A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, DOSE RANGE FINDING STUDY TO ASSESS THE EFFICACY AND SAFETY OF INTRAMUSCULAR INJECTION OF HUMAN PLACENTA-DERIVED CELLS (PDA-002) IN SUBJECTS WITH DIABETIC PERIPHERAL NEUROPATHY

INVESTIGATIONAL PRODUCT:	**PDA-002**
PROTOCOL NUMBER:	**CCT-PDA-002-DPN-001**
DATE FINAL:	**8 June 2015**
AMENDMENT: No. 1:	**02 September 2015**
EudraCT NUMBER:	**Not Applicable**
IND NUMBER:	**016564**
SPONSOR NAME / ADDRESS:	Celgene Corporation 86 Morris Avenue Summit, NJ 07901

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Name:	Denesh K. Chitkara, MD
Title:	Senior Director, Clinical and Medical Affairs
Address:	7 Powderhorn Drive Warren, NJ 07059
Phone:	+1 (732) 564-5751 (Office) +1 (919) 259-6883 (Cell)
E-mail:	dchitkara@celgene.com
Name:	Denesh K. Chitkara, MD

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

Back-up 24 Hour Global Emergency Contact Call Center: +1-877-501-7738

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

A Phase 2, Randomized, Double-Blind, Placebo Controlled, Dose Range Finding Study to Assess the Efficacy and Safety of Intramuscular Injection of Human Placenta-Derived Cells (PDA-002) in Subjects With Diabetic Peripheral Neuropathy

Indication

This study will investigate the efficacy and safety of intramuscular (IM) injections of PDA-002 in subjects who have diabetic peripheral neuropathy (DPN) as a co-morbidity of Type 2 diabetes.

Objectives

The primary objective of the study is to assess the efficacy of PDA-002 versus placebo in subjects with DPN, based on the change from baseline in epidermal nerve histology at 6 months. The secondary objective of the study is to assess the safety and tolerability of IM administration of 2 different doses of PDA-002 or placebo in subjects with DPN.

The key exploratory objectives of the study are to assess potential treatment effects of IM administration of PDA-002 in subjects with DPN as measured by changes from baseline in:

- Epidermal nerve histology at 3 months
- Lower limb microvascular oxygenation
- Vascular reactivity
- DPN signs and symptoms
- Motor and sensory nerve conduction and autonomic function
- Health-related quality of life
- Vascular and immune, biomarkers, and laboratory parameters
- Assessment of the systemic versus local efficacy of PDA-002

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose range finding study in subjects with DPN. The study will enroll approximately 24 subjects. Subjects will be randomized to receive one of 3 treatments: PDA-002 (3×10^6 cells), PDA-002 (30×10^6 cells), or placebo (vehicle control) in a 1:1:1 randomization approach. Investigational product (IP) or placebo will be administered monthly (3 administrations total; Study Days 1, 29, and 57). Subjects will be evaluated for efficacy and safety for approximately one year from the day of the last IP administration.

Study Population

The study population includes subjects with Diabetic Peripheral Neuropathy due to Type 2 diabetes mellitus (DM) as defined by the ADA or WHO criteria (Appendix A).

Length of Study

Subjects are expected to participate in the study from screening (Day 28) to 1 year after the -last IP injection.

Subjects will undergo a Screening Period of up to 28 days. During the Screening Period eligibility will be confirmed and baseline assessments will be performed. Subjects will then enter a 6 month Treatment Period consisting of 8 study visits. During the Treatment Period, IP will be administered on Study Days 1, 29, and 57, and efficacy and safety evaluations will be performed as outlined in the Table of Events (Table 1). Subjects will then enter a Follow-up Period. The Follow up Period will consist of bi-monthly study visits to continue to assess safety and longer-term efficacy.

End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will be randomized 1:1:1 to receive one of the following dose levels of IP:

- PDA-002 Dose Level 1: 3 x 10^6 PDA-002 cells administered IM on Study Days 1, 29, and 57.*
- PDA-002 Dose Level 2: 30 x 10^6 PDA-002 cells administered IM on Study Days 1, 29, and 57.*
- Placebo (vehicle control) subjects will receive placebo (vehicle control) administered in the same manner and at the same time points as the PDA-002 dosing groups.

  *Subjects will be dosed in the same leg. The leg of injection will be the leg with the lowest combined qualifying NTSS-6 and UENS and NIS-LL score. In the case of a subject with an equal score for both legs, the choice of the leg to inject is at the discretion of the investigator.

PDA-002 and placebo (vehicle control) units will be shipped to the study sites as cryopreserved units and will be thawed and filled into syringes prior to IM injection.

Overview of Key Efficacy Assessments

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

The primary efficacy assessment is the evaluation of change from baseline in Epidermal Nerve Fiber Density (ENFD) at 6 months.

Efficacy will also be assessed in an exploratory manner by evaluating changes from baseline in the following:

- ENFD at 3 months
- Microvascular oxygenation of the lower limbs by Hyperspectral Imaging (HSI)

- Vascular reactivity by Laser Doppler Iontophoresis and Nerve Axon Reflex measurements.
- The 6-item Neuropathy Total Symptom Score (NTSS-6) assessment
- The Neurological Impairment Score of the Lower Limb (NIS-LL)
- The Utah Early Neuropathy Scale (UENS)

Additional efficacy signals indicating changes in motor and sensory nerve conduction and autonomic function as evaluated by:

- Nerve conduction studies
- Quantitative Sudomotor Axon Reflex Testing (QSART). QSART is a measurement of autonomic involvement by evaluating postganglionic sudomotor function deficits in the foot, distal leg, and distal thigh.

Changes in health-related quality of life (QOL) will be assessed by the Norfolk QOL-DN.

Various experimental biomarker analyses will be performed to assess changes in the vascular and immune profile. Samples for biomarker analyses will include blood and epidermal tissue. In addition, an assessment of the systemic vs. local efficacy of PDA-002 will be evaluated.

Overview of Safety Assessments

Safety and tolerability will be assessed by the type, frequency, and severity of adverse events (AEs). As such, the following safety assessments will be performed as outlined in the Table of Events (Table 1).

- Assessment of adverse events and serious adverse events (SAEs)
- Physical examinations including complete neurological examinations and vital signs
- Clinical laboratory tests including chemistry, hematology, urinalysis, evaluation; urine pregnancy testing if applicable
- Twelve-lead electrocardiogram (ECGs)
- Retinal assessments
- Concomitant medications and procedures
- Immunological assessments
  - Anti-human leukocyte antigen (HLA) antibodies

Sample Size and Power Considerations

The sample size of 24 subjects total, 8 per treatment arm, was selected in order to provide preliminary efficacy and safety information in a randomized, double-blind fashion. The study is designed to provide an estimation of the treatment effect of active therapy and placebo to plan a sample size for the next study.

Based upon a previous study (Jacobs, 2011), the mean ENFD was 1.56 fibers/mm at baseline and 3.07 fibers/mm after 6 months of treatment with a standard deviation of 1.5 fibers/mm for the mean increase. Assuming the same treatment effect is observed from baseline, the sample size of

16 subjects actively on therapy resulting from combining the 2 active arms has a 96% power to detect a similar mean change at 6 months from baseline, with a two-sided test and a Type I error rate set at 0.05. Assuming the subjects treated with placebo would not have a change from baseline, the study has 60% power to detect similar differences between placebo and active therapy with PDA-002, with a two-sided test and a Type I error rate set at 0.05.

Efficacy and Safety Analyses

The planned efficacy and safety analyses will be fully described in a comprehensive SAP.

The efficacy analyses will also include a descriptive assessment of the exploratory objective to evaluate whether the treatment effect of PDA-002 is systemic or local. This will be done by taking into account the intersubject variability between measurements taken from the left and the right leg.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Diabetes mellitus (DM) 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 DM (adult onset or non-insulin dependent diabetes) is by far the most common form, occurring in about 95% of subjects diagnosed with diabetes. Diabetic polyneuropathy (DPN) is the most common complication of DM. It develops on a background of long standing, chronic hyperglycemia, associated metabolic derangements, and cardiovascular risk factors.

Although the underlying mechanisms of DPN remain unclear, central features in the development and progression of DPN are neural cell degeneration and decreased nerve blood flow, and are usually associated with both axonal degeneration and demyelination. This results in spontaneous pain (burning pain, electrical or stabbing sensations, deep aching pain, etc.), hyperalgesia, and diminished sensation which is typically worse at night.

Therapies for the treatment of DPN are currently limited to pain relief (tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants, opioids, and non-prescription analgesics). There are currently no treatments approved to treat the underlying disease.

