STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: PDA-002

PROTOCOL NUMBER: CCT-PDA-002-DFU-001

DATE FINAL: VERSION 1.1

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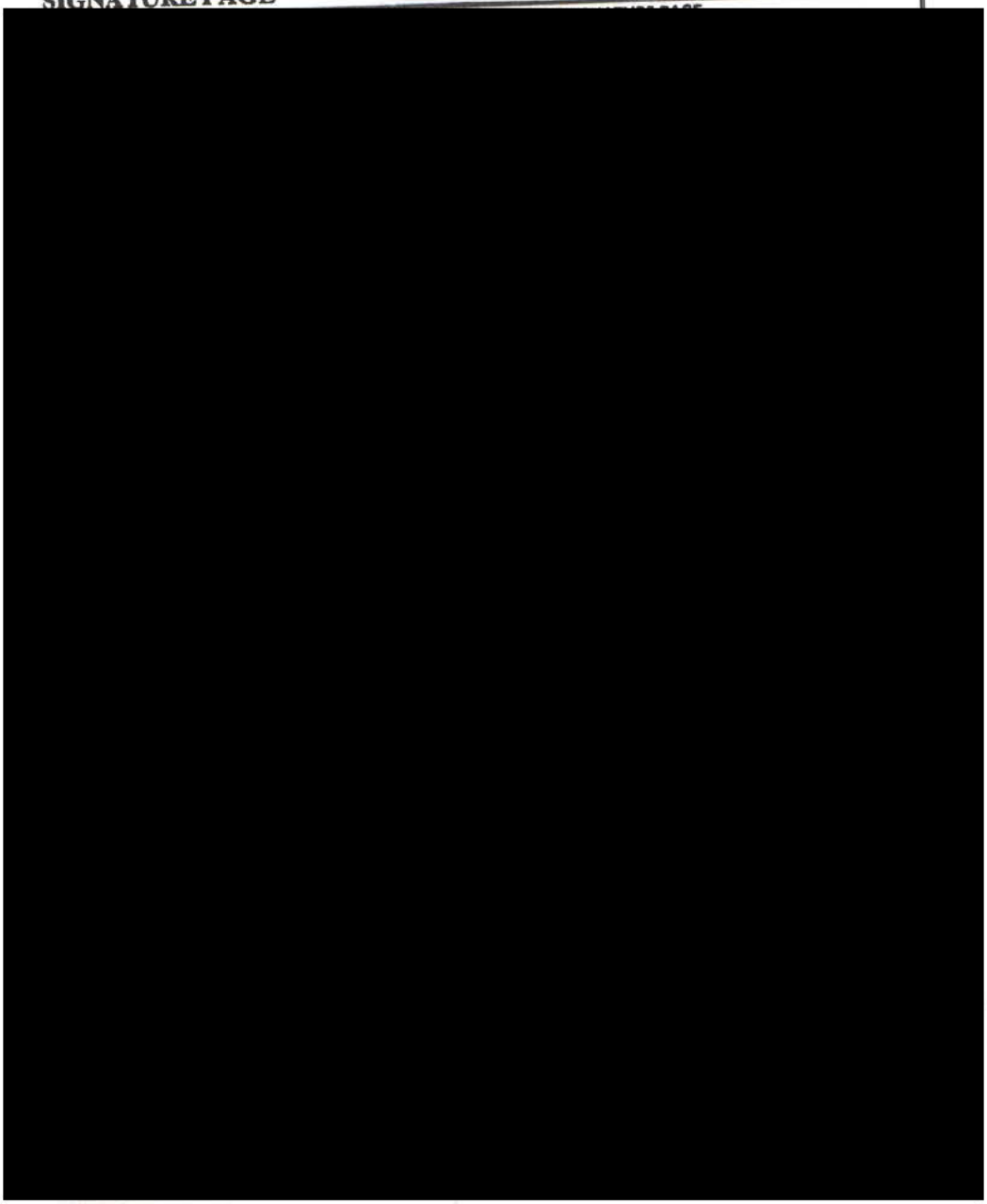
MODIFICATION HISTORY

