STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: PDA-002

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

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ABBREVIATION	MEANING
ABI	Ankle-Brachial Index
AE	Adverse Event
CEC	Circulating Endothelial Cell
CT	Computed Tomography
DFU	Diabetic Foot Ulcer
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EE	Efficacy Evaluable
HLA	Human Leukocyte Antigen
ICGA	Indocyanine Green Angiography
IM	Intramuscular
IP	Investigational Product
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiac Event

MALE	Major Adverse Limb Event
MNSI	Michigan Neuropathy Screening Instrument
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
PAD	Peripheral Arterial Disease
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PGICN	Patients' Global Impression of Change in Neuropathy
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SD	Standard Deviation
TAT	Thrombin Activation Time
TBI	Toe Brachial Index
TcPO2	Transcutaneous Oxygen
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 study of protocol CCT-PDA-002-DFU-002, "A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Range Finding Study to Evaluate the Efficacy and Safety of Intramuscular Injection of Human Placenta-Derived Cells (PDA-002) in Subjects Who Have Diabetic Foot Ulcer (DFU) with and without Peripheral Arterial Disease (PAD)." which was issued on 27 JUN 2014 and the Amendment No.1 effective on 20 APR 2015 and Amendment No.2 effective on 08 SEP 2015. It contains definitions of analysis populations, derived variables and statistical methods for the analysis of efficacy and safety.

These analyses include one final and one administrative interim analysis, although the administrative analysis was canceled later on (see Section 12 for detail). Additional exploratory post hoc analyses may be performed if needed after database lock.

An external Data Monitoring Committee will monitor all safety information to ensure subject safety in accordance with a separate charter. In addition, the external DMC will have access to efficacy data in order to assess the overall benefit risk for subjects participating in the study. The external DMC will be convened to review interim efficacy and safety data when approximately 25%, 50% and 75% percent of subjects complete the Month 3 assessment and all relevant study data have been processed and integrated into the analysis database. The NON-DMC members will be blinded until the last subject has completed Month 6 (Visit 11).

In the analyses described in this SAP, the treatment arms will be referred to as 3×10^6, 10×10^6, 30×10^6 cells, and Placebo. 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 first interim/final analysis. This SAP will be finalized and signed prior to the clinical database lock for the Month 6 (Visit 11) 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 objective of the study is to assess the efficacy and safety of PDA-002 administered intramuscularly (IM) in subjects who have DFU in a population enrolled with and without PAD.

3.2. Secondary Objectives

The secondary objective is to explore potential clinical efficacy of various doses of PDA-002 in effecting changes in assessed vascular parameters including Ankle-Brachial Index (ABI) and/or Toe Brachial Index (TBI), Transcutaneous Oxygen (TcPO2) Measurement.

3.3. Exploratory Objectives

The exploratory objectives of the study are to develop novel approaches

- for the characterization and measurement of immune modulation
- for assessing tissue repair biomarkers that could enable correlation of in vitro, nonclinical and clinical function of PDA-002 , and
- for assessing the improvement of vascular parameters as measured by indocyanine green angiography (ICGA) in a subset of subjects from selected sites who have the equipment.

Data from exploratory objectives will be included in a separate study report.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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

Subjects will undergo a Screening/Run-In/Pre-Treatment Period to determine study eligibility and to ensure that the size of the ulcer does not appreciably change with standard treatment within 28 days of Study Day 1. The Screening/Run-In/Pre-Treatment Period will be at least 2 weeks. After the Screening/Run-In/Pre-Treatment Period, subjects will be randomized to a treatment arm and will receive IP or placebo. In the case of bilateral limb ulcers, the treated limb will be the limb that has the largest qualifying ulcer. During the Treatment Period, subjects will receive IM injections of PDA-002 on Study Days 1 and 8. During the Follow-up Period subjects will be evaluated as indicated in the Table of Events in Section 16.6. All subjects are to receive standard treatment for DFU in addition to IP or placebo throughout the study. All subjects who receive any dose of PDA-002 or placebo will participate in the 24-month Follow-up Period.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

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

4.2.2. Primary Safety Endpoint

The primary safety endpoint is to evaluate the frequency and severity of AEs. To this end, the following safety assessments will be performed as outlined in Table of Events in Section 16.6.

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

4.2.3. Secondary Endpoints

Secondary endpoints will include evaluating clinical, vascular assessment parameters, health related measures (quality of life [QoL] assessments), ulcer and neuropathy assessments in subjects who have DFU with and without PAD. Additionally, the number of wound closures,

time to healing and healing of contra-lateral ulcers will be assessed as outlined in Table of Events in Section 16.6.

1. Time to ulcer closure and complete wound closure of the index ulcer up to 6 months.
2. ABI and TBI will be calculated by dividing the systolic blood pressure at the ankle or toe by the systolic blood pressures (Doppler technique) in the arm.
3. The number, size of all ulcers and 50% closure of the index ulcer will be evaluated and photographed.
4. Transcutaneous oxygen measurements.
5. Time to major amputation (above the ankle) of treated leg, minor amputations, to re-opening of ulcer, to doubling / halving of index ulcer total surface area from baseline, de novo gangrene and foot wound infection up to 6 months.
6. Wagner Grading Scale (Section 16.3).
7. Rutherford Criteria (Section 16.4).
8. Leg rest pain score - visual analog scale (VAS) graded from 0 (pain free) to Grade 10 (maximum pain) (Section 16.5).
9. 36-item Short Form Health Survey (SF-36v2)
10. Diabetic Foot Ulcer Scale Short Form (DFS-SF) index ulcer (Protocol Appendix G).
11. Neuropathy Assessment by Michigan Neuropathy Screening Instrument (screening) and Patient Global Impression of Change in Neuropathy (PGICN).
12. EuroQOL-5D- health utility index assessment (EQ-5D-5L).