Human placenta-derived cells (PDA-002) are characterized as a cellular immune modulating agent that has the potential to induce angiogenesis. 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 and 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 using mouse models have demonstrated that PDA-002 cells do not proliferate in any tissues and are not associated with any observed toxicity or tumor formation. In a biodistribution study, PDA-002 cells were not detectable at Day 8 in the injected muscle by bioluminescence imaging. The cells did not distribute to other organs, including the lungs. The cells were only detected at the site of injection and in the draining lymph nodes.

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.

In rat and mouse models of peripheral neuritis, placental-derived cells have demonstrated dose dependent analgesic effects including pain reduction, suppressed immune cell infiltration, and reduced mechanical sensitivity. The analgesic effects were equivalent to high dose gabapentin.

Additionally, treatment with PDA-002 in mouse hind limb ischemia models demonstrated improvement in blood flow and induced the formation of new collateral blood vessels suggesting angiogenic activity. The effects were comparable to VEGF controls. Please refer to the Investigator's Brochure for details of these studies.

PDA-002 is currently being investigated in 3 independent human studies in subjects with complications of DM. The initial (ongoing) phase 1 open-label, dose escalation study (CCT-PDA-002-DFU-001) is being conducted in 15 subjects with peripheral arterial disease (PAD) with diabetic foot ulceration (DFU) who were refractory to conventional therapy. In this study, intramuscular (IM) injection of either 3 x 10^6, 10 x 10^6, 30 x 10^6, or 100 x 10^6 PDA-002 cells per treatment on Study Day 1 and Study Day 9 in the affected lower limb was being investigated. Though designed as a safety study, results have demonstrated efficacy in the healing or closure of the index ulcer within 3 months following the initial dose of PDA-002 in 15 subjects to date. Five subjects had complete healing, and 2 subjects had approximately 50% healing of their index ulcer within 3 months. There was a trend for subjects to have increases in their peripheral circulation as measured by the ankle brachial index (ABI). The mean increase in ABI from screening to the start of dosing was 0.003. A clinically significant increase in ABI at 3 months was observed following dosing (0.15). PDA-002 was safe and well tolerated in these subjects who had DFU with PAD.

Study PDA-002-DFU-002 is a Phase 2, randomized, double blind, placebo-controlled, dose range finding study in subjects who have DFU with PAD. Three doses of PDA-002 (3 x 10^6, 10 x 10^6 and 30 x 10^6 cells) versus placebo will be evaluated in 2:2:1:2 randomization approach, with the lower number of subjects to be allocated to the highest active dose. Approximately 133 subjects will be enrolled. This study is designed as an efficacy and safety study with wound closure of the index ulcer within 3 months after dosing and retaining wound closure for the subsequent 4 weeks as the primary endpoint. The study is ongoing, and the data remain blinded.

Study CCT-PDA-002-DFU-003 is also a Phase 2, randomized, double blind, placebo-controlled dose range finding study in 24 subjects who have DFU with PAD. The study is designed to assess the safety of repeated monthly IM administration of PDA-002, and to generate the data for a clinical proof of mechanism. The study is investigating 3 monthly doses with PDA-002 dose levels (3 x 10^6 or 30 x 10^6 PDA-002 cells) on Study Days 1, 29, and 57. Vascular functional parameters as well as potential novel biomarkers will be assessed to predict efficacy and to characterize the treatment response in order to evaluate the pharmacodynamics of treatment with PDA-002. The study is ongoing, and the data remain blinded.

To further evaluate the efficacy and safety of PDA-002, this Phase 2, randomized, double blind, placebo-controlled study will enroll 24 subjects with DPN. The study will employ the same doses and dosing schedule of PDA-002 as the aforementioned proof of mechanism study. The primary endpoint of the study is to assess changes in epidermal nerve fiber density (ENFD), an indicator of small nerve fiber involvement in DPN (Jacobs, 2011). Symptoms of small fiber neuropathy correlate with a decrease in the number, density and length of small nerve fibers in the epidermal layer. Therefore, an increase in ENFD may indicate PDA-002 induced neurogenesis. Additionally, since DPN involves both small myelinated and unmyelinated nerve

fibers (including those responsible for autonomic function) as well as large nerve fibers, various neurophysiological tests are required to identify dysfunction of different nerve populations. Therefore, physiological changes, signs, symptoms, and function related to DPN will be measured as exploratory endpoints.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of PDA-002.

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 objective of the study is to assess the efficacy of PDA-002 versus placebo in subjects with DPN, based on the change from baseline in epidermal nerve histology at 6 months.

2.2. Secondary Objective

The secondary objective of the study is to assess the safety and tolerability of IM administration of 2 different doses of PDA-002 or placebo in subjects with DPN.

2.3. Exploratory Objectives

The key exploratory objectives of the study are to assess any potential treatment effects of IM administration of 2 different doses of PDA-002 versus placebo in subjects with DPN as measured by changes from baseline in:

- Epidermal nerve histology at 3 months
- Lower limb microvascular oxygenation
- Vascular reactivity
- DPN signs and symptoms
- Motor and sensory nerve conduction and autonomic function
- Health-related quality of life measures
- Vascular, immune, and/or neural and laboratory parameters
- Assessment of the systemic versus local efficacy of PDA-002

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of the study is to assess the change from baseline in epidermal nerve fiber density (ENFD) at 6 months, an indicator of small nerve fiber involvement, following IM administration of 2 different doses of PDA-002 or placebo in subjects with DPN.

3.2. Secondary Endpoint

The secondary endpoint is to evaluate the safety and tolerability of PDA-002 as measured by the type, frequency, severity, and potential relationship of adverse events to treatment with PDA-002 or placebo.

3.3. Exploratory Endpoints

Exploratory endpoints of the study include measuring changes from baseline in:

- ENFD at 3 months
- Hyperspectral Imaging (HSI) to evaluate lower limb microvasculature oxygenation
- Vascular Reactivity by Laser Doppler Iontophoresis and Nerve Axon Reflex measurements
- Signs/symptoms of DPN as assessed by the 6-item Neuropathy Total Symptom Score (NTSS-6)
- Signs/symptoms of DPN as assessed by the Neurological Impairment Score of the Lower Limb (NIS-LL)
- Signs/symptoms of DPN as assessed by the Utah Early Neuropathy Scale (UENS)
- Motor and sensory nerve conduction and autonomic function as evaluated by electrophysiologic nerve conduction studies
- Quantitative Sudomotor Axon Reflex Testing (QSART)
- Health-Related quality of life (QOL) as measured by the Norfolk QOL-DN
- Vascular, immune, and/or neuronal and laboratory parameters measured in blood and/or epidermal tissues or other biological samples as appropriate
- Patient Global Impression of Change in Neuropathy (PGICN).

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose range finding study in subjects who have DPN. The study will enroll approximately 24 subjects. Subjects will be randomized to receive one of 3 treatments: PDA-002 (3×10^6 cells), PDA-002 (30×10^6 cells), or placebo (vehicle control) in a 1:1:1 randomization approach. Investigational product or placebo will be administered monthly (3 administrations total on Study Days 1, 29, and 57). Subjects will be treated and evaluated as indicated in the Table of Events (Table 1).

Subjects will undergo a Screening Period (up to 28 days in duration) to determine study eligibility and baseline levels of signs and symptoms of DPN will be established. Subjects will then enter a Treatment Period (6 months in duration). During the Treatment Period, subjects will be evaluated on an ongoing basis (at 8 scheduled study visits). Subjects will receive IM injections of IP on Study Days 1, 29, and 57 as fifteen 0.30 mL injections (below the knee and above the ankle) in one lower extremity in a blinded manner. After completing the Treatment Period, subjects will enter the Follow-up Period where they will continue to be evaluated at scheduled study visits over the subsequent months.

An analysis of all study data will occur after the last subject has completed Visit 9 (Month 6) and after the last scheduled study visit. Analyses to be performed can be found in the Statistical Analysis Plan.

The study will be subject to oversight by an independent Data Monitoring Committee (DMC). The DMC will review unblinded efficacy and safety data on an ongoing basis (both scheduled and ad hoc [if needed]) as outlined in the DMC Charter.

4.2. Study Design Rationale

Therapies for the treatment of DPN are currently limited to pain relief (tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, anticonvulsants, opioids, and non-prescription analgesics). Current treatments do not adequately address the symptoms in a large proportion of subjects with DPN, and there are no approved treatments that target the underlying disease.

One of the major pathophysiologic factors that contributes to DPN is damage to the vasa nervorum or the vascular supply to the nerves involved in DPN. In DPN, vascular damage to the vasa nervorum is induced by glycosylated proteins interacting with receptors to cells that are relevant to the atherosclerotic process, oxidative stress to the vessel wall, and hyperglycemia inducing protein kinase C, which is responsible for increased blood vessel permeability, nitric oxide dysfunction, and increased leukocyte adhesion (Kles, 2006).