SIGNATURE PAGE



1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ABBREVIATION	MEANING
ABI	ANKLE-BRACHIAL INDEX
CEC	CIRCULATING ENDOTHELIAL CELL
CT	COMPUTED TOMOGRAPHY
DFU	DIABETIC FOOT ULCER
DLT	DOSE-LIMITING TOXICITY
DMC	DATA MONITORING COMMITTEE
ECG	ELECTROCARDIOGRAM
IM	INTRAMUSCULAR
IP	INVESTIGATIONAL PRODUCT
MRI	MAGNETIC RESONANCE IMAGING
MTD	MAXIMUM TOLERATED DOSE
PAD	PERIPHERAL ARTERIAL DISEASE
PBMC	PERIPHERAL BLOOD MONONUCLEAR CELLS
PCR	POLYMERASE CHAIN REACTION
PT	PROTHROMBIN TIME
PTT	PARTIAL THROMBOPLASTIN TIME

SD	STANDARD DEVIATION
TAT	THROMBIN ACTIVATION TIME
TBI	TOE BRACHIAL INDEX
TF-PCA	TISSUE FACTOR PROCOAGULANT ACTIVITY
VAS	VISUAL ANALOGUE SCALE
VEGF	VASCULAR ENDOTHELIAL GROWTH FACTOR

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CCT-PDA-002-DFU-001, "A Phase I, Multicenter, Open-label, Dose-escalation Study to Evaluate the Safety and Efficacy of Intramuscular Injection of Human Placenta-derived Cells (PDA-002) in subjects with Peripheral Arterial Disease and Diabetic Foot Ulcer, Amendment 3" which was issued on 6 February, 2014. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one interim analysis and one final analysis. In the analyses described in this SAP, the treatment arms will be referred to as Cohort 1, Cohort 2, Cohort 3, and Cohort 4. The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and any data analysis had begun for the interim/final analysis. This SAP will be finalized and signed prior to the clinical database lock for the interim/final analysis. All statistical analyses detailed in this SAP will be conducted using *SAS*® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

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

3.2. Secondary Objectives

The secondary objective is to explore potential clinical efficacy by assessing changes in the ankle-brachial index (ABI) and/or toe brachial index (TBI). Additional assessments will include evaluating changes in Rutherford Criteria; number, extent and size of ulcers; leg rest pain score using a visual analogue scale (VAS); incidence of hospitalization (all cause); overall survival at 24 months; and the time to first occurrence of major amputation (above the ankle) of treated leg, all-cause mortality, doubling of index ulcer total surface area from baseline, de novo gangrene of treated leg reopening of closed ulcer, index ulcer reduction by 50%, or time to ulcer healing.

3.3. Exploratory Objectives

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

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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

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

Cohort 1: 3 x 10^6 cells administered on Study Days 1 and 8.
Cohort 2: 10 x 10^6 cells administered on Study Days 1 and 8.
Cohort 3: 30 x 10^6 cells administered on Study Days 1 and 8.
Cohort 4: 100 x 10^6 cells administered on Study Days 1 and 8.

Initially, 3 subjects will begin dosing at the 3 x 10^6 cells dose level.

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

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

This pattern of enrollment will continue until the MTD is determined or the highest planned dose level is tested. Six subjects must be treated at a given dose level before the MTD can be declared. The MTD is defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects. At any dose level, if 2 or more subjects experience a DLT within 14 days of dosing, that cohort will have exceeded the MTD. If a previous dose level was well tolerated and

no subjects experienced DLT at that level, an intermediate dose level may be defined by protocol amendment.

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

All subjects who receive any dose of PDA-002 will participate in the 24-month follow-up period.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

The primary endpoint is determination of the MTD defined as the highest PDA-002 dose level for which the incidence of DLT is ≤ 1 out of 6 subjects.