4.3. Stratification , Randomization and Blinding

This is a randomized, multicenter, double-blind, placebo-controlled, dose range finding study. Eligible subjects will be assigned into three dose levels of PDA-002 (3×10^6, 10×10^6, 30×10^6) versus placebo at a 2:2:1:2 randomization approaches with the lower number of subjects to be allocated to the highest active dose. Unless otherwise specified, all study site personnel, subjects, and sponsor personnel and their designees involved with the study, including the sponsor

medical monitor, will remain blinded to treatment assignment until the last subject has completed Month 6 (Visit 11) and database has been locked. Subjects will be stratified by PAD status according to vascular parameters as defined in Section 5.3.

A sensitivity analysis will be performed, in which the PAD status will be as determined by the PI assessment prior to randomization and as reflected in the IVRS categorization.

4.4. Sample Size Determination

Assuming a response rate of 10% in the control group, the sample size was chosen to detect with at least 90% power a response rate of greater or equal to 40% in the combined treatment groups. With a sample size of n=38 in the control group and n=95 in the treatment groups, the power is 94%. The power in the comparison of the control group and one of the lower active treatment dose groups (n=38) (either 3×10^6 cells versus control or 10×10^6cells versus control) is 82% without adjusting for multiple analyses.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size, mean, median, Standard Deviation (SD), minimum, maximum and Kaplan-Meier estimates for continuous variables;
- Means and medians will be formatted to one more decimal place than the measured value;
- Standard deviations will be formatted to two more decimal places than the measured value;
- All percentages will be rounded to tenth number and percentage of responses will be presented in the form XX (XX.X), where the percentage is denoted in column header ;
- All listings will be sorted for presentation in order of study center, subject, and date of procedure or event;
- All analysis and summary tables will display the analysis population sample size (i.e., number of subjects)

5.2. Analysis Populations

5.2.1. Randomized Population

All subjects who received a randomization number from the study and have a non-missing randomization date are included in Randomized Population. Treatment group in Randomized Population is based on study planned treatment.

5.2.2. Safety Population

Safety Population includes all subjects who received any amount of IP. Treatment group in Safety Population is based on study treatment actually received by a subject in the study.

5.2.3. Intent to Treat Population

The Intent to Treat (ITT) population consists of subjects who were randomized, met the eligibility criteria and who per protocol were intended to be treated. The subjects that were randomized but did not receive treatment and were not considered as intended to be treated per the protocol (for example because they failed an exclusion or an exclusion criteria) would not be part of this population.

5.2.4. Efficacy Evaluable Population

The Efficacy Evaluable (EE) Population is a subset of the ITT population who were eligible, received any amount of IP, have a baseline and at least one post baseline efficacy assessment. This analysis set will be used for primary analyses of all efficacy endpoints.

5.2.5. Per Protocol Population

The Per Protocol Population (PP) is a subset of the EE population which includes all eligible subjects who met the criteria for treatment at the end of the screening period, who received all doses of IMP in accordance with the protocol, and who do not have any major protocol violations that may impact on, or confound, the safety or efficacy assessments recorded during the study. This analysis set will be used for sensitivity analysis of primary and selected secondary efficacy endpoints.

5.2.6. Excluded During Run-in Population

Patients that were enrolled into the run-in period, but were ineligible to be randomized (for example due to change in ulcer during the run-in period) fall in this population. The reason for ineligibility to be randomized will be presented in a listing.

5.3. PAD Status

PAD is defined based on data collected at the study baseline, which is the last measurement prior to the first study dose for subjects who receive at least one dose of study drug or the last measurement in the study for screening failure subjects. A subject will be categorized into the

PAD group if the following criteria are met at the study baseline measurement: ABI $\leq$ 0.8, or TBI $\leq$ 0.65, or a TcPO2 $\leq$ 40 mmHg (in either leg). Otherwise, the subject will be categorized as non-PAD.

Statistical analysis tables will be presented for the overall analysis population and stratified by the PAD status.

6. SUBJECT DISPOSITION

Number of subjects entering the run-in period, number of subjects excluded during the run-in period, and number of subjects randomized in total and by sites will be presented in a table.

Subject disposition such as the number of subjects in the various analysis population, the number of subjects that discontinued treatment or from the study with primary reasons for discontinuation, the number of subjects who completed the study or treatment will be summarized by dose and placebo groups and overall using frequency and percentages for the Randomized subjects.

A by-subject listing of subjects that were excluded during run-in will be presented, and a subject disposition listing in Randomized populations will be provided.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by the clinical research physician or designee. For a particular analysis protocol deviations/violations will be defined prior to unblinding of the database i.e. the Month 6. Efficacy endpoints or primary endpoints related deviation/ violation will be considered as major deviation/violation. The major deviation/violation will be identified by the study team based on blinded deviation information. The protocol deviations/violations will be summarized by dose and placebo groups for the enrolled patients for the Safety, ITT, EE and PP populations. A by-subject listing of subjects with protocol deviation in the Randomized Population will be provided. The protocol violation will be flagged.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics and baseline characteristics will be presented for the Safety, EE and PP populations. Individual subject listings will be provided for randomized population to support the tables.

8.1. Demographics

Baseline and demographic characteristics of age (years), gender, baseline weight (kg), height (cm), BMI (Weight (kg)/ (height (m)) ^{2}), ethnicity and race will be summarized by dose/placebo groups and overall. In addition, a summarization by age categories (<65, >=65 and <75, >=75) will also be presented in the same table.

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

8.2. Baseline Disease Characteristics

Rutherford Criteria, Wagner Grading Scale for foot lesions, measurement of ulcers, ABI and TBI, and leg rest pain score using a VAS, TcPO2 content, Michigan Neuropathy Screening Instrument (MNSI), and DFS-SF score, SF-36 scores, EQ5D score will be summarized descriptively at baseline by dose/placebo groups and overall. In addition, the baseline values from central lab will be summarized descriptively by dose/placebo groups and overall.

8.3. Medical History

A summary of medical and surgical history will be presented by system organ class and preferred term using MedDRA version 19.0 or higher. A similar summary will be generated for currently active medical history only, by system organ class and preferred term.