Results from the rat hind limb ischemia model show that mesenchymal like stromal cells isolated from human placenta (formulated for IM injection as PDA-002) have potential clinical use in tissue repair through increasing angiogenesis. Furthermore, PDA-002 cells implanted in a mouse model of chronic hind limb ischemia improved blood perfusion and limb functional recovery (see Investigators Brochure).

The assessment of changes in nerve function and microvascular oxygenation in subjects with DPN will be based on a combination of evaluations that will assess nerve histology, DPN signs and symptoms, and tissue perfusion and oxygenation using measurement methods listed in the Table of Events (Table 1).

With regard to route of administration, IM administration of PDA-002 has demonstrated an acceptable safety profile to date. 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.

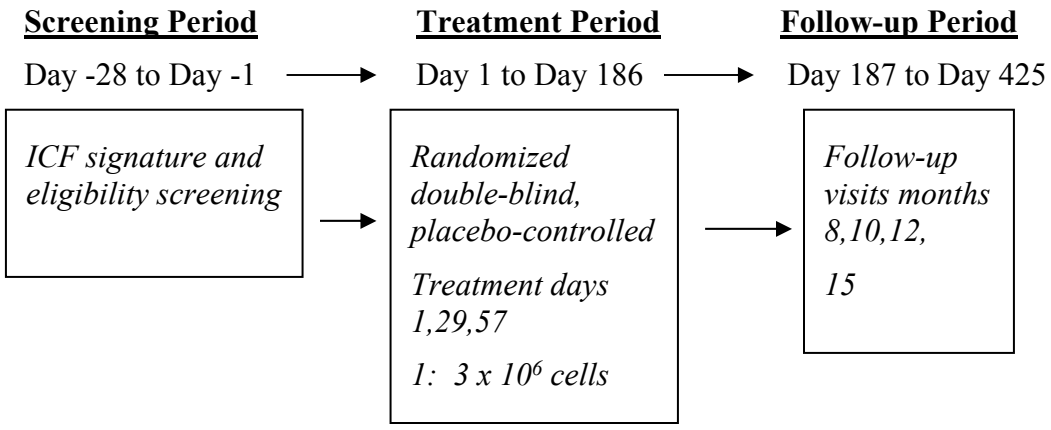
The doses selected for this study are based upon the effective doses adjusted for body weight that were administered in the previously described hind limb ischemia (HLI) animal models, as well as the dosing in the Phase 1 study PDA-002-DFU-001. Data on the first 3 dose cohorts of the Phase 1 study in which subjects were administered 3×10^6 cells, 10×10^6 cells and 30×10^6 cells on Days 1 and 8 demonstrated that the doses were well tolerated with no reported dose limiting toxicity (DLT). To date based upon the observed safety profile from the Phase 1 study, no new risks have been identified for PDA-002 that would preclude dosing in the Phase 2 studies.

For this study, subjects will be randomized to receive PDA-002 or placebo in one lower extremity in a blinded manner. Although PDA-002 is being administered IM, it is unclear if the therapeutic effect is localized to the area of injection or systemic. In pre-clinical HLI studies, the therapeutic effect of PDA-002 was similar in animals administrated the IM and intravenous (IV) formulation. The mechanism of action of PDA-002 is due to a modulation of the immune system from a pro inflammatory to anti-inflammatory state that facilitates angiogenesis both in the area directly in contact with PDA-002 along with other areas that may be affected by inflammation and ischemia. Since DPN causes a symmetrical dysfunction to the nerves of the lower extremities, assessments of nerve function as well as changes in neurologic signs will be assessed in both legs in order to determine if the therapeutic effect of PDA-002 is local vs. systemic.

The dosing schedule of PDA-002 in this study will be 3 repeated monthly administrations. The schedule is based on the safety of 3 repeat IM doses of PDA-002 demonstrated in animal studies. Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of PDA-002.

One additional design feature of this study is that while PDA-002 is injected into one leg, both legs are checked for changes in neuropathy signs and symptoms. This will enable determining if the effects of PDA-002 on DPN are limited to the area in which the cells are injected, or the effect is systemic.

Figure 1: Overall Study Design



4.3. Study Duration

Subjects are expected to participate in the study from screening (up to Day -28) to 1 year after the last IP injection.

Subjects will undergo a Screening Period of up to 28 days. During the Screening Period eligibility will be confirmed and baseline assessments will be performed. Subjects will then enter a 6 month Treatment Period consisting of 8 scheduled study visits. During the Treatment Period, IP or placebo will be administered on Study Days 1, 29, and 57, and efficacy and safety evaluations will be performed. Following this, subjects will then enter a Follow-up Period. The Follow up Period will consist of scheduled bi-monthly study visits to continue to assess safety and longer-term efficacy.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

5. TABLE OF EVENTS

Table 1: Table of Events

	Screening Period	Treatment Period								Follow-up Period				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	
	Day -28 to Day 0	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	Day 57 (±3 days)	Day 93 (±7 days)	Day 120 (±3 days)	Day 155 (±3 days)	Day 186 (±7 days)	Day 246 (±7 days)	Day 306 (±7 days)	Day 365 (±7 days)	Day 425 (±7 days)	Early Termin-ation
Event		Week 1	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 8	Month 10	Month 12	Month 14	
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Demography/medical and surgical history including duration of diabetes and diabetic peripheral neuropathy	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination including vital signs (height [at Visit 1 only], weight, body temperature, blood pressure, respiration, and pulse[a]	X	X	-	X	X	X	X	X	X	X	X	X	X	X
12-Lead electrocardiogram (ECG)[f]	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical laboratory testing (serum biochemistry, hematology, coagulation tests urinalysis). Estimated glomerular (eGFR) filtration rate will be calculated (Screening).	X	X	-	X	X	-	-	-	X	-	-	-	X	X
Anti-HLA antibodies	X	X[e]	-	X[e]	X[e]	X	-	-	-	-	-	-	-	-
HbA1c testing	X	-	-	-	-	X	-	-	X	-	-	X	-	X
Obtain blood for exploratory biomarker evaluation prior to administration of IP[b]	X	X	-	X	X	X	-	-	X	-	-	-	-	X

Table 1: Table of Events (Continued)

Event	Screening Period	Treatment Period								Follow-up Period				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	Early Termination
	Day -28 to Day 0	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	Day 57 (±3 days)	Day 93 (±7 days)	Day 120 (±3 days)	Day 155 (±3 days)	Day 186 (±7 days)	Day 246 (±7 days)	Day 306 (±7 days)	Day 365 (±7 days)	Day 425 (±7 days)	
		Week 1	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 8	Month 10	Month 12	Month 14	
Pregnancy test[c]	X	X	-	X	X	-	-	-	-	-	-	-	-	X
Retinal examination	X	-	-	-	-	-	-	-	X	-	-	X	-	X
6 Item Neuropathy Total Symptom Score (NTSS-6)	X	-	-	X	-	X	-	-	X	-	-	X	-	X
Utah Early Neuropathy Scale (UENS)	X	-	-	X	-	X	-	-	X	-	-	X	-	X
Neuropathy Impairment Score of the Lower Limb (NIS-LL)	X	-	-	X	-	X	-	-	X	-	-	X	-	X
Electrophysiologic nerve conduction studies	X	-	-	-	-	-	-	-	X	-	-	X	-	X
Hyperspectral imaging	X	-	-	X	-	X	-	-	X	-	-	X	-	X
Quantitative Sudomotor Axon Reflex Testing (QSART)	X	-	-	-	-	-	-	-	X	-	-	X	-	X
Skin biopsies	X	-	-	-	-	X	-	-	X	-	-	-	-	-
Histology of Immune Cells (mast cell)	X	-	-	-	-	X	-	-	X	-	-	-	-	-
Norfolk Quality of Life Assessment (Norfolk-QOL-DN)	X	-	-	-	-	X	-	-	X	-	-	X	-	X
Patient Global Impression of Change in Neuropathy (PGICN)	X	X	X	X	X	-	-	-	X	-	-	X	-	X

Table 1: Table of Events (Continued)

	Screening Period	Treatment Period								Follow-up Period				
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	
	Day -28 to Day 0	Day 1 (±3 days)	Day 15 (±3 days)	Day 29 (±3 days)	Day 57 (±3 days)	Day 93 (±7 days)	Day 120 (±3 days)	Day 155 (±3 days)	Day 186 (±7 days)	Day 246 (±7 days)	Day 306 (±7 days)	Day 365 (±7 days)	Day 425 (±7 days)	Early Termin-ation
Event		Week 1	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 8	Month 10	Month 12	Month 14	
Vascular reactivity measurements-(including Laser Doppler Iontophoresis and Nerve Axon Reflex measurements)	X	-	-	-	-	X	-	-	X	-	-	X	-	-
Administration of IP	-	X	-	X	X	-	-	-	-	-	-	-	-	-
IP administration monitoring (including visual inspection of injection areas, vital signs, and collection of blood for coagulation tests and tryptase/histamine evaluation before and after IP administration)	-	X	-	X	X	-	-	-	-	-	-	-	-	-
Assess and record adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: IP=Investigational Product, PBMC=peripheral blood mononuclear cell, RBC=red blood cell, SAE=serious adverse event.