4.2.2. Secondary Efficacy Endpoints

The secondary endpoints are to explore clinical efficacy and include:

1) ABI and TBI will be calculated by dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm. ABI and TBI will be measured during Screening, on Study Days 1 and 8 prior to administration of IP and on Study Days 15 and 29 and Months 3, 6, 9, 12 and 24.

2) The number of ulcers and the size of the index ulcer (length, width, depth and EZ Graph area) will be evaluated and photographs of ulcers taken during Screening and again on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24 (Appendix E, Appendix F of study protocol).

3) Time to major amputation (above the ankle) of treated leg, doubling of index ulcer total surface area from baseline, de novo gangrene of treated leg, reopening of closed ulcer, index ulcer reduction by 50%, and time to ulcer healing. Number of ulcers that completely close at 3 motnhs, if they closed at least 50% at one month.

4) Extent of ulcers will be examined with the Wagner Grading Scale. TheWagner Grading Scale (Section 16.3) is assessed during Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.

5) Rutherford Criteria (Section 16.4) assessed during Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.

6) Leg rest pain score - visual analogue scale (VAS) (Appendix D of study protocol) graded from 0 (pain free) to Grade 10 (maximum pain) during Screening, on Study Days 1 and 8 prior to administration of PDA-002 and on Study Days 15 and 29 and Months 3, 6, 9, 12, and 24.

7) Overall survival at 24 months (time from PDA-002 administration to any cause of death, subjects still alive will be censored at the date of last follow-up).

8) Incidence of hospitalization (all cause).

4.2.3. Exploratory Efficacy Endpoints

Serum samples and peripheral blood mononuclear cells (PBMC) may be collected at Screening and Study Days 1, 8, 15, and 29, and Months 3 and 6 for the development of potential new biomarkers predictive of efficacy as well as for the characterization of the DFU population.

Polymerase chain reaction (PCR)-based evaluation of levels of messenger ribonucleic acid (mRNA), as well as proteomics-based assessment of protein levels in response to treatment will

be the exploratory endpoints in this study. This exploratory efficacy endpoint will be analyzed by the sponsor and will be presented in another document.

4.2.4. Safety Endpoints

The following safety assessments will be performed:

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

4) Assessment of injection sites.

5) Electrocardiograms (ECGs).

6) Retinal examinations.

7) Magnetic resonance imaging (MRI) or computed tomography (CT) of the chest, abdomen, and pelvis.

8) Concomitant medications and procedures.

4.3. Stratification , Randomization and Blinding

This is an open-label study. Eligible subjects will be assigned to a cohort based on the order in which they enter the study according to the dose escalation scheme.

4.4. Sample Size Determination

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

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

[redacted]

5.2. Analysis Populations

5.2.1. Efficacy Evaluable Population

The Efficacy Evaluable (EE) Population includes all subjects who received any amount of IP, and have a baseline and at least one post-baseline efficacy assessment.

5.2.2. Safety Population

The Safety population includes all subjects who received any amount of IP.

6. SUBJECT DISPOSITION

Total number of subjects with screen failures will be summarized.

Subject disposition (number of subjects entered, discontinued, primary reason for discontinuation) by cohort will be summarized using frequency and percent for all enrolled patients.

A summary of subjects enrolled by site will be provided.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations were identified and assessed by clinical research physician or designee. The protocol deviations/violations will be summarized by cohort for the EE population.

A by-subject listing of subjects with protocol violations in the Safety population will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline characteristics will be summarized for the EE population. Individual subject listings will be provided to support the tables.

8.1. Demographics

Baseline and demographic characteristic will be summarized by cohort for the EE population.

Age (years), height (cm), weight (kg), and BMI (weight (kg)/ height (m^2)) will be summarized using descriptive statistics for the following: Age category (<65 versus≥ 65 and < 75 versus ≥ 75 years), sex, race, and ethnicity.