Prior amputations data will be summarized in a table by treatment group for index ulcer leg and non-index ulcer leg respectively, which include reasons for amputation, type of amputation, time from earliest amputation and the most recent amputation to first treatment date. Prior amputations include those collected prior to the date of first treatment.. Subject level amputation data will be presented in a listing with a flag for prior amputations.

8.4. Prior and Concomitant Medications

All medications (prescription and non-prescription), treatments and therapies taken from 30 days prior to Visit 1 (the Screening/Run-In Visit/) until Month 24 must be recorded on the appropriate page of the eCRF. Prior and concomitant medications will be tabulated for WHO drug class and generic drug name by study treatment in the safety population and presented in a statistical listing for the randomized population.

8.4.1. Prior Medications

Prior medications are defined as medications that started and stopped before the start date of the study treatment. A summary by dose/placebo groups and overall in the safety population 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 01MAR2016 or higher.

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 end of the wound closure assessment period (6 months).

For the safety population, a summary by dose/placebo groups and overall 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 01MAR2016 or higher.

Treatment-emergent medication, a subset of concomitant medications which initiated on or after the date of the first dose of study treatment will be presented in a separate table as count and percentage of subjects by therapeutic drug class and generic drug name coded with WHO drug dictionary.

8.4.3. Concomitant Procedures

Concomitant procedures are defined as any procedures that were either: initiated before the first dose of study drug and successive follow-up procedures continued during the study treatment; or initiated on/after the date of the first dose of study drug and on/before the end of the wound closure assessment period (6 month). Treatment-emergent co-procedure, a subset of co-procedures which initiated on or after the date of the first dose of study treatment, will be presented in a separate table.

All will be presented as count and percentage of subjects per treatment group, as coded by WHO dictionary 01MAR2016 or higher.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study Treatment and extent of exposure summaries will be provided based on the Safety, ITT, EE and PP populations. Descriptive statistics will be provided by dose/placebo groups and overall.

9.1. Treatment Duration

Number of subjects treated and duration of treatment in days (calculated as last dose date – first dose date + 1) will be summarized.

9.2. Treatment Compliance

Treatment compliance is defined as the number of injections a subject received as a percentage of the number of injections 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 dose/placebo group, including any interruptions and/or discontinuation of injections and the reason for discontinuation.

10. EFFICACY ANALYSES

Primary efficacy analyses will be conducted using the Efficacy Evaluable Population (EE), and sensitivity efficacy analyses will be carried out in the PP populations for primary and all secondary efficacy endpoints. Additional post hoc exploratory analyses may also be performed.

10.1. General Approaches to Efficacy Analyses

Formal statistical analyses of the primary efficacy endpoint of complete wound closure of the index ulcer in subjects with DFU with or without PAD within 3 months across treatment groups will be performed.

Descriptive statistics will also be provided for secondary efficacy endpoints as outlined in the following part of this document.

The general rules listed below will apply to all efficacy analysis:

- All analyses and plots on continuous efficacy endpoints will be based on observed data only the missing data will not be imputed, unless otherwise specified.
- For summaries of change from baseline values, only subjects with both baseline and post-baseline values will be included in the analyses.
- Subject data listings sorted by dose and placebo groups, subject ID and the date or/and visit of measurement, question response and event time (including censorship indicator) will be provided to support or supplement the tables.
- Percentages reported in the categorical data summary table will be based on the number of subjects observed in a specific analysis population by dose/placebo group unless otherwise specified.
- Baseline is defined as the last measurement before the first study drug administration.
- Post-baseline assessments, the last measurement will be used if there are multiple measurements taken in the same scheduled Visit, unless otherwise specified.

- For all Kaplan-Meier method, stratified log-rank tests, stratified by the PAD status randomization strata, will be used to test for differences in outcome between treatment groups.
- The binary primary endpoint will be analyzed by a logistic regression with treatment and PAD status as terms in the model. The results will be described by treatment estimates, treatment differences and 95% CI for the treatment differences.

10.2. Primary Analysis of Primary Endpoint: Complete Wound Closure of the Index Ulcer

Ulcer closure is defined as skin closure of the index ulcer without drainage or need for dressing.

Complete Wound Closure is defined as closure of the index ulcer and retaining wound closure for the subsequent 4 weeks. The duration of the complete wound closure event will be defined as starting from the day when the initial ulcer closure was identified and ending at the last visit day before the closed ulcer is re-open if applicable. And the duration of complete wound closure of patients who have no re-opening will be censored on the date of the last assessment showing wound closure. A last observation carried forward (LOCF) approach will be used to impute closure status for amputated ulcers, early termination and other reasons with insufficient assessment to define closure status.

A subject will be defined as a responder of complete wound closure if the subject achieves index ulcer closure within 3 months (99 days) since the first study drug administrated, or prior to or on the date of study Visit 8 and retaining wound closure consecutively for at least 28 days. The response rate and its two-sided 95% exact confidence interval estimated using the Clopper-Pearson method will be presented in a table by dose groups and placebo.

The null hypothesis of no difference in response rate will be tested by using two-sided Fisher exact test in the three PDA-002 doses combined group, the 3×10^6 dose group, 10×10^6 dose group, or 30×10^6 versus the placebo group respectively. The four p-values will be reported in the same summary table without adjustments for multiplicity. The analysis of primary endpoint will be conducted on the EE population.

10.3. Sensitivity Analysis of Primary Endpoint: Complete Wound Closure of the Index Ulcer

Unless otherwise specified, LOCF imputation strategy will be used in sensitivity analyses of primary endpoint. The analyses will be conducted in the EE population.

- One set of sensitivity analyses of primary endpoint will be conducted in the Randomized, ITT, and PP populations and the same analysis methods and presentation format described in 10.2 for primary analysis.
- A sensitivity analysis will be carried out on the primary endpoint in the EE population stratified by PAD status identified per PI's diagnosis at Screening. And reflected by the IVRS coding of PAD or not-PAD.
- The binary primary endpoint will be analyzed with a logistic regression with treatment and PAD status as covariates in the model in the EE population. The results will be described by treatment estimates, treatment differences and 95% CIs for the treatment differences.
- Frequency counts of complete wound closure status across the categories of ABI, TBI and TcPO2 of Baseline defined above, at each visit will also be provided in the EE population.
- A sensitivity analysis for the primary endpoint will be performed with data as observed in the EE population. In this analysis, subjects with amputation resulting in removal of the index ulcer, early termination before 6 months from the first dose date, or if any reason for the closure status is unable to be defined will be included in the analysis using the data as currently recorded in the database.
- Analysis with exclusion of subjects with amputation resulting in removal of the index ulcer or early termination before 6 months from the first dose date.

