AMG0001

Protocol AG-CLI-0209

A PHASE IIB PILOT STUDY TO CONFIRM THE FEASIBILITY AND TOLERABILITY OF A MODIFIED DOSAGE REGIMEN OF AMG0001 IN SUBJECTS WITH CRITICAL LIMB ISCHEMIA

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List of Abbreviations and Definitions of Terms

ABI	Ankle Brachial Index
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BLQ	Below Level of Quantitation
CLI	Critical Limb Ischemia
CRF	Case Report Form
FDA	U.S. Food and Drug Administration
HGF	Hepatocyte Growth Factor
LOCF	Last Observation Carried-forward
LTFU	Long Term Follow-Up
MI	Myocardial Infarction
PCR	Polymerase Chain Reaction
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPA	Special Protocol Assessment
SD	Standard Deviation
TASC II	Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease II
TBI	Toe Brachial Index
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analog Scale
VascuQol	Disease-Specific Vascular Quality-of-Life questionnaire
WHODrug Dictionary	World Health Organization Drug Dictionary

1 Overview

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy, rationale, and statistical methods to be used to assess clinical efficacy and safety. The purpose of the SAP is to ensure the credibility of the study findings in the pre-specified statistical approaches to the analysis of study data prior to the database lock. This SAP provides additional details concerning the statistical analysis outlined in the protocol.

2 Investigational Plan

A phase 3 study AG-CLI-0206 was planned as a registration study and received Special Protocol Assessment (SPA) approval by the U.S. Food and Drug Administration (FDA). Prior to undertaking the phase 3 study, a pilot study will confirm the feasibility of the study-related activities in study AG-CLI-0206 and the tolerability of the dosage regimen of AMG0001.

2.1 Study Objectives

The primary objectives of the clinical trial are:

1. To confirm the feasibility of study-related activities and the tolerability of a modified dosage regimen of AMG0001 in CLI
2. To evaluate the safety of AMG0001

2.2 Study Design

This is a single center, open-label pilot study of AMG0001 (Hepatocyte Growth Factor [HGF] plasmid) in approximately 8-10 subjects (40-90 years old) with Chronic Critical Limb Ischemia (CLI). Subjects eligible for the study will have a diagnosis of CLI (due to atherosclerotic arterial disease of the lower limb) with no option for revascularization by surgical bypass or endovascular intervention or with a poor option (high risk) for revascularization by surgical bypass but no option for an endovascular intervention (Type D lesions or worse using the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Artery Disease (TASC) II classification).

In this pilot study, subjects will receive 4 sets of injections of HGF plasmid two weeks apart starting at Day 0. This process will be repeated at Month 3 (first cycle) and at Month 9 (second cycle) and Month 12 (second cycle), see table below.

Table 1: Dosage Regimen for the AG-CLI-0209 Study

First Cycle	**Day 0, Day 14, Day 28, and Day 42** (4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline) **Month 3, Month 3+14 days, Month 3+28 days, and Month 3+42 days** (4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline)

Second Cycle	**Month 9, Month 9+14 days, Month 9+28 days, and Month 9+42days** (4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline or matching placebo) **Month 12, Month 12+14 days, Month 12+28 days, and Month 12+42 days** (4 sets of injections, 2 weeks apart; each set is 4 mg subdivided into 8 injections of 0.5 mg of HGF plasmid in 3 mL saline)

Note that for the purposes of this study, a month is defined as 30 days; days 14, 28, and 42 are calculated from either Day 0, Month 3, Month 9, or Month 12.