[a] Physical exams during the Screening Period and Early Termination will be full physical examinations. At all other assessments, physical examinations should only be directed to evaluate reported adverse events. Assessments for vital signs can be performed within15 minutes for the 1 and 2 hour post dose assessments.

[b] Biomarkers assessed at Screening, Visit 2 Day 1 and Visit 4 Day 29, and Visit 5 Day 57 prior to injection of IP. Biomarkers will also be assessed on Day 93 when there is no IP injection. Biomarker samples will include blood immune biomarkers and RBC-lysed PBMC sample for the chip cytometry assay. The chip cytometry assay will only be performed at selected sites.

[c] Serum pregnancy testing at Screening and urine pregnancy testing at all other visits of females of childbearing potential. At Visit 2 a urine pregnancy needs to be performed if a serum pregnancy test was not done within 0-72 hours predose. Prior to treatment on Study Days 1, 29, and 57.

[d] Adverse events will be followed for 28 days after the last dose of IP. SAEs will be followed until the last study visit.

[e] Prior to injection on Days 1, 29 and 57.

[f] If performed within 28 days of signing the informed consent it does not need to be repeated.

6. PROCEDURES

6.1. Study Entry/Screening Period (Visit 1)

Visit 1 and Visit 2 can occur up to 28 days apart. All Screening Period procedures should be performed as per Table 1.

Informed Consent/Previous Participation: The initial screening visit will occur up to 28 days prior to the initial administration of IP. Before or at Visit 1, qualified site personnel will explain the study to the subject, answer all of his/her questions, and obtain written informed consent/ Health Insurance Portability and Accountability Act (HIPAA) authorization before performing any study-related procedures. A copy of the signed informed consent will be given to the subject, and the date of the signing of the informed consent will be recorded in the electronic case report form (eCRF) and in the source documents. Previous participation in any other CCT-PDA study will be recorded in the eCRF and in the source documents.

Assessment of Adverse Events: Adverse events (AEs) will be collected from the time the subject signs the informed consent throughout the study. The type, frequency and severity of adverse events and potential relationship to IP will be collected as described in the full study protocol.

Demographics/Medical and Surgical History: Demographics and medical history will be obtained during screening. Demographics will include subject's initials, date of birth, sex, ethnicity, and race. A thorough medical and surgical history including date of diagnosis of DM and DPN, psychiatric conditions, current medical conditions, and any known allergies will be performed.

Prior/Concomitant Medications: All medications taken (including contraception measures) within the last **35 days** should be recorded. All medications that a subject is currently taking will also be recorded from the time the subject signs the informed consent throughout the study.

Physical Examination/Vital Signs: Subjects will undergo a routine physical examination.

Vital signs including height (cm) (Visit 1 only), weight, (kg) body temperature (°C), pulse (beats/minute), respiration (breaths/minute), and resting systolic and diastolic blood pressure (mmHg) will be measured and recorded in the eCRF and in the source documents.

Pregnancy Testing

Serum pregnancy testing at Screening and urine pregnancy testing at all other visits of females of childbearing potential. At Visit 2 a urine pregnancy needs to be performed if a serum pregnancy test was not done within 0-72 hours predose. Pregnancy testing will be conducted prior to treatment on Study Days 1, 29, and 57.

Electrocardiogram: A 12-lead ECG will be obtained. At screening, if a 12-lead ECG was performed as part of the subject's previous routine care within 28 days prior to signing of the informed consent, it does not need to be repeated. The following will be recorded in the eCRF and in the source documents:

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

Clinical Laboratory Tests: Blood and urine samples for routine laboratory testing as well as blood for exploratory biomarker analysis will be obtained as per the Table of Events (Table 1) and will be evaluated by a central laboratory. Please refer to the Laboratory Manual for detailed information on the collection, storage, and shipment of laboratory samples.

Serum Chemistry

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

- Calcium
- Chloride
- Potassium
- Sodium
- 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 as indicated in the Table of Events (Table 1) and will include the following:

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

Urinalysis

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

Urine albumin and creatinine to be collect with the morning void

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

Immunological/Inflammation Assessments

Immunological/inflammation assessment will include the following testing:

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

Hemoglobin A1c

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

Coagulation Tests

Coagulation tests including assessment of PT/PTT, D-dimers, fibrinogen, and platelets will be assessed as indicated in the Table of Events (Table 1) prior to dosing with IP and approximately 2 hours post-dose. Assessments can be performed within 1 hour of the 2 hour post dose time frame.

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 as indicated in the Table of Events (Table 1).

Exploratory Biomarkers

Exploratory biomarkers will be measured as indicated in the Table of Events (Table 1).

Skin Biopsies: Two 3mm thickness skin punch biopsies will be taken at the lateral aspect of the distal legs (2 biopsies; 1 per leg) approximately 10 cm above the lateral malleolus, and two biopsies will be taken at the volar aspect of the forearm (2 biopsies on 1 forearm). Instructions for tissue collection, handling, and shipping instructions are located in the Laboratory Manual.

Contraception: Females of childbearing potential[1] must use adequate contraception for the duration of their participation in the study (which includes 28 days prior to starting IP, during the Treatment Period [including dose interruptions], and during the Follow-up Period). Adequate contraception is defined as the simultaneous use of 2 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 females of child bearing potential (FCBP) for the duration of their participation in the study, including the Follow-up Period.

Retinal Assessment: Retinal assessment conducted by an ophthalmologist or optometrist will be performed and scored using the International Clinical Diabetic Retinopathy Disease Severity Scale (Appendix B). Results will be recorded in the eCRF and in the source documents.

6-Item Neuropathy Total Symptom Score (NTSS-6): To be completed as outlined in Efficacy Procedures Section 6.4.

Neurological Impairment Score of the Lower Limb (NIS-LL): To be completed as outlined in Efficacy Procedures Section 6.4.

Utah Early Neuropathy Scale (UENS): To be completed as outlined in Efficacy Procedures Section 6.4.

Nerve Conduction Studies: To be completed as outlined in Efficacy Procedures Section 6.4.

Quantitative Sudomotor Axon Reflex Testing (QSART): To be completed as outlined in Efficacy Procedures Section 6.4.

Norfolk QOL-DN: To be completed as outlined in Efficacy Procedures Section 6.4.

Patient Global Impression of Change in Neuropathy (PGICN): To be assessed as outlined in Efficacy Procedures Section 6.4.

Vascular Reactivity Measurements*: To be completed as outlined in Efficacy Procedures Section 6.4.

*This procedure will only be measured if it is available for this study protocol at the participating site.

Hyperspectral Imaging (HSI)*: To be completed as outlined in Efficacy Procedures Section 6.4.

* This procedure will only be performed if it is available for this study protocol at the participating site.

Final Review of All Inclusion/Exclusion Criteria: The investigator or designee will review all inclusion/exclusion criteria once the subject has completed all screening assessments. If the subject meets all of the study entrance criteria, the subject will be randomized and scheduled for dosing with IP. Study site personnel will contact the Interactive Web Response System (IWRS)

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

for each subject's treatment group assignment, and the randomization number will be recorded in the eCRF and in the source documents.

6.2. Treatment Period (Visit 2 through Visit 9)

Visit 2 through Visit 9 should occur on the days specified within the allowable variance. All Treatment Period procedures should be performed as per Table 1.

Administration of IP (Visit 2, Visit 4, and Visit 5)

IP will be administered on Study Days 1, 29 and 57. Preparation and administration of IP is discussed in Section 8.2.

IP Administration Information: IP thaw time, start and stop time of injections, and administration interruption/completion will be recorded in the eCRF and in the source documents.

IP Administration Vital Signs: Vital signs including heart rate, respiration, blood pressure, and body temperature will be monitored prior to starting the injections and at 1 and 2 hours after completion of the injections (± 15 minutes).

IP Administration Additional Blood Sampling: Blood samples for tryptase and histamine, coagulation assessments (PT/PTT), and exploratory biomarkers will be collected 2 hours before (± 15 minutes) IP administration and also at 2 hours after IP administration for tryptase and histamine assessments as indicated in the Table of Events (Table 1).

IP Administration Adverse Event Monitoring: A visual inspection of injection sites will be conducted periodically from the initial injection until 2 hours after the last injection (minimum). Any clinically significant findings will be recorded as AEs in the eCRF and in the source documents.

6.3. Follow-Up Period

All subjects will be followed for 28 days after the last dose of IP for AE reporting, as well as SAEs that will be followed until the last study visit and made known to the investigator at any time thereafter that are suspected of being related to IP, as described in Section 11.1.