Age will be calculated as follows: age = Integer ≤ [(Date of enrollment – Date of Birth + 1) / 365.25].

8.2. Baseline Characteristics

Ulcer assessment (efficacy endpoints) will be summarized descriptively at Baseline by cohort. In addition, the baseline values for all laboratory parameters from the central laboratory will be summarized descriptively by cohort.

8.3. Medical History

A summary of medical and surgical history will be presented by system organ class and preferred term using MedDRA version 17.0. A similar summary will be generated for the currently active abnormalities only, per body system.

8.4. Prior and Concomitant Medications

Medications that started before the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

8.4.1. Prior Medications

Prior medications are defined as medications that started before the start of the study treatment and, either ended before the start of the study treatment, or continued after study treatment. A summary will be presented showing the number and percentage of subjects who took prior medications by WHO therapeutic drug class and generic drug name, as coded by WHO dictionary 01Mar2014.

8.4.2. Concomitant Medications

Concomitant medications are defined as the medication that was either initiated before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug and on/before the date of treatment discontinuation.

A summary will be presented showing the number and percentage of subjects who took concomitant medications by WHO therapeutic drug class and generic drug name, as coded by WHO dictionary 01Mar2014.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study Treatment and extent of exposure summaries will be provided based on the Safety population. Descriptive statistics will be provided by cohort.

9.1. Treatment Duration

Treatment duration in days (calculated as last dose date – first dose date + 1) will be summarized by cohort using the Safety population.

9.2. Treatment Compliance

Treatment compliance is defined as the number of treatments a subject received as a percentage of the number of treatments he or she should have received. Subjects will receive up to 15 injections on Study Days 1 and 8. A subject listing of treatment compliance will be provided by cohort, including any interruptions and/or discontinuation of injections and the reason for discontinuation.

10. EFFICACY ANALYSIS

All efficacy evaluations will be conducted using the EE population.

10.1. Multiplicity

Formal statistical testing will not be performed and interpretation of the statistical significance of results from analyses will not be performed. For this reason, methods to control Type I error for multiple testing are not applicable in this study.

10.2. Analysis of Primary Efficacy Endpoint

The MTD will be reported, including the maximum dose and corresponding incidence of DLT.

10.3. Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed based on the EE population.

10.3.1. Secondary Endpoint 1 – ABI and TBI

ABI and TBI will be summarized using descriptive statistics at Screening, on Study Days 1 and 8 prior to administration of IP and on Study Days 15 and 29 and Months 3, 6, 9, 12 and 24. ABI and TBI will be calculated by dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm. Spaghetti plots of ABI and TBI over time will also be provided.

10.3.2. Secondary Endpoint 2 – Number of Ulcers and Size of Index Ulcer

The number of ulcers (total on both legs) and the size of the index ulcer (length, width, and depth, and area with the EZ Graph measures) will be summarized separately by cohort at Screening and again on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24. Spaghetti plots of ulcer area, length, width, and depth over time will also be provided.

10.3.3. Secondary Endpoint 3 – Time to Major Amputation

Descriptive statistics for time to major amputation (above the ankle) of treated leg, time to doubling of index ulcer total surface area from baseline in treated leg, de novo gangrene in treated leg, time to reopening of closed ulcer, time to index ulcer total surface area reduction from baseline by 50%, and time to ulcer healing will be presented by cohort.

10.3.4. Secondary Endpoint 4 – Wagner Grading Scale

Wagner Grading Scale (Section 16.3) will be summarized using descriptive statistics by cohort at Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.

10.3.5. Secondary Endpoint 5 – Rutherford Criteria

Rutherford Criteria (Section 16.4 of the study protocol) will be summarized using descriptive statistics by cohort at Screening and on Study Days 1, 8, 15, and 29 and Months 3, 6, 9, 12, and 24.