Clinic visits will occur for screening, Days 0, 14, 28, 42, Month 3, Month 3+14 days, Month 3+28 days, Month 3+42 days, Month 6, Month 9, Month 9+14 days, Month 9+28 days, Month 9+42 days, Month 12, Month 12+14 days, Month 12+28 days, Month 12+42 days, Month 15, and Month 18. Additional visits for HGF protein and HGF plasmid DNA sample collection will be conducted on Day 4 and Month 12+4 days for all subjects, and additionally HGF plasmid DNA assay sample collection on Month 9+4 days for the first 5 enrolled subjects (i.e. subjects who receive any study treatment). Long-term safety follow-up data using a questionnaire will be obtained every 6 months following the Month 18 visit at the Month 24, Month 30 and Month 36 time points. Subject data collection during the Long Term Follow-up (LTFU) period (post-Month 18 visit) will be limited to Serious Adverse Events (SAEs) and the visit questionnaire data intended to assess the occurrence of any potential gene-therapy related delayed AEs. The total duration of the study will be up to 37 months.

Subjects will not be eligible to receive the subsequent doses of the study product if major amputation of the index leg has occurred, where the index leg is defined at the leg with the greater severity of CLI disease (also referred to as the treated leg or affected leg).

All eligible subjects will receive AMG0001 intramuscularly in the muscles of the index leg based on the location of disease.

Schedule of Study Procedures

PROCEDURES — Study Day (visit window*) – Visit # (V); *d=days	Screening Period	Dosing Visits: First Cycle								Follow-Up		Dosing Visits: Second Cycle								Follow-Up			Post-Month 18 Long Term Follow-up		
	Days -30 to -1	*Day 0 - V1*	*Day 14 (±2d) - V2*	*Day 28 (±2d) - V3*	*Day 42 (±3d) - V4*	*Month 3 (±7d) - V5*	*Month 3+14 Days (±2d) - V6*	*Month 3+28 Days (±2d) - V7*	*Month 3+42 Days (±2d) /- V8*	*Month 6 (±7d) - V9*	*Month 7.5 (±5d)*	*Month 9 (±7d) - V10*	*Month 9+14 Days (±2d) /-V11*	*Month 9+28 Days (±2d) -V12*	*Month 9+42 Days (±2d) - V13*	*Month 12 (±7d) - V14*	*Month 12+14 Days (±2d) -V15*	*Month 12+28 Days (±2d) - V16*	*Month 12+42 Days (±2d) - V17*	*Month 15 (±7d) - V18*	*Month 16.5 (±5d)*	*Month 18 (±7d) - V19*	Month 24	Month 30	Month 36
Subject Consent & Medical History	X																								
Vital Signs, Weight & Height[3]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X					
12-Lead ECG	X																								
Physical Examination[6]	X[10]	X[10]	X[11]	X[11]	X[11]	X[10]	X[11]	X[11]	X[11]	X[10]		X[10]	X[11]	X[11]	X[11]	X[10]	X[11]	X[11]	X[11]	X[10]		X[10]			
Peripheral Vascular Intervention Update[6]	X[1]	X[1]				X				X		X				X				X		X			
CLI Assessment [7]	X[1]	X[1]				X				X		X				X				X		X			
Hemodynamic Measurements[6,7]	X[1]	X[1]				X				X		X				X				X		X			
Angiogram [7]	X																								
QOL (VascuQOL)[6, 7]		X				X				X		X				X				X		X			
VAS (pain scale)[6, 7]	X[1]	X[1]				X				X		X				X				X		X			
Ulcer Tracings	X[1,2]	X[1]																							
Ulcer Photos [4, 7]	X[1,2]	X[1]				X[5]				X[5]		X[5]				X[5]				X[5]		X[5]			
Retinopathy Exam [6]	X															X						X			
HbA1C and FBG	X																								
Urine Pregnancy Test [6,8]	X	X				X						X				X									