The Follow-up Period will take place from Visit 10 through Visit 13 and include Early Termination. Visits should occur on the day specified ± 3 days or ± 7 days as specified in the Table of Events (Table 1).

All other procedures (as discussed in Section 6.1 and Section 6.2) will be conducted as per the Table of Events (Table 1).

6.4. Efficacy Procedures

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

Epidermal Nerve Fiber Density (ENFD): This assessment relies on an immunohistochemical localization of a neural antigen within axons. Histological specimens will consist of serial 3mm thickness punch biopsies of the epidermis taken bilaterally at the lateral aspect of the distal legs. To quantify ENFD (fibers/mm of epidermis), the pathologist manually counts the number of

epidermal nerve fibers in 3 to 5 sections and divides the value by the lengths of the epidermal specimens in millimeters. In addition, a quantification of the autonomic sudomotor (sympathetic cholinergic) and pilomotor (sympathetic adrenergic) nerve fibers will be conducted within the same biopsy.

Histology of Immune Cells: Two skin biopsies will be taken from the volar aspect of the forearm. The first biopsy will be used for histology analysis to evaluate the inflammatory response by assessing inflammatory cell infiltration. The second biopsy will be used to perform mRNA / protein analysis.

Circulating Blood Biomarkers: Blood collected to be used for biomarker analysis will include whole blood collection for blood immune biomarkers and red blood cell (RBC)-lysed peripheral blood mononuclear cell (PBMC) sample for the chip cytometry immune phenotyping assay*.

> * These assessments for RBC-lysed peripheral blood mononuclear cell (PBMC) by the chip cytometry assay will only be performed at selected sites.

Hyperspectral Imaging *: Hyperspectral imaging (HIS) obtains multiple images at discrete wavelengths, providing a diffuse reflectance spectrum of each pixel in the image. The system uses wavelengths between 500 and 600 nanometers which serve to obtain oxy- and deoxy-hemoglobin absorption peaks. Tissue oxygenation images or "maps" are then constructed from oxy- and deoxy-hemoglobin values determined from each pixel in the image. HSI will be measured in both lower limbs.

> *This procedure will be measured only if it is available for this study protocol at the participating site.

6-item Neuropathy Total Symptom Score (NTSS-6): The NTSS-6 questionnaire is used to evaluate the frequency and intensity of neuropathy sensory symptoms identified by subjects with DPN (ie, numbness and/or insensitivity, prickling, and/or tingling; burning pain; aching pain and/or tightness, sharp shooting lancinating pain and allodynia and/or hyperalgesia). Symptoms are graded based on the experience of the subject during the past 24 hours. Each symptom question can be assigned a maximum score of 3.66 points. The symptom scores are summed, and the total score can range from 0 points to 21.96 points. A higher score indicates greater disability.

Neurological Impairment Score of the Lower Limb (NIS-LL): The NIS-LL is an assessment tool composed of a sensory subscore (which evaluates sensory perceptions to touch, prickling pain, vibration, joint position, and to 1 gram and 10 gram monofilaments), and a motor subscore (which evaluates muscle strength, muscle wasting, and deep tendon reflexes) in the lower limbs. The scale is additive for all deficits and is applied in a bilateral manner for each modality tested. The subscores are totaled and can range from 0 points (normal neurological function) to 88 points (absence of all motor, sensory, and reflex activity). An increase of 2 points is clinically significant.

Utah Early Neuropathy Scale (UENS): The UENS uses a physical examination specific to early sensory predominant polyneuropathy which emphasizes severity and spatial distribution of sharp sensory loss in the foot and leg. The total score can range from 0 to 42. A higher score indicates greater disability.

Electro physiologic Nerve Conduction Studies: Nerve conduction studies allow for the quantification of the conduction amplitude, velocity, and latency of the tibial and peroneal nerves, and the amplitude and latency of the sural nerve. Reduction of amplitudes of recorded responses generally indicates a loss of axons. Nerve conduction will be measured in both lower limbs.

Quantitative Sudomotor Axon Reflex Testing (QSART): QSART is a measurement of autonomic involvement by evaluating postganglionic sudomotor function deficits in the foot, distal leg, and distal thigh.

Patient Global Impression of Change in Neuropathy (PGICN): The PGICN is a subject's self assessment to describe and change in symptoms of neuropathy such as pain, tingling, or numbness.

Health-Related Quality of Life (QOL) as measured by the Norfolk QOL-DN: The Norfolk QOL-DN is composed of 5 domains (physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic nerve function) encompassing 35 scored questions related to subjects' neuropathy signs and symptoms, as well as to the impact of DPN on subjects' activities of daily life. The total score can range from -2 to 138. A higher score indicates higher disability.

Vascular Reactivity Measurements*: Vascular reactivity will be measured by using Laser Doppler Iontophoresis and Nerve Axon Reflex measurements in both lower limbs. By applying acetylcholine chloride, the endothelium-dependent vasodilatation may be measured. The MIC1 iontophoresis system will be used in this study. Specifically, a small quantity (<1 ml) of 1% acetylcholine chloride solution will be used on the forearm of the participating subjects; subsequently a constant current of 200 microampere will be applied for 60 seconds achieving a dose of 6 $mC.cm^{-2}$. The single spot reaction will be measured by Laser Doppler Flowmetry using a DRT4 Laser Doppler Blood Flow Monitor.

The Nerve Axon Reflex measurement will be performed at the foot level by using a single point Laser Probe during the acetylcholine iontophoresis. The single spot reaction will be measured by Laser Doppler Flowmetry using a DRT4 Laser Doppler Blood Flow Monitor. The probe will be attached to the center of the iontophoresis chamber. As the probe is not in direct contact with the foot, it will only measure the nerve axon-related vasodilation. The results are expressed as percentage of increase over the baseline blood flow.

> *This procedure will be measured only if it is available for this study protocol at the participating site.

6.5. Safety

Safety will be assessed by an ongoing review of clinical laboratory tests (hematology, serum chemistry, coagulation, pregnancy, urinalysis, physical examination results, vital sign measurements, 12-lead ECG at screening only, weight, 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.

6.5.1. External Data Monitoring Committee

An external unblinded DMC will monitor safety and efficacy information to ensure subject safety in accordance with a separate charter. The external DMC will be comprised of members who are not involved in the day-to-day activities of the PDA-002 DPN study team. Data review packets will be forwarded to the DMC members for review at least 7 days prior to each scheduled DMC teleconference/meeting. Data will be current through 14 days prior to each scheduled DMC teleconference/meeting.

The external DMC will be convened to assess the benefit risk of PDA-002 when approximately 25% and 50% of subjects complete the Month 3 (Visit 6) assessment. Study enrollment will be ongoing during these scheduled reviews.

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

- Identification of 1 or more subjects within a dosing treatment arm with ≥ Grade 3 allergic reaction that is suspected to be related to the IP.
- Identification of 1 or more subjects experiencing a suspected unexpected, treatment-related SAE (SUSARs) within 14 days following the initial dose of the IP suspected unexpected serious adverse reactions.
- Identification of 1 or more subjects with a new malignancy.

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

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Approximately 24 subjects with diabetic peripheral neuropathy will be enrolled at about 5 sites in the United States.

7.2. Inclusion Criteria

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

1. Males and females who are at least 18 years of age at the time of signing the informed consent document.
2. Subject must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures are conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Diabetes mellitus (DM) Type 2 as defined by the ADA or WHO criteria (Appendix A).
5. Meet established criteria for DPN due to Type 2 diabetes with the following:
    a. Abnormal symptoms (NTSS-6 ≥ 6 points (total score) or ≥ 2.0 points for one or more symptoms)

       AND

    b. Abnormal signs (UENS score of 2-24 and/or NIS-LL score of 2-10).
6. 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 Females of Child Bearing Potential (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.
7. 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.

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. Other causes of neuropathy in diabetic subjects: chronic inflammatory demyelinating polyneuropathy; neuropathy due to vitamin B12 deficiency, hypothyroidism, and uremia syndrome; and neuropathy due to entrapment or trauma.