10.3.6. Secondary Endpoint 6 – Leg Rest Pain

Leg rest pain will be summarized using descriptive statistics by cohort at Screening, on Study Days 1 and 8 prior to administration of PDA-002 and on Study Days 15 and 29 and Months 3, 6, 9, 12, and 24. Leg rest pain score will be measured on the visual analogue scale (VAS) graded from 0 (pain free) to Grade 10 (maximum pain).

10.3.7. Secondary Endpoint 7 – Overall Survival

Overall survival at 24 months (time from PDA-002 administration to any cause of death) will be summarized using descriptive statistics by cohort. Subjects still alive will be censored at the date of last follow-up.

10.3.8. Secondary Endpoint 8 – Incidence of Hospitalization

The incidence of hospitalization (all cause) will be summarized using descriptive statistics (frequency of hospitalizations, as well as duration) by cohort.

10.4. Subgroup Analysis

Due to the small sample size of this study, subgroup analyses for the primary endpoint will not be performed.

10.5. Analyses of Exploratory Efficacy Endpoints

Serum samples and peripheral blood mononuclear cells (PBMC) may be collected at Screening and Study Days 1, 8, 15, and 29, and Months 3 and 6 for the development of potential new biomarkers predictive of efficacy as well as to characterize the DFU population. Specific goals include: contribution to evaluation of safety and efficacy, evidence for repair and regeneration activity, and identification of universal pharmacodynamic biomarkers for PDA-002. Analysis of biological fluids and PBMCs will include the examination of research biomarkers as well as vascular and standard inflammatory markers.

Exploratory endpoints will be analyzed by the sponsor and a will not be described in this SAP.

11. SAFETY ANALYSIS

All summaries of safety data will be based on the Safety population. Descriptive statistics will be provided for safety summaries; no inferential testing for statistical significance or calculation of confidence intervals will be performed.

Adverse events observed will be classified using the Medical dictionary for Regulatory activities (MedDRA –version 17.1) classification system. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 whenever possible. The frequency of adverse events will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by NCI CTCAE grade. Adverse events leading to discontinuation from treatment, events classified as NCI CTCAE Grade 3 or higher, study-drug-related events, and serious adverse events will be tabulated and listed separately. By-subject listings of all adverse events, serious adverse events, discontinuations due to AEs, and deaths will be provided.

11.1. Dose Limiting Toxicities

A DLT is defined as a Grade 2 toxicity not resolving within 14 days suspected to be related to the IP or any toxicity ≥ Grade 3 suspected to be related to the IP. Imputation of missing data will be used to define a DLT as follows:

- If the grade is missing, the grade will be imputed as ≥ Grade 3.
- If the relationship is missing, the relationship will be imputed as suspected.

The frequency of DLTs will be tabulated. A by-subject listing of all DLTs will be provided.

11.2. Adverse Events of Special Interest

No adverse events of special interest have been pre-specified for this study.

11.3. Clinical Laboratory Evaluations

The change from baseline in the following laboratory parameters will also be summarized descriptively over time, by cohort and visit:

a. Serum chemistry, lipid profile, fatty acids, hematology, urinalysis and pregnancy

b. Coagulation tests

- Prothrombin time (PT), partial thromboplastin time (PTT), and thrombin activation time (TAT)
- D-dimers
- Fibrinogen
- Tissue factor procoagulant activity (TF-PCA)
- Platelets

c. Immunologic/Inflammation Assessments

- Anti-HLA antibodies
- C-reactive protein
- Quantitative assessment of serum immunoglobulins (IgA, IgM, and IgG)
- Vascular endothelial growth factor (VEGF)
- Cytokines: interleukin (IL)-1β, tumor necrosis factor (TNF-α), IL-6, IL-8, IL-10, and transforming growth factor-β (TGF-β)

d. Tryptase and Histamine

e. Troponin I

f. Hemoglobulin A1c

g. Circulating endothelial cells (CECs)

Spaghetti plots of individual lab values and change from baseline values over time will be provided for these lab parameters.

By-subject listings will also be provided for the laboratory data.

