. 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 document 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.

14.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a 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.

The 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.

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 (see Section 8.5);
- Record of any body fluids or tissue samples retained;

- 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. Before the study is initiated at a site visit or at an Investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. 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. At each monitoring visit, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

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 and/or designee 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.

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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.

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

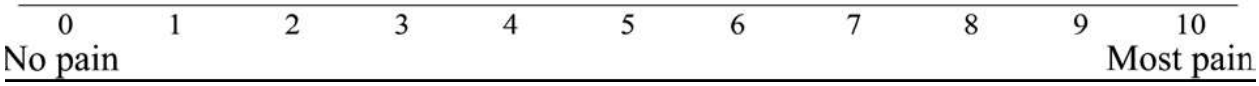
Table A2: New York Heart Association Classification

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.

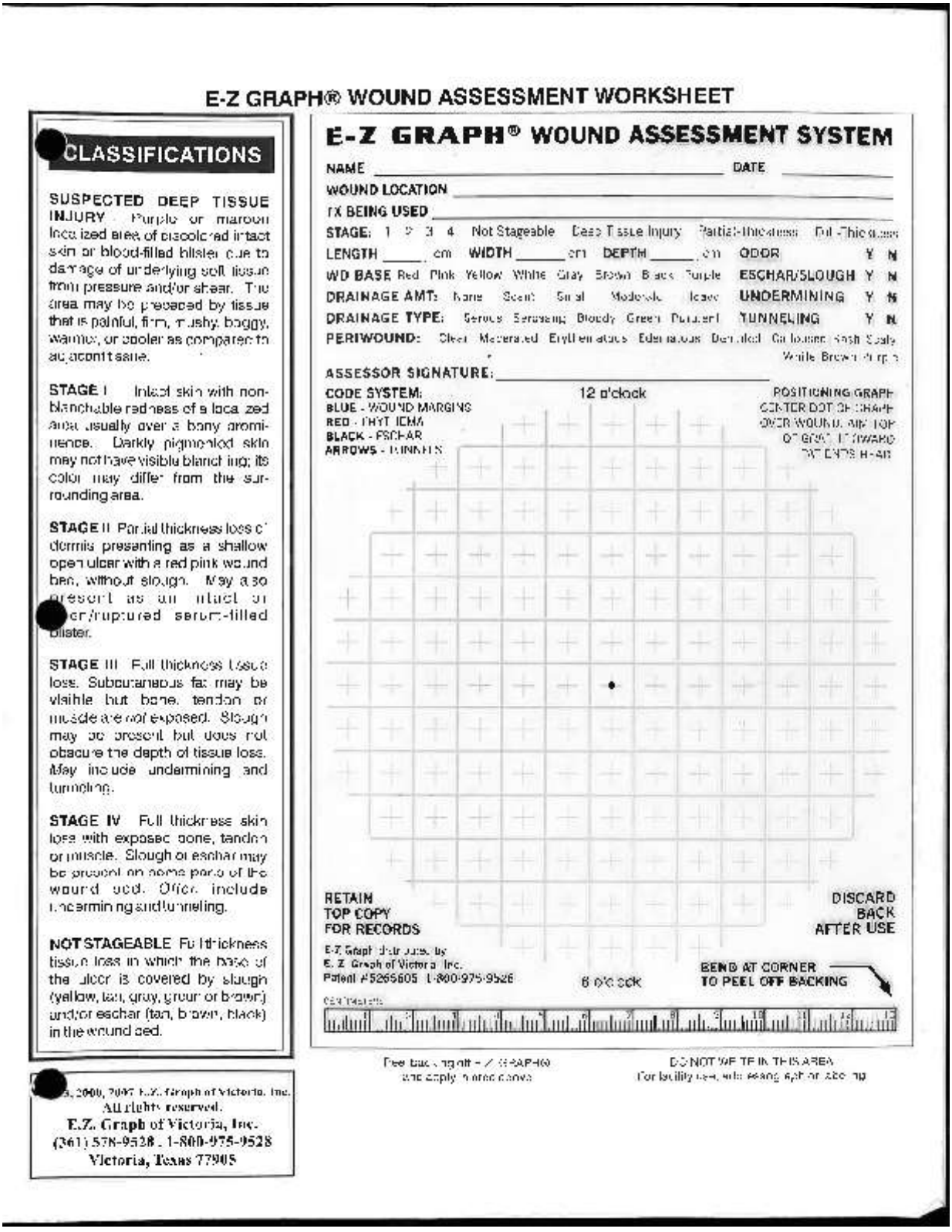
Appendix D: Visual Analog Scale Pain

Numeric Pain Scale



Source: Johnson, 2005.

Appendix E: E-Z Graph Wound Assessment



E-Z GRAPH® WOUND ASSESSMENT WORKSHEET

CLASSIFICATIONS

SUSPECTED DEEP TISSUE INJURY Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared to adjacent tissue.

STAGE I Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

STAGE II Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or ruptured serum-filled blister.

STAGE III Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

STAGE IV Full thickness skin loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunneling.

NOT STAGEABLE Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown, black) in the wound bed.

E.Z. Graph of Victoria, Inc.
(361) 578-9528 . 1-800-975-9528
Victoria, Texas 77905