PROCEDURES — Study Day (visit window*) – *Visit (V)* — **d=days*	Screening Period	Dosing Visits: First Cycle								Follow-Up		Dosing Visits: Second Cycle								Follow-Up			Post-Month 18 Long Term Follow-up		
	Days -30 to -1	**Day 0** - *V1*	**Day 14** (±2d) - *V2*	**Day 28** (±2d) - *V3*	**Day 42** (±3d) - *V4*	**Month 3** (±7d) - *V5*	**Month 3+14 Days** (±2d) - *V6*	**Month 3+28 Days** (±2d) - *V7*	**Month 3+42 Days** (±2d) - *V8*	**Month 6** (±7d) - *V9*	**Month 7.5** (±5d)	**Month 9** (±7d) - *V10*	**Month 9+14 Days** (±2d) - *V11*	**Month 9+28 Days** (±2d) - *V12*	**Month 9+42 Days** (±2d) - *V13*	**Month 12** (±7d) - *V14*	**Month 12+14 Days** (±2d) - *V15*	**Month 12+28 Days** (±2d) - *V16*	**Month 12+42 Days** (±2d) - *V17*	**Month 15** (±7d) - *V18*	**Month 16.5** (±5d)	**Month 18** (±7d) - *V19*	**Month 24**	**Month 30**	**Month 36**
FSH and Estradiol testing [9]	X																								
Hematology, Chemistry, Urinalysis[6]	X	X				X				X		X				X				X		X			
Anti-HGF Antibodies Assay[6]		X				X				X		X				X				X		X			
Study product administration		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X						
Injection site photos		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X						
Adverse Events [7]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X			
Concomitant Medication[7]	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X			
Telephone Contact											X										X				
LTFU Questionnaire																							X	X	X

(1) Procedures required for assessment of CLI status and ulcers must be conducted during screening ≥14 days prior to Day 0 and Pre-dose at Day 0. Stability of CLI must be confirmed by the investigator prior to dosing on Day 0.

(2) Photos of largest ulcer on the index leg as well as a photo or photos (if necessary) of the entire index leg to show all ulcer/gangrene locations. Debridement should be performed prior to these evaluations;

(3) Height obtained at Screening only

(4) Ulcer healing of the largest ulcer on the index limb (determined at Screening) will be assessed clinically by the Investigator by direct visual inspection at each study visit. If the largest ulcer on the index leg heals during the study period the subject should be brought and re-evaluated 2 weeks after healing to confirm it has remained healed and ulcer photography must be completed at that time.

(5) Photos of largest ulcer on the index leg as well as a photo or photos (if necessary) of the entire index leg to show all ulcer/gangrene locations. Debridement should be performed prior to these evaluations, if necessary.

(6) Conduct pre-dose when obtained during a dosing visit.

(7) Procedure must be performed prior to a planned interventional treatment (revascularization or amputation) while on study.

(8) Urine pregnancy tests will be performed prior to dosing on all women aged 55 years or less. For women who have been determined as premenopausal and are not surgically sterile, per the study requirements will continue with the scheduled urine pregnancy tests throughout the course of the study.

(9) Performed on all women under the age of 55

(10) Complete physical exam should be performed. If a dosing visit, perform prior to dosing.

(11) Abbreviated physical exam should be performed. If a dosing visit, perform prior to dosing.

Schedule of Sample Collection for the Serum HGF Protein & PCR for HGF Plasmid Assays

Study Day	Day 0	Day 4	Day 14	Day 28	Day 42	Month 3	Month 3 + 14 Days	Month 3 + 28 Days	Month 3 + 42 Days	Month 6	Month 9	Month 9 + 4 Days	Month 9 + 42 Days	Month 12	Month 12 + 4 Days	Month 12 + 42 Days	Month 15
Serum HGF protein Assay	X*	X	X*	X*	X*	X*			X*		X*			X*	X		X
PCR for HGF plasmid DNA Assay	X*	X	X*	X*	X*	X*	X*	X*	X*	X	X*	X**	X*	X*	X	X*	X

*At Dosing Visits (indicated by the shaded column), two (2) samples should be drawn one pre-dose and a second drawn four (4) hours post dosing.

**The first 5 subjects who are enrolled will have a blood sample drawn for HGF Plasmid DNA sampling 4 days following their Month 9 Visit.

2.4 Statistical and Analytical Procedures

2.4.1 General Statistical Considerations

This study is not powered for statistical inference, and any testing will be considered descriptive and exploratory. All data summarized in tabular form will have accompanying listings. Figures may also be provided.