3. A reversible course of acute painful diabetic neuropathy syndrome: treatment-induced diabetic neuropathy that presents in the setting of rapid glycemic control; diabetic neuropathic cachexia; and diabetic anorexia, a diabetic neuropathy that is seen with intentional weight loss.
4. History of a prior diagnosis of severe peripheral arterial disease (PAD).
5. Thrombocytopenia and coagulopathy, to avoid severe bruising or bleeding due to multiple intramuscular (IM) injections.
6. Any condition including the presence of laboratory abnormalities that places the subject at unacceptable risk if he or she were to participate in the study.
7. Any condition that confounds the ability to interpret data from the study.
8. Subjects who are taking opioids for the treatment of DPN.
9. Pregnant or lactating females.
10. Subjects with a body mass index > 40 kg/m^2 at screening.
11. Neuropathy resulting from a condition other than DM and/or significant co-morbid neurological diseases (eg, Parkinson's disease, epilepsy, multiple sclerosis, alcoholic peripheral neuropathy), or exposure to agents suspected to cause symptoms of neuropathy (such as but not limited to metronidazole, antituberculosis medications, and heavy metals).
12. Advanced neuropathy as measured by the absence of sural sensory nerve action potential, or a UENS>24 and or a NIS-LL>10.
13. History of a prior diagnosis of Critical Limb Ischemia.
14. History of diabetic foot ulceration (at any time) and/or or undergoing a limb revascularization procedure(s) and/or amputation(s) due to DM.
15. Diagnosis of Type 1 DM and/or any of the following: diagnosis of DM prior to age 35 years; insulin required to treat DM within 1 year after DM diagnosis; history of diabetic ketoacidosis.
16. AST, ALT, or alkaline phosphatase ≥ 2.5 x the upper limit of normal (ULN) at screening.
17. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at Screening calculated using the Modification of Diet in Renal Disease Study equation (Levey, 2006) or history of an abnormal eGFR < 60 and decline > 15 mL/min/1.73 m^2 below normal in the past year.
18. Bilirubin level > 2 mg/dL (unless subject has known Gilbert's disease) at screening.
19. Untreated chronic infection or treatment of any infection with systemic antibiotics within 4 weeks prior to dosing with IP.
20. 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).

21. History of significant cardiac disorders including but not limited to malignant ventricular arrhythmia, CCS Class III-IV angina pectoris, myocardial infarction/ percutaneous coronary intervention (PCI) / coronary artery bypass graft (CABG) in the 6 months prior to signing the informed consent ICF, pending coronary revascularization in the following 3 months, transient ischemic attack/cerebrovascular accident in the 6 months prior to signing the informed consent form, and/or New York Heart Association [NYHA] Stage III or IV congestive heart failure (Appendix C). Note: Stable Canadian Cardiovascular Society (CCS) Class I-II angina is allowed (Appendix D).
22. Poorly controlled DM (hemoglobin A1c > 10%) at screening.
23. Untreated proliferative retinopathy at screening.
24. Life expectancy less than 2 years due to concomitant illnesses.
25. History of malignancy within 5 years except for the following circumstances: basal cell or squamous cell carcinoma of the skin, remote history of cancer now considered cured or positive Pap smear with subsequent negative follow-up.
26. History of hypersensitivity to any of the components of the product formulation (including bovine or porcine products, dextran 40, and dimethyl sulfoxide [DMSO]).
27. 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 or has received previous gene or cell therapy at any time.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Investigational Product

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 as a plastic-adherent, undifferentiated in vitro 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.

These cells demonstrate a range of potential biological activities which include the ability to (1) induce endothelial cell survival, migration and tube formation, showing angiogenic and cytoprotective potential, and (2) modulate T-cell repertoire and affect the M1/M2 balance of macrophages demonstrating an immune modulatory effect. Based on these properties, the proposed study will evaluate the safety of PDA-002 in subjects with DPN.

PDA-002 or placebo (vehicle control) units will be shipped to the study sites as cryopreserved units and will be thawed and filled into syringes prior to IM injection. A PDA-002 unit are supplied at 2 dosage strengths and contains approximately 3 or 30 million cells in 4.5 mL of a 5.75% dextran 40/10% human serum albumin (HSA) solution containing 2.5% DMSO for cryopreservation. The solution also contains Plasma-Lyte and saline to maintain the cells' osmotic environment. Placebo (vehicle control) units contain the above-mentioned components, without any cells. The product is intended for allogeneic use.

8.2. Treatment Administration and Schedule

Investigational product (IP) will be administered on Study Days 1, 29 and 57. Thawing of the IP should not begin until it is confirmed that the subject meets the inclusion/exclusion criteria. Investigational product thawing will be performed by qualified site personnel according to the instructions in Appendix E. Three 3 mL syringes will each be filled with 1.5 mL of IP, and then capped. Syringes will be masked to preserve blinding, and transferred to the personnel administering the injections.

Subjects will receive IP administered as fifteen 0.30 mL injections (approximately 4.5 mL total) in one 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. The administrator will be blinded to treatment.

PDA-002 is not intended for intravenous 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 re-aspirated. If no blood is seen, the IP may be injected.

Vital signs (including heart rate, respiration, blood pressure, body temperature) will be monitored prior to starting the injections and at 1 and 2 hours (± 15 minutes) after completion of

the injections. Blood samples for tryptase and histamine, coagulation assessments, and exploratory biomarkers will be collected as indicated in the Table of Events (Table 1).

The investigational centers must also offer appropriate supplemental services that support clinical care to ensure that the protocol specified IP administration and monitoring will be followed.

Administration Instructions. Under aseptic conditions, PDA-002 or placebo will be injected IM at 15 sites in one limb on Study Days 1, 29, and 57. The injection volume will be 0.30 mL per injection site. A 3.0 mL syringe with a 20 to 22-gauge 1.5-inch long needle will be used to inject the IP. 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. The administrator and the subject will be blinded to treatment.

A diagram of the recommended injection grid and anatomical site selection is provided in Appendix E.

The entire thawed IP must be administered within 4 hours of thaw start time and within 1 hour of the syringe fill time. In the event that it becomes medically necessary to stop the injections, the stop time of the injections as well as the time the injections are resumed must be noted in the eCRF and in the source documents. If less than the total injection volume is administered, the volume injected should be recorded and the sponsor should be notified.

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

8.2.1. Discontinuation

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

Subjects who discontinue will have the procedures performed as listed in the Early Termination column as per the Table of Events (Table 1).

8.2.2. Overdose

An overdose is defined for this protocol as a subject receiving any dose of greater than 30 x 10^6 cells in a 24 hour period. Adverse events associated with an overdose must be collected as an Adverse Event as outlined in Section 11.2. Evaluation of Adverse Events.

Eligible subjects will be randomized to one of 3 treatment arms (3 x 10^6 PDA-002 cells, 30 x 10^6 PDA-002 cells, or placebo) via Interactive Voice Response System (IVRS) across sites in a double-blind fashion.

8.3. Method of Treatment Assignment

Eligible subjects will be randomized to one of 3 treatment arms (3×10^6 PDA-002 cells, 30×10^6 PDA-002 cells, or placebo) via Interactive Voice Response System (IVRS) across sites in a double-blind fashion.

The unblinded pharmacist/designee at the study site will prepare the appropriate IP and deliver it to the personnel performing the injections. All other site staff, including the principal investigator and research coordinator and sponsor will remain blinded to study treatment assignment.

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

Each vial of IP supplied by the sponsor will bear Celgene Cellular Therapeutics' name and address, study product name and descriptor, and traceable lot number. Additional product information including the date of manufacture, the volume of product contained within the vial, and cell concentration (for active cells) will also be noted. Finally, the label will contain the standard caution statement for investigational products.

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

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

The investigator(s) or designee is responsible for taking an inventory and performing a visual inspection of each shipment of items received and for completing the "Human Placenta-Derived Cells (PDA-002) Product Receipt Record" enclosed within the envelope provided with the shipment. The investigator(s) or designee will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to the sponsor.

At the study site, all investigational IP will be stored in a locked, safe area to prevent unauthorized access. The IP should remain in the cryogenic shipper provided by Celgene until time of use.

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

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

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

To facilitate an effective tracking process:

- Affix the PDA-002 tracking labels provided with the units to the recipient's medical records and/or other pertinent records, if any, for each unit of PDA-002 that is administered to a subject.
- Maintain the records described above and any other records necessary to permit prompt tracking of each unit of PDA-002 to its recipient or other final disposition.
- Ensure all such records are legible, accurate, indelible, and secure.
- Ensure all such records are readily available and allow the sponsor and any authorized government officers prompt access to such records to the extent required by law.
- Ensure that the record security systems are adequate to ensure the confidentiality of recipients who were administered PDA-002.
- Retain the records referenced in this document for at least 10 years after the date of the administration of PDA-002 to the recipient or, if that date is not known, the date the product is received or disposed, whichever is latest.
- Do not further distribute PDA-002.

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

Celgene (or designee) will review with the investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

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 in the source documents.