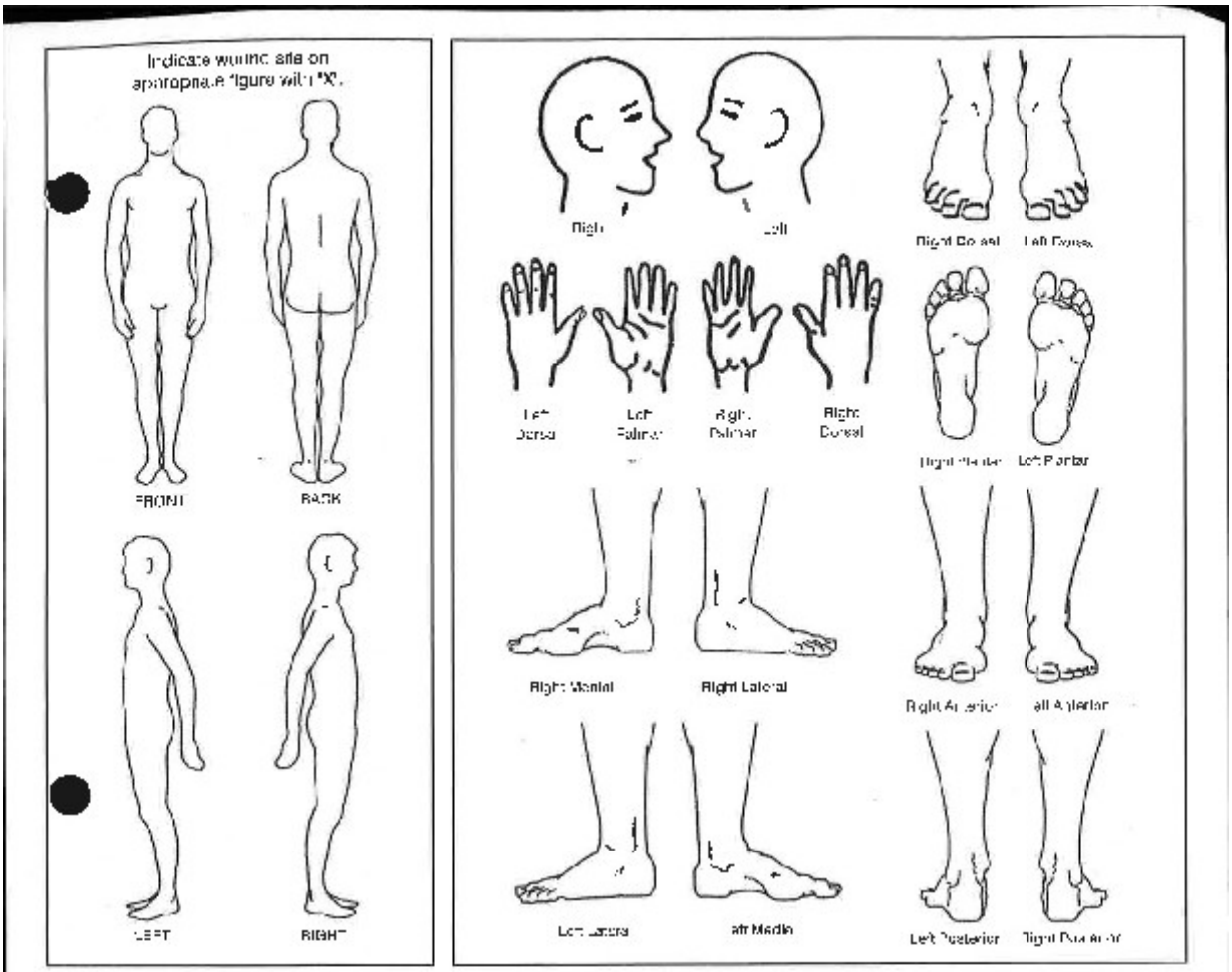
E-Z GRAPH® WOUND ASSESSMENT SYSTEM

NAME _____ DATE _____
WOUND LOCATION _____
TX BEING USED _____
STAGE: 1 2 3 4 Not Stageable Deep Tissue Injury Partial-thickness Full-Thickness
LENGTH _____ cm WIDTH _____ cm DEPTH _____ cm ODOR Y N
WD BASE Red Pink Yellow White Gray Brown Black Purple ESCHAR/SLOUGH Y N
DRAINAGE AMT: None Scant Small Moderate Heavy UNDERMINING Y N
DRAINAGE TYPE: Serous Serosang Bloody Green Purulent TUNNELING Y N
PERIWOUND: Clear Macerated Erythematous Edematous Denuded Callused Rash Scaly White Brown Purple
ASSESSOR SIGNATURE: _____
CODE SYSTEM:
BLUE - WOUND MARGINS
RED - PHYTHEMA
BLACK - ESCHAR
ARROWS - DRAINAGE
12 o'clock
POSITIONING GRAPH: CENTER DOT OF GRAPH OVER WOUND, AIM TOP OF GRAPH TOWARD 12 O'CLOCK
RETAIN TOP COPY FOR RECORDS
DISCARD BACK AFTER USE
E-Z Graph Distributed by E. Z. Graph of Victoria, Inc. Patent #5266605 1-800-975-9528
6 o'clock
BEND AT CORNER TO PEEL OFF BACKING
CENTIMETERS

See back right - / GRAPHO and apply wound care

DO NOT WRITE IN THIS AREA For facility use with easy light or stamp

Appendix E: E-Z Graph Wound Assessment (Continued)



Circle appropriate choices below. **Signature** _____ **Date** _____

THIS WOUND IS Present on Admission Newly Acquired Previously documented Arterial Venous Diabetic or neuropathic Pressure Surgical Traumatic Undetermined at this time Burn Other: _____

AGE OF WOUND Acute (duration less than 6 wks) Date occurred: _____ Chronic (duration greater than 6 wks) Date occurred: _____

PAIN PRESENT On touch Only when performing wound care All the time With weight bearing Positional - with elevation When dependent No pain at all Other: _____