Unless otherwise noted, the term "descriptive statistics" will refer to frequency and percent (%) for categorical data and number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous data.

Biodata (serum HGF protein) values reported as below the level of quantitation (10 copies/ uL) will be reported as BLQ and excluded in calculation of the mean and SD.

All analyses will be conducted using SAS 9.4 or later.

2.4.2 Missing Data

For endpoints involving the VascuQoL assessment, non-missing data after revascularization or major amputation will be included in analysis, and missing values for subjects who are dead at the time point of interest will be scored as 0.

For the Visual Analogue Scale (VAS), each subject's data after revascularization or major amputation will be imputed using the value of the last available assessment prior to intervention, and the worst score available will be imputed for assessments after death.

2.4.3 Study Day, Analysis Visit Windows and Baseline

Subject visits will be analyzed by nominal visit and/or time point as recorded on the CRFs, given that the day on which the visit occurs falls into the appropriate window as described in the table below. If a visit date does not fall into the correct window, data from that visit will not be summarized in the tables, but it will be included in the listings.

Study Day will be calculated from the reference date, and will be used to show the start and stop day of assessments and events.

The reference date is defined as the day that the first injection is administered, that is, Day 0.

Study Day = (date of event – date of Day 0).

The analysis will utilize less stringent visit windows than defined in the protocol, as defined below. If a subject has more than one visit in a visit window, the visit closest to the scheduled day will be considered for the analyses. If the difference is a tie, the day before the scheduled day will be used in the statistical analyses.

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (excluding unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

Unscheduled visit measurements will not be used to provide a measurement for either baseline values or post-treatment values. Unscheduled data will be included in the standard subject listings but not in the summary tables.

Table 2 Visit Window

Analysis Visit	Scheduled Day	Start of Window (Study day)	End of Window (Study day)
Screening	-30	-30	<0
Day 0	0	0	0
Month 3	90	80	100
Month 6	182	167	197
Month 9	273	258	288
Month 12	365	335	395
Month 15	455	420	490
Month 18	548	503	593
LTFU 1 (Month 24)	730	685	775
LTFU 2 (Month 30)	912	867	957
LTFU 3 (Month 36)	1095	1050	1140

2.5 Statistical Methods

2.5.1 Study Population

A single study population will be used for all efficacy and safety analyses, that is, the modified Intent-To-Treat population (mITT) population. The population is defined as all subjects who received at least one injection of study treatment.

2.5.2 Disposition, Demographics, Protocol Deviations, and Background Characteristics (Including Medical History)

The number of subjects enrolled (i.e. those who received at least one injection of study treatment) and subjects who completed the study or prematurely discontinued with the primary reason for study discontinuation, completion of the Month 18 clinic visit, and completion of the Month 36 LTFU questionnaire will be summarized.

A table showing number of subjects in the study will be tabulated at Day 0, month 3, month 6, month 9, month 12, month15, month 18, LTFU (24 month, 30 months, 36 months).

A major protocol deviation is defined as any divergence from the protocol that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data, i.e., non-adherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or Good Clinical Practice (GCP) guideline. A minor protocol deviation is defined as either any deviation from the protocol that does not have a significant effect on the participant's safety, rights or welfare, and / or the integrity of the study data or as defined in the protocol or any non-adherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines and do not impact the study. A listing of subjects with major protocol violations will be provided together with a description of the criteria in the footnotes.

The following demographics, baseline characteristics, and Disease History at baseline will be reported.

- Demographics: age in years, age group (≤79 years, >80 years), sex, race, height, weight, ethnicity
- Baseline characteristics: past tobacco use, current tobacco use, alcohol use, mobility, self-care, anxiety/depression
- Disease History at baseline: Rutherford class, diabetes status with diabetes type, peripheral neuropathy, cardiovascular/lipid history (myocardial infarction, stroke, hypertension, hyperlipidemia), history of index limb (type of peripheral vascular intervention, minor amputation, ulcer status), ischemic rest pain, ankle brachial index (ABI), and toe brachial index (TBI).