10.4. Analysis of Secondary Endpoint

10.4.1. Secondary Endpoint 1: Time to Index Ulcer Halving, Index Ulcer Closure and Complete Wound Closure

Time to event statistical analyses for Index Ulcer Halving, Ulcer Closure and Complete Wound Closure will be performed separately and analysis results will be presented in three tables. The

event of Ulcer closure and complete wound closure are defined in Section 10.2. An event of halving in size of the Index Ulcer is defined as the Index ulcer's total surface area has been firstly found halved compared to its size at Baseline. Once an ulcer is closed, measurements of all dimensions of the ulcer, area, depth, length, and width are considered as zeros in data analysis, unless the ulcer re-opens; the closed ulcer will remain in the denominator for calculation of the mean and other summary statistics. Ulcers that are removed due to amputation prior to wound closure will not be scored as closed.

[redacted]

The Kaplan-Meier plot of the event probability at each event time point (Days) for each of dose, combined doses and placebo group will also be provided in a graph.

10.4.2. Secondary Endpoint 2: Rutherford Criteria

The count and percentage of subjects per Rutherford Criteria category will be summarized by dosage groups, combined doses and placebo at baseline and all relevant scheduled visits in one table. Subjects who improve by at least one numeric category from Baseline will be defined as responder, while non-zero at Baseline Rutherford category subjects who fail to improve or deteriorate from Baseline by at least one category will be defined as non-responder. The count and percentage of responders will be summarized by dosage groups, combined doses and placebo at baseline and all relevant scheduled visits in the same table.

10.4.3. Secondary Endpoint 3: Wagner Grading Scale

The index and all ulcers including bilateral ulcers will be graded using the Wagner Grading Scale and will be photographed. The count of subjects per each Wagner Grading Scale category of the index ulcer will be summarized by dosage groups, combined doses and placebo at baseline and all other relevant scheduled visits in one table. The count and percentage of subjects on Wagner Grading Scale shift from Baseline to each post-baseline visit will also be presented in another table. The total number of all ulcers and the count of subjects with at least one ulcer per Wagner Grading Scale category will also be summarized the same way as index ulcers. And count and percentage of ulcers on Wagner Grading Scale shift from Baseline to each post-baseline visit will be provided in a separate table. For the shift table of all ulcers, a category “not present at baseline” will be created’, which allow to include ulcers that developed after baseline (new ulcers).

10.4.4. Secondary Endpoint 4: ABI and TBI

The value, the change from Baseline, and percent change from Baseline of ABI and TBI will be summarized using continuous variable reporting convention by doses, combined doses and placebo at baseline and all relevant scheduled visits. Mean and 95% CI plots of the raw data as well as change from baseline will be provided. In summary tabulation and plot, if a subject has multiple assessments of ABI or TBI at a study visit, average of multiple values at the visit will be used for statistical analysis.

In addition to summary tables stratified by PAD status, the summarizations of the primary endpoint and time to closure and the change in ABI and change in TBI will be stratified by

ABI: ≥0 and < 0.4 (severe PAD)

≥0.4 and <0.6 (moderate PAD)

≥0.6 and ≤ 0.8 (mild PAD)

>0.8 and <1.3 (normal)

≥1.3 (calcified)

or TBI<0.4, ≥0.4 and ≤0.65, and >0.65 at Baseline, respectively.

Furthermore, summary statistics and box plots of the values of ABI, TBI or TcPO2 will be provided at each visit separating by complete wound closure status.

10.4.5. Secondary Endpoint 5: Leg Rest Pain

Leg rest pain score will be measured on the visual analogue scale (VAS) from 0 for pain free to 10 for maximum pain. The value and the change from Baseline in VAS score will be summarized using continuous variable reporting convention by dose groups, combined doses and placebo at baseline and all relevant scheduled visits. Box plots of the value as well as change from baseline will be provided.

10.4.6. Secondary Endpoint 6: Transcutaneous Oxygen Measurement

Transcutaneous Oxygen measurement will be performed at Screening, Visit 8, Visit 11 and early termination. The primary analysis location will be the dorsum of the foot of the index leg. The dorsum of the foot from the contralateral leg will also be analyzed in an exploratory fashion. The primary analysis will be determined as the difference from the value measured in leg elevation position minus the value of leg in supine 5 minutes before. The value in supine position alone will also be analyzed in an exploratory fashion. These values at each study visit and change from Baseline as well as percent change from baseline at each post-baseline visit of TcPO2 measures and differences between supine and elevation positions will be summarized

using continuous variables reporting convention by dose, combined doses and placebo at baseline and all relevant scheduled visits in two statistical tables, one table for index leg and the other table for non-index leg. Reporting of TcPO2 values will be stratified by PAD status. Box plots of the raw data as well as change from baseline will be provided.

All individual TcPO2 measurement will be presented in a listing.

10.4.7. Secondary Endpoint 7: Number of Ulcers and Size of Index Ulcer

The value and the change from Baseline of the number of ulcers, the length, width, depth and the surface area of the Index Ulcer will be summarized using continuous variable reporting convention by doses, combined doses and placebo at baseline and all relevant scheduled visits in one table. Once an ulcer is closed, measurements of all dimensions of the ulcer, area, depth, length, and width are considered as zeros in data analysis, unless the ulcer re-opens. If a patient undergoes amputation of the appendage that had the ulcer, the ulcer will be imputed by LOCF strategy.