WOUND STATUS Improved Healed Unchanged Deteriorated Initial Assessment

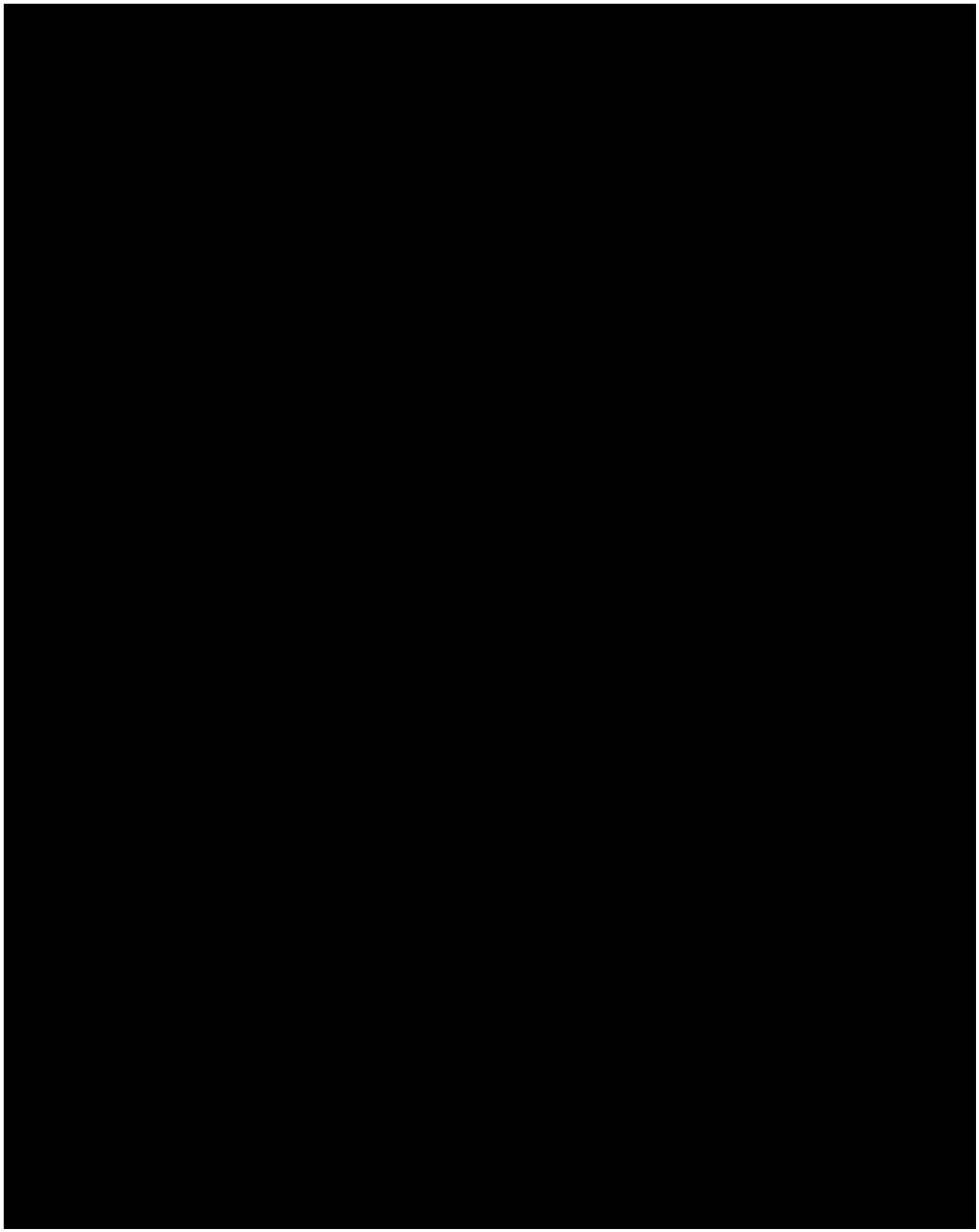
____% epithelialized ____% granulation ____% clean, nongranulating ____% slough ____% eschar ____% smaller in size