2.5.3 Exposure

A listing of subjects' study product administration will be provided. Additionally, a table showing the number of subjects who received only the first course of injections, and the number of subjects who received both the first and subsequent courses will also be provided.

2.5.4 Concomitant Medication

Concomitant medications are medications which started prior to, on, or after the first dose of study medication and taken concomitantly during the treatment period. Concomitant medications will be coded using WHO Drug dictionary version September 2013.

The following concomitant medication listings will be provided: all, medications with indications for MI, stroke, pain, hypertension, and hyperlipidemia by treatment. A listing for subject secondary prevention status at baseline will be provided.

Medications reported as being taken at Screening and Day 0 along with concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification level 4 description and preferred name.

In addition, the use of statin and anti-platelet agents at screening will be summarized and listed.

2.5.5 Efficacy Analysis

- **Ulcer improvement**

  A table showing the number of subjects completely healed in the target ulcer will be provided at up to 6 months, > 6 months to 12 months, from >12 months to 18 months. If available, the number of subjects with at least 20% reduction in bi-dimensional size (by measuring largest diameters) will be provided. The reduction in bi-dimensional size will be calculated by taking the product of the largest diameters for each baseline and postbaseline measurement, then subtracting the baseline result from the postbaseline result.

- **Ischemic Rest pain (of the index leg) using a 10 cm VAS scale**

  Rest pain severity will be assessed at the specified predetermined time points. Rest pain severity will also be assessed prior to surgical revascularization or major amputation (of the index leg). A table showing the number of subjects reduced by $\geq$ 20 mm from baseline in VAS score will be provided at up to 6 months, > 6 months to 12 months, from >12 months to 18 months. Summary statistics will be provided for baseline and change from baseline for each visit and LOCF. One sample t-test for change-from-baseline will be performed. If death occurs, the worst score prior to death instead of last observation will be carried forward.

- **Hemodynamic Measurements**

  Summary statistics will be provided for baseline and change from baseline for hemodynamic parameters (right/left brachial systolic pressure, ankle systolic pressure measured at dorsalis pedis and posterior tibial, toe systolic pressure, calculated ABI, and calculated TBI) by visit. At each visit, only subjects who have a non-missing value at both baseline and the specific visit will be summarized. Two-sided one-sample t-test will be performed for each visit and LOCF.

- **Subjects with any worsening CLI event of index leg**

  A summary table and listing of worsening CLI-related events of the index leg including any new or worsening events, worsening rest pain, new ulcer or worsening ulcer, new or worsening wound infection, peripheral vascular intervention, complication of a peripheral vascular intervention, cellulitis, and amputation due to worsening CLI will be provided.

- **Subjects who either died, had MI, Stroke, revascularization (by surgical bypass, by endovascular intervention, by hybrid procedure), major amputation, or all-cause death**

  A summary table including counts and percentages and a listing will be provided for these parameters for the following time periods: up to Month 6, 0 to Month 12, and 0 to Month 18.

As a supplemental analysis, time to major amputation or death will be performed, and the Kaplan-Meier (KM) estimates with 2-sided 95% confidence interval using Greenwood's formula will be computed up to the end of the study and plotted. If a subject undergoes major amputation followed by death, it will counted as an event. If a subject does not experience major amputation or death, the subject will be censored at the date of last contact as recorded on the CRFs.

- **Shift from baseline in Rutherford classification**

  Shift from baseline in Rutherford classification will be summarized by study visit.

- **Quality of life (QoL)**

  Quality of life (QoL) measurements will be assessed using the disease-specific vascular Quality-of-Life questionnaire (VascuQol). The VascuQol contains 5 domains (pain, symptom, activities, social, and emotional functioning), and responses are scored from 0 (lowest QOL imputed after death) to 7 (best QOL, maximum health). Responses are averaged for composite overall and domain-specific scores, giving equal weight to each question and domain. Subjects' data after revascularization or major amputation will be included in the analysis. However, after death, subjects will be scored as 0. For the effect of treatment on individual domains, pain, symptoms, and activity will be considered the most important of the 5 domains.