10.4.8. Secondary Endpoint 8: Conditional Assessment of Ulcer Closure at Month 3 Given that Index Ulcer Halved from baseline at Month 1

The subjects will be categorized into two groups based on ulcer closure status by Visit 6: one group with index ulcer surface area achieving half or more closure and the other group with that area achieving less than half by Visit 6 (Month 1). This categorization based on half closure status by month 1 will be cross tabulated with the index ulcer full closure status by month 3 by doses, combined doses and placebo.

10.4.9. Secondary Endpoint 9: Incidence of Ulcer Closure, Complete Wound Closure, New Ulcers, Doubling /Halving in Size of the Index Ulcers and Major and Any Types of Amputation

The incidence of Ulcer closure and complete wound closure are defined in section 10.2. An incidence of new ulcer at a specific post baseline visits is defined as a subject who has at least one new ulcer being confirmed at that visit. Similarly, an incidence of doubling or halving in size of the Index Ulcer at a specific post baseline visit is defined as a subject whose Index ulcer's total surface area has been found doubled or halved in comparison with its baseline at that visit.

Major Amputation and Any type amputation at the treated leg and non-treated leg will be defined respectively.

The count and percentage of the incidence of Ulcer Closure, Complete Wound Closure, new ulcers, doubling or halving of the Index ulcer's size will be summarized in a table by doses, combined doses and placebo groups at each post baseline visit. The count and percentage of subjects suffering Major or Any Type of Amputation will be presented for the treated leg, non-treated leg, and either leg, respectively. In these analyses, percentage is based on number of subjects with assessment at each study visit.

10.4.10. Secondary Endpoint 10: Time to First occurrence of New Ulcer, Doubling of Size of the Index Ulcer, Major and Any Amputation, de novo Gangrene and Foot Wound Infections

An event of new ulcer is defined as the first new ulcer confirmed after the first dosing of IP. An event of doubling in size of the Index Ulcer is defined as the first observation of doubling of the Index ulcer's total surface area has been firstly found doubled in relative to its size at Baseline after the first dosing of IP. Major Amputation is an event defined as occurring above the ankle and Any Type Amputation is defined as any amputations performed during study period. Time to the first Major Amputation or Any Amputation in the treated leg, non-treated leg, and either leg will be defined respectively. Time to the two composite endpoints will be defined and analyzed: one is time to any of first occurrence in new ulcer, ulcer doubling, major amputation, any amputation, or death; the other one will include events wound infection, cellulitis or abscess, osteomyelitis, or gangrene in any ulcer in addition to those events described in the previous composited endpoint.

[redacted]

[redacted]

The Kaplan-Meier plot of survival probability at each event time point (Days) for each of dose, combined doses and placebo group will also be provided in a graph.

10.4.11. Secondary Endpoint 11: Time to First Reopening of Index Ulcer

An event of reopening of index ulcer is defined as the first observation of re-opening of the closed index ulcer since the first observation of ulcer closure. The time to the event will be calculated as:

Date of onset of event – date of first confirmed index ulcer closure + 1 day

[redacted]

10.4.12. Secondary Endpoint 12: Questionnaires for Health Quality of Life

The following three standard assessment tools will be used to evaluate the health quality of the treated subjects: 36-item Short Form Health Survey (SF-36v2), Diabetic Foot Ulcer Scale Short Form (DFS-SF) and EuroQOL-5D Health Utility Index assessment (EQ-5D-5L).

Data of response to SF-36v2 questionnaire will be converted to scores for 8 domains, physical component summary, mental component summary, and SF-6D utility index by relevant study visits. Categorical responses to DFS-SF will be transferred to 6 domains scores for statistical description at each study visit. Three level categorical responses of 5-dimension questions in EQ-5D-5L will be scored to a utility index by study visit.

The domain and utility index value and the change from Baseline of each domain or index will be summarized using continuous variable reporting convention by dose groups and placebo at baseline and all relevant scheduled visits. DFS-SF will also be performed at index ulcer wound closure.

10.4.13. Secondary Endpoint 13: Michigan Neuropathy Screening Instrument (MNSI) and Patient Global Impression of Change in Neuropathy (PGICN)

The MNSI scores for Part A (History) and Part B (Physical Assessment) are summarized in Section 8.2 of baseline characteristics.

The count and percentage of each question in PGICN will be summarized in a table by dose and placebo group at all relevant scheduled visits. The PGICN change degree will be summarized using continuous variable reporting convention by dose groups and placebo at all relevant scheduled visits.

10.5. Exploratory Analysis and Subgroup Analysis

To research potential interaction effect and covariates on complete wound closure and time to complete wound closure, following exploratory analyses will be carried out.

- To research interaction effect of treatment with ABI, TBI, or TcPO2 at Baseline respectively, logistic regression analyses will be performed with complete wound closure as the outcome, treatment, and categorized ABI (<0.4 / ≥0.4 and <0.6 / ≥0.6 and ≤0.8 / >0.8 and <1.3 / ≥1.3), TBI (<0.4 / ≥0.4 and ≤0.65 / >0.65), or TcPO2 in index leg ((a) supine ≤40 / >40 and ≤60 / >60 and (b) supine minus elevated <10 / ≥10) at Baseline, and interaction term of

treatment with ABI, TBI, or TcPO2 at Baseline as covariates. The results presented from these analyses will be treatment estimates and the treatment differences versus placebo and the 95% CIs and p-value for the treatment differences.

- Age, BMI, smoking status, treatment groups, and PAD status will be fitted in a logistic regression model with a complete wound closure (the primary endpoint) as the response variable. The results will be described by treatment estimates, treatment differences versus placebo and the 95% CI and P-value for the treatment differences.
- For time to complete ulcer closure, a Cox proportional hazards model with treatment and one of baseline ABI, TBI or TcPO2 as covariates will be implemented to estimate hazard ratio of each active treatment group versus placebo.
- Age, BMI, smoking status in treatment groups, and PAD status will be fitted in a Cox proportional hazards model with time to wound closure (main secondary endpoint) as the response variable. The results will be described by estimated hazard ratio of each active treatment group versus placebo.