NARRATIVE: _____

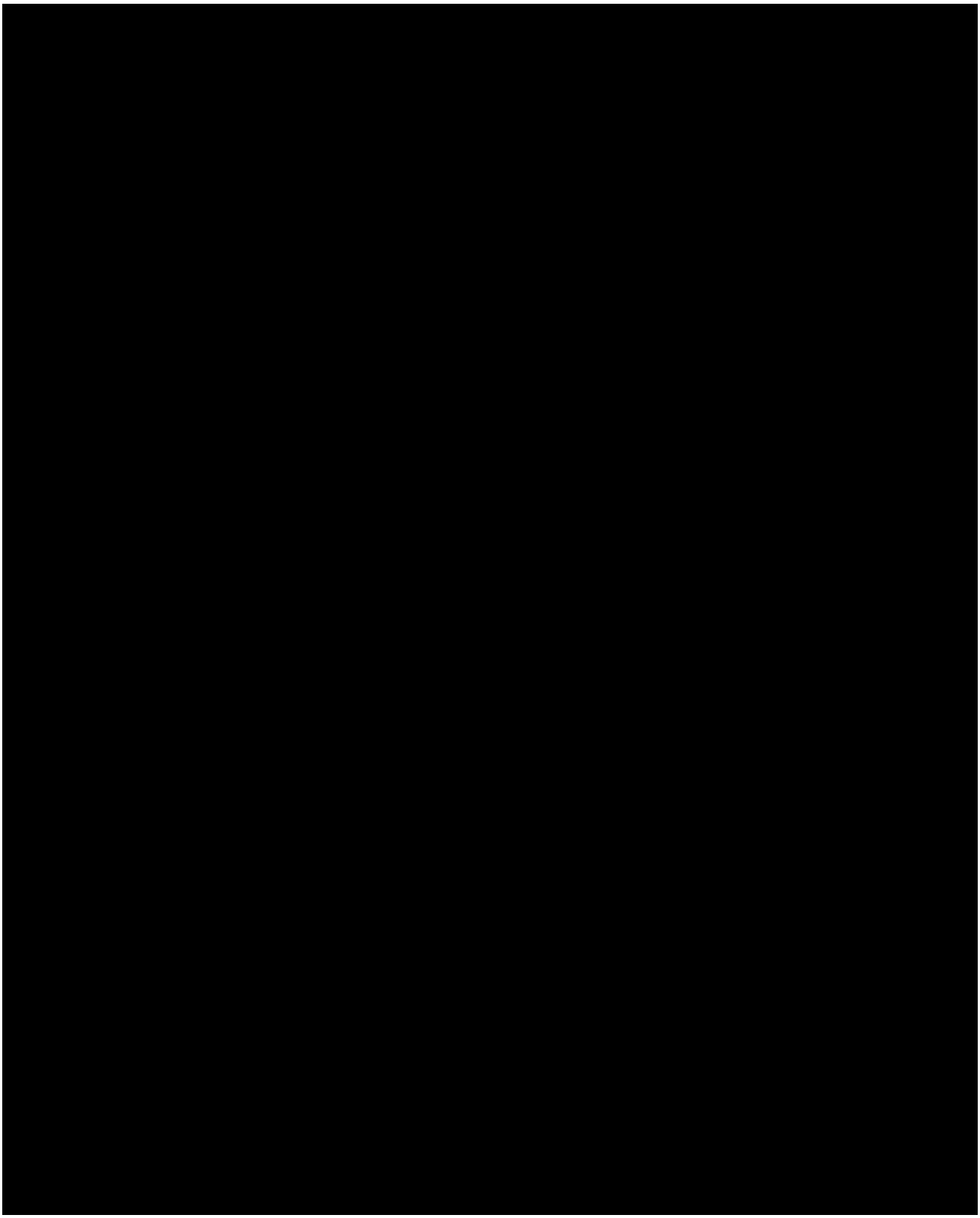
TREATMENT GOALS

1. Pressure redistribution.
2. Improve nutrition.
3. Promote circulation.
4. Control or reduce bacterial bioburden.
5. Decrease or remove nonviable tissue.
6. Promote comfort or decrease pain.
7. Decrease exudate / odor / edema.
8. Promote granulation / contraction / re-epithelialization.