  Summary statistics will be provided for baseline and change from baseline by visit for each score including total and domain scores. At each visit, only subjects who have a non-missing value at both baseline and the specific visit will be summarized, and two-sided one-sample t-tests for the change-from-baseline will be performed for each visit and LOCF.

2.5.6 PK Analyses

A listing with summary statistics (n, mean, SD, min, and max) will be provided for Serum HGF protein, and a listing of PCR for HGF plasmid DNA Assays will be provided.

For Anti-HGF antibody and confirmation from fusion test, the antibody indication (Yes/No) and fusion test result (Yes/No, if available) will be presented on one listing.

2.5.7 Safety Analysis

- **Adverse Events**

Adverse event (AE) data will be collected using the standard AE CRF. All AEs will be coded using MedDRA dictionary version 16.1.

Treatment-emergent adverse events (TEAEs) will be evaluated, and a table showing the number and percentage of subjects with occurrences categorized by System Organ Class and Preferred Term will be provided by causality (relationship to study drug), whether the AE led to discontinuation, and whether the AE was deemed serious. For the causality, "Likely Related" and "Possibly Related" will be classified as "Related," and the most related AE will be summarized if multiple coded AEs occurred for the same subject. AEs that led to discontinuation and those that were deemed serious will be presented in separate columns. If a subject has more than one occurrence of the AE, the subject will be counted once. An additional table will be provided for the total number of AEs occurring during the study, presented by system organ class, causality, and severity, including all AEs, AEs from Day 0 up to Month 3, from Month 3 up to Month 6, from Month 6 up to Month 12, and Month 12 up to Month 18. To take the most conservative approach in categorizing severity during a period, the worst rating reported will be used in the

categorization. For example, if the severity is rated moderate one week and severe another week during the period, severe will be used as the severity rating category over the period.

Death or other serious AE (non-fatal MI or non-fatal stroke) are not in all cases recorded as an adverse event in the AE CRF, but could also be recorded in the outcome of adverse events. For those subjects who either died, had a serious AE, or discontinued participation in the study because of revascularization or other reason, a summary table and a subject line listing will be provided during the periods listed for the previous table along with the post-Month 18 LTFU period up to Month 24, Month 24-30 and Month 30-36.

- **Laboratory Data**

Listings of subjects with abnormalities will be provided with abnormal values flagged.

The following clinical laboratory tests will be listed:

- Hematology: including hemoglobin, hematocrit, RBC count, WBC count (total and differential) and platelet count.
- Urinalysis: including protein, glucose, blood, ketones, bilirubin, and microscopic examination.
- Blood chemistry: glucose (fasting), uric acid, total cholesterol, HDL, calculated LDL, triglycerides, aspartate transaminase (AST), alanine aminotransferase (ALT), calcium, phosphorus, total bilirubin, alkaline phosphatase, total protein, albumin, globulin, lactic acid dehydrogenase (LDH), serum creatinine, creatinine clearance (estimated using the Cockcroft-Gault formula), blood urea nitrogen (BUN), and electrolytes (Na^+, K^+, Cl^-).

- **Physical Examination**

The number of subjects with abnormalities will be provided for the following visit windows: Day 0 to Day 42, Month 3 to Month 3+42 Days, Month 6, Month 9 to Month 9+42 Days, Month 12 to Month 12+42 Days, Month 15, and Month 18/ET. A listing of subjects with abnormalities will be presented.

- **Retinopathy Examination**

Summary statistics will be provided for baseline and change from baseline for Early Treatment Diabetic Retinopathy Study (ETDRS) score by visit. At each visit, only subjects who have a non-missing value at both baseline and the specific visit will be summarized. The number and percent of normal, abnormal (clinically significant, not clinically significant, and all) retinopathy examinations will be presented for baseline, Month 12, and Month 18. A listing of ETDRS scores and abnormalities will also be provided.

Statistical Analysis Plan Signature Page

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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