The following exploratory analysis and subgroup analysis may be conducted post hoc.

- Exploring association between treatment efficacy (primary and/or main secondary endpoints) and the treatment interval between administration of the two doses of PDA002.
- Exploratory analyses may also be performed to examine the effect of poor glycaemic control; previous arterial bypass surgery; osteomyelitis; and local infection associated with sepsis, on complete wound closure (the primary endpoint) and time to wound closure (main secondary endpoint)

11. SAFETY ANALYSIS

11.1. General Approaches to Safety Analyses

The Safety analyses will be conducted using the Safety Population stratified by PAD status and overall.

Adverse events, vital sign measurements, clinical laboratory test results, injection site assessments, retinal examination results, ECG interpretations, concomitant medications and procedures will be tabulated and summarized as appropriate.

- All safety analyses and plots will be based on observed data only - the missing data will not be imputed.
- For summaries of change from baseline values, only subjects with both baseline and post-baseline values will be included in the analyses.
- Percentages reported in the categorical data summary table will be based on the total number of subjects in Safety Population in each respective dose and placebo group unless otherwise specified.
- Baseline is defined as the last measurement before the first study drug administration.
- The last measurement will be used if there are multiple measurements taken in the same scheduled Visit.

11.2. Adverse Events

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. Treatment-emergent adverse events (TEAE) is an AE event which newly started on or after the first dosing of the study drug or an existing condition being worse on or after first dosing of the study drug. All TEAEs will be divided into three periods, according to their date of onset in calendar days from the first dose date. The periods are: Day 1 through Day 15, Day 16 through Month 6 (Day 180), and beyond Month 6

(Day 180+). Adverse events with unknown onset dates or unknown end dates will be counted in the TEAE.

The frequencies of TEAEs and their incidence will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-subject (incidence) analysis, a subject having the same event more than once will be counted only once. The TEAEs and their incidence will also be summarized by NCI CTCAE grade. TEAEs and their incidence, leading to discontinuation from treatment, death, study-drug-related events, and serious adverse events will be tabulated by dose/placebo groups and overall and listed separately. A listing will display all AEs recorded in the database in the randomized Population. All TEAE related tables will be summarized separately by the three study periods based on AE onset date, as described above.

11.3. Adverse Events of Special Interest.

Major adverse cardiac event (MACE) and major adverse limb event (MALE) will be flagged in AE database based on coded preferred term. Count and percentage of subjects with treatment-emergent MACE and MALE will be presented in a table for the Safety and the populations.

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

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

11.4. Clinical Laboratory Evaluations

The value and the change from baseline for continuous parameters and the count and percentages for categorical parameters will be summarized descriptively over time by dose, combined doses and placebo groups and relevant visit. The shift from baseline at each post baseline visit will also

be presented in a table for those categorical parameters. For parameters with both pre-dose and post-dose measurements at the treatment dates, the value and the change from the pre-dose value at each post-dose time points on each respective treatment date will be present in a separate table.

a. Serum chemistry: Calcium, Total Bilirubin, Chloride, Indirect Bilirubin, Potassium, Direct Bilirubin, Sodium, Glucose, Phosphorus, Bicarbonate or Carbon Dioxide, Uric acid, Lactic Dehydrogenase (LDH), Alanine Aminotransferase (ALT: SGPT), Alkaline Phosphatase (ALK), Aspartate Aminotransferase (AST: SGOT), Total Protein, Creatinine, Albumin, Blood Urea Nitrogen (BUN);
b. Hematology: Hemoglobin, Hematocrit, Red Blood Cell (RBC) Count, Platelet Count, Absolute Neutrophil Count (ANC), White Blood Cell (WBC) Count and Differential Count
c. Urinalysis: Protein, Glucose, Ketones, Blood (hemoglobin), pH, Specific Gravity, Bilirubin, Urinary Albumin, Creatinine, Leukocyte Esterase, Microscopic (if gross findings are positive, then a microscopic examination, including WBCs/high power field (HPF) and RBCs/HPF, will be performed).
d. Coagulation tests: PT/PTT, TAT, D-dimers, fibrinogen, and platelets.
e. Tryptase and Histamine
f. Immunologic/Inflammation Assessments: Anti-HLA antibodies.
g. Hemoglobin A1c.

By-subject listings will also be provided for the laboratory data. The value and change from baseline for parameters of Immunologic and Inflammation and Hemoglobin A1c will be plotted in figures respectively. A frequency summary table of shifts from baseline to post-baseline time point, and end of treatment period will be provided by treatment group for immunological and inflammation tests.

In table of statistical summary in tryptase and histamine, descriptive statistics of measurement by visit/time point and change from Day 1 post-dose will be presented.

11.5. Vital Sign Measurements

Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented by dose, combined doses and placebo groups and relevant visits for the following vital signs. The value and the change from

the pre-dose value at each post-dose time points on each respective treatment date will be present in a separate table.

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

A by-subject listing of vital signs will be provided. This listing will identify vital sign values higher or lower than the normal range.

The shift from baseline at any visit in normality status will also be tabulated for each vital sign parameter.

11.6. Electrocardiogram

Summary statistics (n, mean, SD, median, and range) for observed values and changes from baseline at each relevant visit will be provided by dose, combined doses and placebo group for

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

The shift from baseline at any visit in normality status will also be tabulated for each ECG parameter.

11.7. Retinal exam

Retinal exam data will be summarized by dose, combined doses and placebo group and visit. The shift from baseline at any visit in normality status will also be tabulated.

11.8. 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 and its incidence will be presented by severity grade, system organ class as well as dose, combined doses, placebo group and overall.

11.9. Overall Survival at 24 Months

Time from PDA-002 administration to any cause of death will be analyzed by dose, combined doses, placebo groups and overall using the median statistics estimated by KM method and using a stratified log-rank test to test for differences between treatment arms. Hazard ratios will be calculated with a Cox proportional hazards model with treatment group and PAD status as covariates. The number of subjects with death and censored will also be summarized. Subjects still alive will be censored at the date of last follow-up.

