STATISTICAL ANALYSIS PLAN

Protocol No.:	**AG920-CS302**
Protocol Title:	**A Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Evaluation of the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution**
Drug Name:	**Articaine Sterile Topical Ophthalmic Solution (AG-920)**
Indication:	**Topical Ocular Anesthetics**
Sponsor:	**American Genomics, LLC** [redacted]
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STATISTICAL ANALYSIS PLAN

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BCVA	Best Corrected Visual Acuity
CMH	Cochran Mantel Haenszel
CI	Confidence Interval
CRF	Case Report Form
ET	Early Termination
ITT	Intention to Treat
IOP	Intra-Ocular Pressure
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
OD	Oculus Dexter (Right Eye)
OS	Oculus Sinister (Left Eye)
PK	Pharmacokinetics
PP	Per protocol
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1 INTRODUCTION

1.1 Trial Objectives

The primary objective of this study is to evaluate anesthetic efficacy of AG-920 administered by topical ocular route as compared to placebo.

The secondary objectives of this study are:

- To evaluate the onset of anesthetic effect of AG-920, i.e., how long it takes one dose of two drops 30 seconds apart of AG-920 to anesthetize the eye;
- To evaluate the duration of anesthetic effect of AG-920, i.e., how long the anesthetic effect lasts in the eye following one dose of two drops 30 seconds apart of AG-920;
- To evaluate the safety and tolerability of AG-920 administered by topical ocular route.

This document describes the statistical analysis methods and data presentations for the data analyses of Protocol AG920-CS302. Related documents to this SAP are the study protocol and case report form (CRF or eCRF). Data analysis will be based on the final dataset(s) provided by Sponsor or designee Data Management group, which is InFocus Clinical Research.

The study database(s) includes all of the CRF-based clinical data and all of central laboratory data. The original EDC database constructed by InFocus Clinical Research will be converted into CDISC SDTM version 3.1 and/or 3.1.1 database. InFocus Clinical Research will provide the treatment code for treatment unblinding after database lock.

1.2 Background Information

Injections of pharmacologic agents into the vitreous cavity for the purpose of treating various disorders of the retina as well as intraocular inflammatory disease have become the mainstream. In almost all cases, these injections are made through the pars plana. An injection into the eye in this location, with the needle oriented properly, will be posterior to the human lens or an intraocular implant, but anterior to the retina, thereby avoiding damage to these important structures. The pars plana is a zone that rings the eye extending from 3.0 mm to 5.5 mm from the edge of the cornea.

While topical agents such as proparacaine achieve excellent anesthesia on the external surface of the eye, they do not numb the internal aspect of the pars plana, which is extremely sensitive. Currently, physicians fall into one of two methodologies: either injecting lidocaine under the conjunctiva first and then executing a second injection through the pars plana, or by using topical lidocaine gel and then performing the intravitreal injection. Patients often report moderate to severe discomfort with each of these approaches. Thus, it is important that a new tool is developed for physician to use in assisting the intravitreal injection.

For that purpose, American Genomics is evaluating the formulation of articaine, an approved local anesthetic, for topical ocular use to provide local anesthesia for intravitreal injections. The Sponsor intends to develop Articaine Sterile Topical Ophthalmic Solution (coded named AG-920) for topical ocular use to induce local anesthesia for intravitreal injection. [redacted]

In summary, AG-920 is a sterile topical ophthalmic solution made from articaine for physicians to apply on the pars plana area of the eye to assist performing the intravitreal injection of pharmacologic agents for the treatment of various disorders of the retina.

2 STUDY DESIGN

2.1 Rationale

The AG-920 topical drop would allow a technician to apply the topical solution to the eye, allow the articaine to penetrate the pars plana sufficiently to permit the intravitreal injection without undue discomfort. AG-920 is selected for this procedure based upon being made from Articaine which has clinical use in dental procedures, suggesting it penetrates soft tissue and bone.

2.2 Description of Trial Design

This is a Phase 3, randomized, placebo-controlled, double-masked, parallel-group design study of safety and anesthetic efficacy of AG-920 topical drop versus placebo in healthy subjects. The study will evaluate the safety and anesthetic efficacy following one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920), in comparison with placebo. Eligible subjects will be randomized in a 1:1 ratio to receive a single dose of AG-920 or matching placebo into one eye, designated as subject's study eye. The application of one single dose of AG-920 involves two drops 30 seconds apart into the subject's study eye.

The study consists of two visits and a follow-up phone call: one screening visit on Day -2 (Visit 1), one baseline/assessment visit on Day 1 (Visit 2), and one follow-up phone assessment on Day 2-5 (Phone Follow-Up).

Following the screening visit, eligible subjects will return to the clinic on Day 1 to have their study eye randomly assigned (right eye=OD or left eye=OS) and to be randomized to receive the study medication into the study eye. Subjects will undergo a conjunctival pinch procedure, and the pain associated with the pinch will be rated. Dosing of the study medication and conjunctival pinch procedure will be performed by the study staff.