11.4. Vital Sign Measurements

Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented by cohort and visit for the following vital signs:

- Temperature (°C),
- Pulse (beat/minute),
- Respiration (breaths/minute)
- resting systolic blood pressure (mmHg)
- resting diastolic blood pressure (mmHg).

A by-subject listing of vital signs during IP administration will be provided, including heart rate, respiration, blood pressure, body temperature, and pulse oximetry. This listing will identify vital sign values higher or lower than the normal range (Appendix XX.X).

11.5. Physical Examination

Physical exam results will be summarized in frequency tables by body systems and cohort.

11.6. Electrocardiogram

The average of the triplicate values taken on the same day will be calculated for each quantitative measure. Summary statistics (n, mean, SD, median, and range) for observed values and changes from baseline will be provided by cohort and visit for QT, QTcB, QTcF, PR, RR, QRS intervals, ST deviation, QRS axis, and heart rate. Individual values and day means will be presented in the listing.

11.7. MRI/CT Scans

Results of MRI/CT scans of the chest, abdomen, and pelvis will be summarized by cohort and visit. Cross-tabulations presenting shifts from baseline category (normal and abnormal values) by cohort and visit will also be presented.

11.8. Retinal exam

Retinal exam data will be will be summarized by cohort and visit. Cross-tabulations presenting shifts from baseline category (normal and abnormal values) by cohort and visit will also be presented.

11.9. Injection Site Assessment

An injection-related reaction is defined as any sign or symptom experienced by a subject during the injections or any event occurring within 24 hours of the IP administration. Summaries of injection-related reactions will be presented by cohort, including the duration and severity of injection-related reactions.

12. INTERIM ANALYSIS

An interim analysis of efficacy and safety will be performed after the last subject in the study has completed Visit 5 (Month 3) and all relevant study data have been processed and integrated into the analysis database.

12.1. Statistical Approaches for Control of Alpha

Formal statistical testing and interpretation of the statistical significance of results from analyses will not be performed. For this reason, statistical approaches for control of alpha for interim analyses are not applicable to this study.

13. DATA MONITORING COMMITTEE

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

14. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The analysis of secondary endpoints of De Novo gangrene and doubling of index ulcer (Section 10.3.3) will be restricted to the treated leg only.

The time to event analysis of re-opening of closed ulcer, time to index ulcer reduction by 50% and time to ulcer healing described in Section 4.2.2 and 10.3.3 are additional analysis to that described in the protocol.

Urinary cotinine is listed in Section 3.1 of the protocol as a primary endpoint. The test is a measure of nicotine use. Since the protocol was amended to include smokers, it is not necessary to track nicotine use in patients and, therefore, an analysis of urinary cotinine values will not be performed..

15. REFERENCES

Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Physician 2002;66:1655-62.

Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg 1997;26:517-38.

16. APPENDICES

16.1. Dates Handling

[redacted]

16.1.1. Calculation Using dates

[redacted]

16.2. Date Imputation Guideline

16.2.1. Impute Missing AE Start Dates

Missing day and month

- [redacted]
- [redacted]
- [redacted]

Comparison to AE Start Date: Based on the rules of imputation above, if the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

16.2.3. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

16.2.4. Medical History

Partially missing medical history start dates will be imputed in the dataset for medical history. The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

16.3. Wagner Grading Scale

Wagner Ulcer Classification System:

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

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

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

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

Grade 4: Gangrene localized to portion of forefoot or heel

Grade 5: Extensive gangrenous involvement of the entire foot

Source: Frykberg 2002.

16.4. Rutherford Classification of Chronic Limb Ischemia

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

Abbreviations: AP = ankle pressure; PVR = pulse volume recording; TM = transmetatarsal; TP = toe pressure.

[a] Five minutes at 2 mph on a 12% incline.

[b] Grades II and III, categories 4, 5, and 6, are embraced by the term chronic critical ischemia.

Source: Rutherford, 1997.