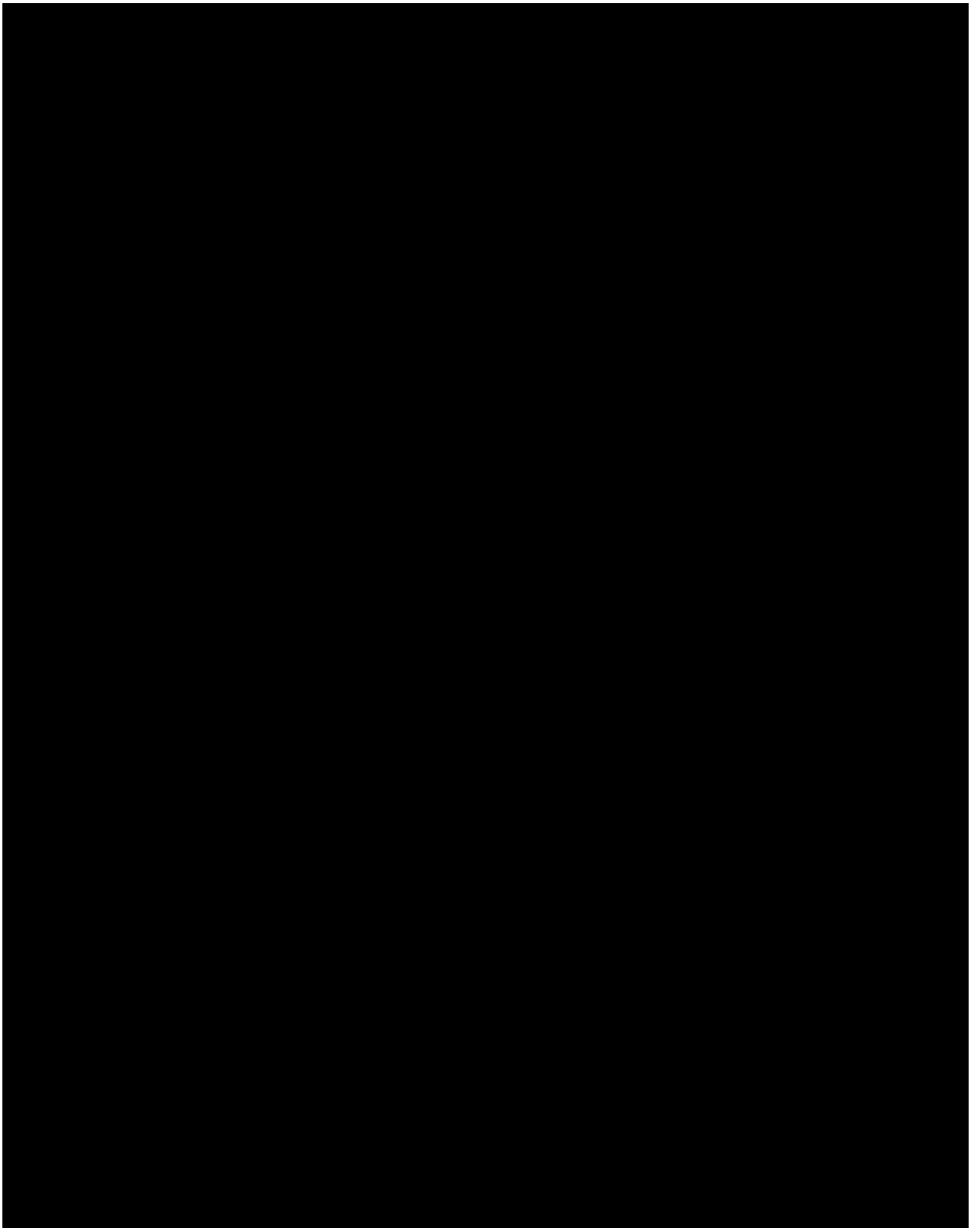
Appendix F: Guidelines for Digital Images Documenting Ulcer Healing Over Time



Appendix G: Thawing and Dilution Protocol



Appendix G: Thawing and Dilution Protocol (Continued)



Appendix G: Thawing and Dilution Protocol (Continued)

Appendix H: 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.

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