12. INTERIM ANALYSIS

An administrative interim analysis of unblinded efficacy and safety data was planned to be conducted by members outside of the study team. The purpose of the analysis was to determine whether to allocate future resources to the program. The members outside of the study team who will be unblinded to the study results will consist of a clinical research physician, a statistician, and non-research members of senior management. The results of this analysis will not be distributed outside of this group and this group will not disclose the results to members of the study team. [redacted]

13. STATISTICAL APPROACHES FOR CONTROL OF ALPHA

Type I error rate will be set at 5% for any formal statistical testing and interpretation of the statistical significance of results from analyses. Methods to control Type I error for multiple testing will not be implemented.

14. DATA MONITORING COMMITTEE

An external DMC will be convened to review interim efficacy and safety data when approximately 25%, 50%, and 75% of subjects complete the Month 3 assessment 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 DFU study team. The external DMC will recommend whether continued dosing is appropriate, 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 external DMC will make recommendations 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.

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

Dates will be stored as numeric variables in the SAS analysis files and reported in YYYY-MM-DD format (ISO8601). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 16.2 (e.g., for duration or cycle assignment etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases they are derived either from a milestone (e.g., the survival date is derived from the death date), or a procedure date (e.g., the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.

- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules (see section 16.1.1 below).

Dates recorded in comment fields will not be imputed or reported in any specific format.

16.1.1. Calculation Using dates

Calculations using dates (*e.g.*, subject's age or relative day after the first dose of study medication) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study medication plus 1 day. The generalized calculation algorithm for relative day: STUDY DAY = [(TARGET DATE – DSTART) + 1 where DSTART = the start day of study drug]. Note that Study Day 1 is the first day of treatment of study drug. For dates of interested before the first date of dosing of study medication the study day will be calculated as: STUDY DAY = TARGET DATE – DSTART. Negative study days are reflective of observations obtained during the screening period. Note: Partial date for the first study drug is not imputed in general. All effort should be tried to avoid incomplete study drug start date.
- Age (expressed in year) is calculated: integer of (DATE of CONSENT – DATE of BIRTH + 1)/365.25.
    - Prefer using calculated age from clinical database. When not available, may use calculated age from CRF or IVRS
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7.
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

MONTHS = DAYS /30.4167.

16.2. Date Imputation Guideline

16.2.1. Impute Missing AE Start Dates

Missing day and month

- If the year is **same** as the year of first day on study medication, then the day and month of the start date of study medication will be assigned to the missing fields
- If the year is **prior to** the year of first day on study medication, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first day on study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the year and month of first day on study medication, then the start date of study medication will be assigned to the missing day.
- If the month and year are **before** the year and month of first day on study medication, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the year and month of first day on study medication, then the first day of the month will be assigned to the missing day.
- If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- If the date (day, month , and year) is missing, the imputed start date will be the first day on study medication

16.2.2. Impute Missing AE Stop Dates

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dose date of study medication, then the day and month of the last dose date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dose date of double-blind study medication, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dose date of study medication, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dose date of study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dose date of the study medication, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dose date of study medication, then the first day of the month will be assigned to the missing day.

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/procedures will be imputed. For prior/concomitant medications/procedures, 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, i.e. any records with missing year will be imputed as null; otherwise, missing month will be imputed as January and missing day will be imputed as 1st.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date, i.e. any records with missing year will be imputed as null; otherwise, missing month will be imputed as December and missing day will be imputed as the last day of the month imputed or actually recorded.

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
1	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.

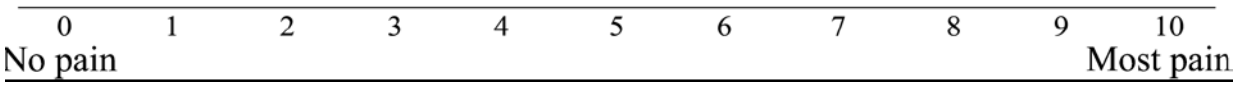
[a] Five minutes at 2 mph on a 12% incline.

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

Source: Rutherford, 1997.

16.5. Visual Analog Scale Pain

Numeric Pain Scale



Source: Johnson, 2005.

16.6. Table of Contents

ADDENDUM TO STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: PDA-002

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

DATE: 1 August 2018

Prepared by:

PPD

On behalf of

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TABLE OF CONTENTS

SIGNATURE PAGE

SAP ADDENDUM APPROVAL SIGNATURE PAGE

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

ABBREVIATION	MEANING
ABI	Ankle-Brachial Index
AE	Adverse Event
CEC	Circulating Endothelial Cell
CT	Computed Tomography
DFU	Diabetic Foot Ulcer
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EE	Efficacy Evaluable
HLA	Human Leukocyte Antigen
ICGA	Indocyanine Green Angiography
IM	Intramuscular
IP	Investigational Product
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiac Event

MALE	Major Adverse Limb Event
MNSI	Michigan Neuropathy Screening Instrument
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
PAD	Peripheral Arterial Disease
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PGICN	Patients' Global Impression of Change in Neuropathy
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SD	Standard Deviation
TAT	Thrombin Activation Time
TBI	Toe Brachial Index
TcPO2	Transcutaneous Oxygen
TF-PCA	Tissue Factor Procoagulant Activity
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor

2. INTRODUCTION

The final Statistical Analysis Plan (SAP), dated 03 Oct 2017, describes the planned analyses and data presentations for Celgene's study of protocol CCT-PDA-002-DFU-002, "A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose Range Finding Study to Evaluate the Efficacy and Safety of Intramuscular Injection of Human Placenta-Derived Cells (PDA-002) in Subjects Who Have Diabetic Foot Ulcer (DFU) With and Without Peripheral Arterial Disease (PAD)." The study protocol was issued on 27 Jun 2014, Amendment 1 took effect on 20 Apr 2015, and Amendment 2 took effect on 08 Sep 2015. Following finalization of the SAP and prior to database lock, the Sponsor decided to terminate the study early. Therefore, there were changes to the planned analyses that are described in the final SAP. This addendum summarizes all changes to the planned analyses.