8.7. Blinding

With the exception of individuals noted below, all study site personnel, subjects, and sponsor personnel and their designees involved with the study, including the sponsor medical monitor will remain blinded to treatment assignment until the last subject has completed Month 6 and all relevant study data have been processed and integrated into the clinical database and the data base is locked. At that time the sponsor and their designees will be unblinded. Study site personnel and subjects will remain blinded during the course of the study. The personnel in the Clinical Supply Management Group responsible for shipping IP and Global Drug Safety personnel will be unblinded. A scientist outside of the study team will be unblinded to assess the data on biomarkers. The following personnel external to the sponsor will also be unblinded to treatment assignment: the pharmacist, or designee responsible for mixing/ thawing IP, at each study site and the IVRS group. Members of the external DMC will have access to unblinded data as specified in Section 6.5.1.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Concomitant medications and procedures for treatment of DPN are allowed; however, subjects should maintain stable doses and stable dose regimens of neuropathy medications (such as anticonvulsants like pregabalin, gabapentin, and antidepressant medications such as duloxetine) for at least 2 months prior to the initial dose of IP.

An effort should be made to maintain the subject's standard medical care through the Treatment Period (through Visit 9) unless changes are necessary to ensure the best care for the subject.

9.2. Prohibited Concomitant Medications and Procedures

It is recommended that subjects continue to maintain stable doses /dose regimens of DPN therapies through the Treatment Period (Study Visit 9) whenever possible.

9.3. Required Concomitant Medications and Procedures

Subjects should receive standard of care prior to and throughout the study.

10. STATISTICAL ANALYSES

10.1. Overview

The primary objective of the study is to assess efficacy of PDA-002 in subjects with DPN as measured by the change in epidermal nerve histology at 6 months following IM administration of 2 different doses of PDA-002 or placebo. Assessment of epidermal nerve histology will be quantified using an immunohistochemical technique to determine ENFD.

The secondary objective of the study is to assess the safety and tolerability of IM administration of 2 different doses of PDA-002 or placebo in subjects with DPN. Safety will be assessed by the type, frequency, severity, and potential relationship of adverse events to treatment with IP.

A detailed Statistical Analysis Plan (SAP) will be provided in a separate document. Exploratory biomarker analysis and other experimental evaluations will be outlined in separate documents and will not be included as part of the Clinical Study Report.

10.2. Study Population Definitions

The following analysis populations are planned for this study:

Screening Population (Screen): The Screening Population includes all subjects who provide informed consent and screen for eligibility during the Screening Period (Day -28 to Day -1).

Safety Population (Safety): The Safety Population includes all subjects who receive any amount of IP.

Modified Intent To Treat (mITT): The mITT population includes all subjects who receive any amount of IP and subsequently provide at least one efficacy assessment.

Other study populations or subgroup populations may be identified during the course of this study. Any additional study populations or subgroups will be clearly identified either in the SAP or, if after database lock, then as post-hoc study populations in the clinical study report.

10.3. Sample Size and Power Considerations

The sample size of 24 subjects total, 8 per treatment arm, was selected in order to provide preliminary safety and efficacy information in a randomized, double-blind fashion. The study is designed to provide an estimation of the treatment effect of active therapy and placebo to plan a sample size for the next study.

Based upon a previous study evaluating the therapeutic effect of a combination of L-methylfolate, methylcobalamine, and pyridoxal 5 phosphate in subjects with DPN (Jacobs, 2011), the mean ENFD was 1.56 fibers/mm at baseline and 3.07 fibers/mm after 6 months of treatment with a standard deviation of 1.5 fibers/mm for the mean increase. Assuming the same treatment effect is observed from baseline, the sample size of 16 subjects actively on therapy resulting from combining the 2 active arms has a 96% power to detect a similar mean change at 6 months from baseline, with a two-sided test and a Type I error rate set at 0.05. Assuming the subjects treated with placebo would not have a change from baseline, the study has

60% power to detect similar differences between placebo and active therapy with PDA-002, with a two-sided test and a Type I error rate set at 0.05.

10.4. Background and Demographic Characteristics

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

10.5. Subject Disposition

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

10.6. Efficacy Analysis

The planned analyses will be fully described in a comprehensive SAP.

The primary efficacy analysis will be an evaluation of change from baseline in ENFD at 6 months following treatment with either dose of PDA-002 or placebo. Results will be used to assess the proof of concept for further study of PDA-002 in subjects with DPN. The analyses will also take into account the possible inter-subject variability of measurements evaluated in both the treated leg (with active or placebo) and the other leg that received placebo.

Changes in the various exploratory efficacy endpoints including within subject differences between left and right leg measurements will be evaluated using descriptive statistics.

In general, exploratory endpoints that are categorical will be examined using descriptive summaries such as counts and percentages, whereas exploratory endpoints that are continuous will be examined using means, standard deviations and medians. The results of the exploratory analyses will allow for better definition of the clinical efficacy endpoints.

10.7. Safety Analysis

The safety analyses will be conducted using the Safety Population (all subjects who receive any amount of IP). Adverse events, vital sign measurements, physical examination findings, clinical laboratory test results, injection site assessments, retinal assessment results, ECG interpretations, and concomitant medications and procedures will be tabulated and summarized as appropriate.

Adverse events observed will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. If clinically significant, any or all laboratory evaluations should be reported as AEs and repeated more frequently, if clinically indicated. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 whenever possible.

The frequency of AEs will be tabulated by MedDRA system organ class and preferred term. In the by-subject analysis, a subject having the same event more than once will be counted only

once. Adverse events will be summarized by NCI CTCAE grade. Adverse events leading to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, study-drug-related events, and SAEs will be tabulated and listed separately. By-subject listings of all AEs, SAEs, discontinuations due to AEs, and deaths will be provided.

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

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

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

10.8. Interim Analysis

An interim analysis will be conducted when the last subject completed Visit 9 (Month 6).

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

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

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. See Section 8.2.2 for the definition of overdose. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE eCRF. In previous studies doses that were one half log greater than the highest dose in this study were not associated with any drug related adverse events. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF but should not be reported as an SAE itself.

In the event of overdose, 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 findings from other tests and/or procedures.

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

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

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

- Results in death
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

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

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

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

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

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

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

11.2.2. Severity / Intensity

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

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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

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

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

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

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

Grade 5 = Death - the event results in death

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

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

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

11.2.3. Causality

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

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

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

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

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

The investigator will report the outcome of the event of both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3. Abnormal Laboratory Values

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

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

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

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

11.4. Pregnancy

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

11.4.1. Females of Childbearing Potential

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

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

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

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

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

11.4.2. Male Subjects

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

11.5. Reporting of Serious Adverse Events

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

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

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug

Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

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

11.5.1. Safety Queries

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.

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

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

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

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

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

Celgene Drug Safety Contact Information:

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

12. DISCONTINUATIONS

12.1. Treatment Discontinuation

12.1.1. Events Leading to Suspension of Enrollment Pending DMC Evaluation

The following events in any subject will trigger a suspension of additional enrollment pending an evaluation by the Data monitoring Committee (DMC) of the event at an ad hoc meeting. Should such an event occur, the DMC will review the available data from the subject's history and the event itself as well as available data on all other previously treated subjects. The committee will recommend if it is appropriate to resume enrollment without study modifications, to resume enrollment with study modifications or to permanently discontinue further enrollment into the study. Operational details are specified in the DMC Charter.

- Identification of 1 or more subjects within a dosing treatment arm with ≥ Grade 3 allergic reaction that is suspected to be related to the IP.
- Identification of 1 or more subjects experiencing a suspected unexpected, treatment-related SAE (SUSARs) within 14 days following the initial dose of the IP suspected unexpected serious adverse reactions.
- Identification of 1 or more subjects with a new malignancy.

12.1.2. Mandatory Treatment Discontinuations

Should subjects experience any of the following events, they may not receive additional doses of PDA-002. They should stay on study however, and all scheduled evaluations are to be performed.

- A Grade 3 or higher allergic reaction within 24 hours of PDA-002 administration.
- An episode of symptomatic arterial vasospasm within 24 hours of PDA-002 administration. Examples include acute coronary ischemia and retinal artery spasm.
- An episode of new venous thrombosis within 3 days of PDA-002 administration.

12.1.3. Additional Treatment Discontinuations

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

- Adverse event(s)
- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol violation
- Pregnancy

- Recovery
- Non-compliance with IP
- Study terminated by sponsor
- Physician decision
- Screen failure
- Technical problems
- Disease relapse
- Failure to meet randomization criteria
- Site terminated by sponsor
- Completed
- Other (to be specified in the eCRF)

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

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

Subjects who discontinue will have laboratory assessments performed as specified in the Early Termination Column in the Table of Events (Table 1).

12.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event(s)
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified in the eCRF)

The reason for study 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).

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

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

13.2. Emergency Identification of Investigational Products

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

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The investigator should ensure that the code is broken only in accordance with the protocol. The investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the investigator through the Interactive Response Technology (IRT) by using an emergency unblinding personal identification number (PIN), and the Investigator should call IRT for unblinded dose information.