3. SUMMARY OF CHANGES TO PLANNED ANALYSES

3.1. Changes to SAP Section 5

- Section 5.2.1 states "All subjects who received a randomization number from the study and have a non-missing randomization date are included in Randomized Population."

  Change: This was revised to "All subjects who met eligibility criteria, received a randomization number from the study and have a non-missing randomization date are included in Randomized Population."

- Section 5.2.6 defines the Excluded During the Run-in Population as "Patients that were enrolled into the run-in period, but were ineligible to be randomized (for example due to change in ulcer during the run-in period) fall in this population." The reason for ineligibility to be randomized were to be presented in a listing.

  Change: This population is not defined. Instead, all subjects who did not satisfy eligibility criteria will be captured in summaries for screen failures in tables and listings.

3.2. Changes to SAP Section 7

Section 7 states that "The protocol deviations/violations will be summarized by dose and placebo groups for the enrolled patients for the Safety, ITT, EE and PP populations."

Change: Tabular summaries will be presented for the EE population only.

3.3. Changes to SAP Section 8

- Section 8 states that "Summaries for the demographics and baseline characteristics will be presented for the Safety, EE, and PP populations."

  Change: Summaries for demographics and baseline characteristics will be provided for the Safety and EE populations only.

- Sections 8.4.2 defines concomitant medications 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 end of the wound closure assessment period (6 months)".

Change: The definition of concomitant medications was revised and now includes classification of prior and concomitant medications, as follows: Concomitant medications are defined as the medications that were initiated after the first dose of study drug and continued on/before the end of study. A medication is defined as prior and concomitant if it was initiated before the first dose of study drug and continued after the first dose and on/before the end of study.

- Section 8.4.3 defines concomitant procedures as "any procedures that were either: initiated before the first dose of study drug and successive follow-up procedures continued during the study treatment; or initiated on/after the date of the first dose of study drug and on/before the end of the wound closure assessment period (6 month)."

  Change: This definition was revised as follows: Prior and concomitant procedures are defined as any procedures that were either: initiated before the first dose of study drug and successive follow-up procedures continued after first dose and before study discontinuation; or initiated on/after the date of the first dose of study drug and on/before end of study.

3.4. Changes to SAP Section 9

- Section 9 states "Study Treatment and extent of exposure summaries will be provided based on the Safety, ITT, EE and PP populations."

  Change: These summaries will be provided for the Safety and EE populations only.

- Section 9.2 states that the treatment compliance listing will include "any interruptions and/or discontinuation of injections and the reason for discontinuation."

  Change: These data will not be presented in the listing for treatment compliance.

3.5. Changes to SAP Section 10

- Section 10 states that "sensitivity efficacy analyses will be carried out in the PP populations for primary and all secondary efficacy endpoints".

Change: The PP population will be used only for one sensitivity analysis of the primary efficacy endpoint and 3 sensitivity analyses of the secondary efficacy endpoints. The specific sensitivity analyses that will be presented in the PP population are:

- Responder analysis for index ulcer complete wound closure
- Incidence of index ulcer complete wound closure by post-baseline visits
- Incidence of index ulcer closure by post-baseline visits
- Summary of time to first foot wound infection

- Section 10.3:
  - The first bullet states that sensitivity analysis of the primary endpoint will be conducted using the Randomized, ITT, and PP populations.

    Change: This sensitivity analysis will be conducted for the PP population only.
  - The fifth bullet states that the data as observed analysis would include early termination before 6 months from the first dose date.

    Change: Early termination for this sensitivity analyses of the primary endpoint will be based on termination before 3 months from first dose.
- Section 10.4:
  - Section 10.4.1 states "In the event 2 separate ulcers coalesce, the coalesced ulcers to remain as n=2 with the total area of the single coalesced ulcer nominally split across the two parent ulcers according the ratio of their surface areas as last recorded prior to coalescence."

    Change: This calculation will not be performed in the final analysis of the study data because data will not be available to determine whether 2 separate ulcers have coalesced.
  - Section 10.4.4 indicates that "summary statistics and box plots of the values of ABI, TBI or TcPO2 will be provided at each visit separating by complete wound closure status."

Change: Box plots for ABI, TBI, and TcPO2 will not be presented. Similarly, box plots as indicated in Section 10.4.5 will not be provided for value and change from baseline for leg rest pain.

- Section 10.4.9 states that "the count and percentage of subjects suffering Major or Any Type of Amputation will be presented for the treated leg, non-treated leg, and either leg, respectively."

  Change: Summaries will not be provided for patients having major or any amputation in the non-treated leg.

- Section 10.4.10 describes a time to event analysis for a second composite endpoint comprising events of wound infection, cellulitis or abscess, osteomyelitis, or gangrene in any ulcer in addition to those events described in the first composite endpoint (comprising new ulcer, ulcer doubling, major amputation, any amputation, or death)

  Change: The time to event analysis of the second composite endpoint will not be performed.

- In Section 10.5, the planned exploratory analyses are changed as follows:

  - The logistic regression analysis categorized by ABI or TBI will not be performed. Additionally, analyses for TcPO2 (b) will be based on elevated minus supine (<10/≥10) at baseline, rather than supine minus elevated; interaction term with treatment will not be included in the model.

  - The Cox proportional hazards analysis by age, BMI, smoking status, and PAD status will be performed with time to complete wound closure as the response variable and not time to wound closure (main secondary endpoint).

3.6. Changes to SAP Section 11

Section 11.2 indicates that all "TEAE related tables will be summarized separately by the three study periods based on AE onset date." The periods defined in the SAP are: Day 1 through Day 15, Day 16 through Month 6 (Day 180), and beyond Month 6 (Day 180+).

Change: All TEAEs will be divided into two periods, according to their date of onset in calendar days from the first dose date. The periods are: Day 1 through Month 6 (Day 180), and beyond Month 6 (Day 180+). A summary of AEs with onset occurring between Day 1 through Day 15 will no longer be provided. Additionally, analyses of TEAEs leading to discontinuation of treatment by period of AE onset date will not be provided.