14. REGULATORY CONSIDERATIONS

14.1. Good Clinical Practice

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

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. 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, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

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

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

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or his/her institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public; Celgene will provide Investigators with a summary of the results that is written for the lay person. The investigator is responsible for sharing these results with subjects and/or their caregiver as agreed by the subject.

14.3. Subject Information and Informed Consent

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

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

14.4. Confidentiality

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

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

14.5. Protocol Amendments

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

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

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

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. Termination 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
- 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 SOPs

16.1. Study Monitoring and Source Data Verification

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

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

16.2. Audits and Inspections

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

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency (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

As described in Section 14.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be used in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure that Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and 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.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation on the study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

18. REFERENCES

Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105(4):1815-22.

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1):S81–S90.

Campeau L. Grading of angina pectoris (Letter to the Editor). Circulation. 1976; 54: 522-523.

Centers for Disease Control and Prevention, National diabetes fact sheet, 2011. Fast facts on diabetes. Atlanta, GA: US Department of Health and Human Services, 2011.

Heart Failure Society of America. http://www.hfsa.org/hfsa-wp/wp/stages-of-heart-failure Accessed 25 February 2015.

Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-35.

International Clinical Diabetic Retinopathy Disease Severity Scale. one.aao.org/asset.axd?id=321d1c98-7ded-45a6-b663-8edbd2ef55dd International clinical diabetic retinopathy disease severity scale. Accessed 07 May 2014.

Jacobs AM, Cheng D. Management of diabetic small-fiber neuropathy with combination L-methylfolate, methylcobalamin, and pyridoxal 5'-phosphate. Reviews in Neurological Diseases 2011;8(1/2):39-46.

Kles KA, Vinik AI. Pathophysiology and treatment of diabetic peripheral neuropathy: the case for diabetic neurovascular function as an essential component. Curr Diabetes Rev 2006; 2:131-145.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247-54.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood 2007;110(10):3499-506.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Great Vessels. 9th ed; 1994: 253-256.

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 September 28, 2012.

World Health Organization http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf. Accessed 23 Feb 2015.

19. APPENDICES

Appendix A: American Diabetes Association (ADA) and World Health Organization (WHO) Diabetes Mellitus Type 2 Definition

Diagnostic Criteria by the American Diabetes Association (ADA) (ADA, 2014) include the following:

1. A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher,
   or
2. A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT),
   or
3. A random plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher in a subject with classic symptoms of hyperglycemia or hyperglycemic crisis
   or
4. HbA1C of 6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

Whether a hemoglobin A1c (HbA1c) level of 6.5% or higher should be a primary diagnostic criterion or an optional criterion remains a point of controversy.

WHO Definition

Currently HbA1c is not considered a suitable diagnostic test for diabetes or intermediate hyperglycemia.

The following summarizes the 2006 WHO recommendations for the diagnostic criteria for diabetes and intermediate hyperglycemia (WHO 2006).

Diabetes

Fasting plasma glucose

1. 2–h plasma glucose*≥7.0 mmol/l (126 mg/dl)

   or

2. ≥11.1mmol/l (200 mg/dl)

Impaired Glucose Tolerance (IGT)

Fasting plasma glucose 2–h plasma glucose[a]

1. <7.0 mmol/l (126mg/dl) and ≥7.8 and <11.1 mmol/l (140 mg/dl and 200 mg/dl)

Impaired Fasting Glucose (IFG)

Fasting plasma glucose 2–h plasma glucose[a,b]

1. 6.1 to 6.9 mmol/l (11 0mg/dl to 125 mg/dl)

   and

2. (if measured) <7.8 mmol/l (140 mg/dl)

[a] Venous plasma glucose 2–h after ingestion of 75 g oral glucose load.
[b] If 2–h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded.

Appendix B: International Clinical Diabetic Retinopathy Disease Severity Scale

AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

International Clinical Diabetic Retinopathy Disease Severity Scale

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

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

Appendix C: New York Heart Association (NYHA) 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. Nomenclature and Criteria for the Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, 1994: 253-6. Heart Failure Society of America. http://www.hfsa.org/hfsa-wp/wp/stages-of-heart-failure. Accessed 25 February 2015.

Appendix D: 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.

Appendix E: Thawing Protocol

Instructions for Thawing and Preparing PDA-002

Thawing Protocol and Vial Preparation

This section must be conducted by an unblinded pharmacist or by delegated, trained study personnel.

1. Obtain confirmation of enrollment from delegated personnel responsible for registering subject's demographic information in the Interactive Web Response System (IWRS). You will need this information to cross-check the subject ID number and the information on the vial.
2. Wearing appropriate personal protective equipment, obtain frozen vial from the shipping container.
3. Record start time of the thaw procedure.

   If using a water bath, follow steps in bullet 4.
4. Water Bath Instructions
   a. Rapidly transfer the frozen vial into a water bath float.
   b. Transfer the float and vial into a 37°C water bath such that the vial body is immersed in the water and the lid of the vial is supported by the float.
   c. Remove the vial from the water bath after 9 minutes. Investigational product (IP) should be predominantly thawed, but may contain a small residual ice crystal.
   d. Remove the thawed vial from float, and dry off any excess moisture from the outside of the vial.

If Celgene Cellular Therapeutics (CCT) supplies alternate equipment for thawing, a separate manual for the thawing process will be provided.

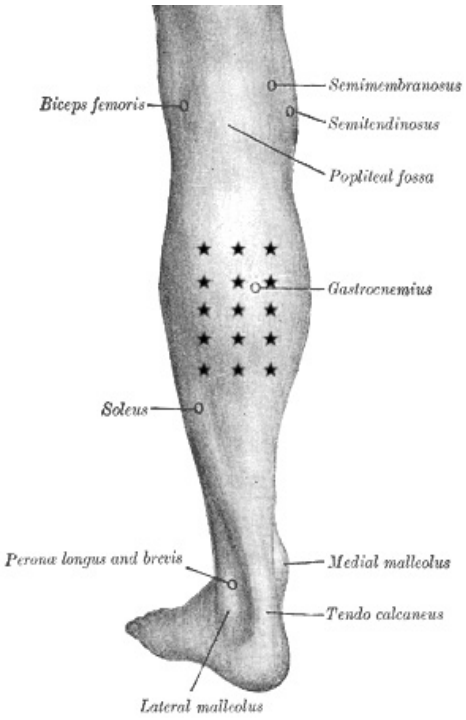
5. Ensure the vial is well mixed by gently inverting the vial 3 times.
6. Confirm the contents of the vial by verifying that the vial label matches the information on the appropriate forms.
7. Prepare the vial by removing the lid cap from the vial. Wipe the vial septum with 70% isopropyl alcohol, allow the alcohol to dry, and insert a self-venting Mini-Spike through the septum.
8. Cover the vial label with the provided product expiration sticker.
9. Blind the vial using the provided blinding bag and secure in place. Place a second product expiration label on the blinded vial.
10. Blind and label the provided 3 mL syringes using the provided syringe blinding labels.
11. Record the date, time of thaw, expiration time, and subject identifier on the appropriate forms. The product expiration time is 4 hours from the time the vial was thawed.

Syringe Filling Protocol

Prepare as per your institutions' Standard Operating Procedure by a delegated, trained study personnel. Use aseptic technique.

1. Ensure that the vial is well mixed by gently inverting the vial 3 times.
2. Remove the cap from the Mini-Spike and attach a blinded/labeled 3 mL syringe to the vial.
3. Orient the vial above the syringe such that the contents can be withdrawn into the syringe, and retrieve 1.5 mL of the solution. Ensure that no air bubbles are present in the syringe.
4. Disconnect the syringe from the Mini-Spike and connect it to a 22 gauge needle. If not used immediately (within 30 minutes), the IP may be stored in capped syringes oriented vertically (needle side down) for up to 1 hour in the syringe rack provided.
5. Attach the next syringe to the vial then repeat Steps 3 and 4 until all 3 syringes have been filled.
6. Record the time the syringes are filled on the Subject Dispensation Log. The product should be administered within 1 hour from the time the syringes are filled.

Suggested Injection Pattern in the Gastrocnemius or Soleus Muscle.



The following recommendations are made with the understanding that the investigator or designee will use his/her own judgment on how best to administer the treatment.

- Subjects will be treated with IP administered intramuscularly (IM) on Study Days 1, 29 and 57.
- The target region on the limb is below the knee and above the ankle in the gastrocnemius or soleus muscle.
- Injections are to be at least 1 cm apart horizontally and laterally and at a depth of approximately 1 to 4 cm. For subjects near their ideal weight, inject at 2 to 3 cm depth. For obese subjects, inject toward the deeper end of the range; for thin subjects, inject toward the shallower end of the range.
- PDA-002 is not intended for intravenous (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 observed the IP may be injected.
- Injections are to be administered in a pattern of 3 x 5 injections around the leg and injections should not be near a blood vessel. See diagram above for injection pattern.