To assess the anesthetic effect of the study medication, all subjects will be pinched at 20, 40, 60 seconds and 5 minutes post dose, defined as after the second drop of the dose application. If the subject feels no pain at 5 minutes, the subject will be considered "anesthetized." Pinching of anesthetized subjects will resume at 10 minutes and pinching will continue every five minutes for up to 30 minutes or until pain resumes. If the subject experiences pain 5 minutes post dose, pinching will be concluded and this subject will be considered to NOT have reached anesthesia.

All subjects who are randomized and who receive the study medication on Day 1 will be followed up with a phone call to on Day 2-5 for safety assessment.

2.3 Schedule of Assessments

The complete schedule of assessments for this entire study is shown in Table 1 of the study protocol (see Protocol No. AG920-CS302 Amendment 1, Page 10).

The effects of anesthesia is assessed, following the application of study medication, by conjunctival pinch procedure on the study eye and verbal asking of pain from the subject at

20, 40, 60 seconds and 5 minutes after the second drop as well as every five minutes afterward.

2.4 Randomization

As stated in the protocol, randomization schedule generated by the Sponsor or designee will be used to assign subjects to each of the two treatment groups with a 1:1 allocation ratio to receive AG-920 drops or matching placebo.

Study medication will be pre-packaged into individual medical product application packs with one pack being used per application according to the randomization schedule. All of the medical product packs will be identical in appearance except that each pack bears a unique randomization number (or kit number). The prepackaged packs will be shipped to a study site once the first subject is screened at the site and re-shipments of the supplies will be sent to a site as needed during the study.

Each eligible subject will be assigned to one of the prepackaged packs available at a site. The kit number associated with the prepackaged pack will be recorded on the CRF for this subject. Actual treatment assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day to day study management, Monitors, Data Managers, and Statisticians), and the subjects.

Only in case of medical emergency or occurrence of adverse events that warrant unmasking in the opinion of the Investigator, will the treatment assignment(s) be unmasked and made available to the Investigator and the Sponsor Safety Officer. In the absence of medical need, the randomization code will not be available to the above personnel until after the study is completed and the database is locked.

2.5 Sample Size Estimation

The study is intended to test for a difference in proportion of subjects with anesthetic response (i.e., no pain) between AG-920 and placebo at 5 minutes post dose.

Assuming a 25% delta in proportion between AG-920 and placebo groups and an anesthetic response (i.e., no pain at 5 minutes post dose) to placebo of 15%, a sample size of 60 per group will provide a statistical power of 88% at the significance level of 0.05 (2-sided), with a Chi-square test without continuity correction.

Therefore, a total of 120 subjects randomized with an equal allocation ratio (1:1) of the active versus placebo will be needed in the present study.

2.6 Efficacy and Safety Measurements

In this study, primary efficacy endpoint will be assessed using the proportion of subjects with anesthetic response defined as no pain by conjunctival pinch at 5 minutes post application of the dose. The secondary efficacy endpoints will be: 1) the onset of anesthetic effect defined as the time to no pain by conjunctival pinch within 5 minutes post application of the dose; and, 2) the duration of anesthetic effect defined as the time from the onset of anesthetic effect to the time point when pinch pain resumes.

Safety will be assessed through subject early terminations, adverse events, best corrected visual acuity (BCVA), biomicroscopy and external eye exam, and concomitant medications.

2.6.1 Primary efficacy measure

The primary efficacy endpoint for this study is the proportion of subjects with anesthetic response defined as no pain at 5 minutes post application of the dose. Pain is assessed using conjunctival pinch procedure. Dosing of the study medication and conjunctival pinch procedure will be performed by the study staff.

To assess the anesthetic effect of the study medication, all subjects will be pinched at 20, 40, 60 seconds and 5 minutes post dose application. If the subject feels no pain at 5 minutes, the subject will be considered "anesthetized." Pinching of anesthetized subjects will resume at 10 minutes and pinching will continue every five minutes for up to 30 minutes or until pain resumes. If the subject experiences pain 5 minutes post dose application, pinching will be concluded and this subject will be considered to NOT have reached anesthesia.

2.6.2 Secondary efficacy measure

The secondary efficacy endpoints include the following:

- Time in minutes to no pain within 5 minutes post application of the dose defined as post the 2nd drop of the dose. Once a subject achieves no pain or anesthetic effect, the time to the onset of anesthetic effect will be calculated as the time interval in number of minutes between the time of dose application completion and the time point when the first observation of no pain is recorded. All timepoints post dose will be converted to minutes so the 20, 40 and 60 second timepoints will be 0.33, 0.67 and 1.0 minutes, respectively. For those subjects who drop out after dose application without achieving anesthesia or who do not achieve the anesthetic effect within 5 minutes post dose, the time to the anesthetic effect will be considered being censored at the last assessment of pinch test or at 5 minutes (censored time point), whichever occurs earlier.

- Duration in minutes from the onset of anesthetic effect to the time point when pinch pain resumes. For those subjects who have achieved an anesthetic effect post dose, the duration of anesthetic effect is calculated by subtracting the anesthetic effect onset time from the time of the first observation of pinch pain return. For those subjects who did not achieve an anesthetic effect post dose, this duration is not applicable and will be set to missing.

2.6.3 Safety measures

Adverse events (AEs) are recorded at each visit and at follow-up phone call. When applicable, adverse events will be noted specifically in association with the study and non-study eyes.

Best corrected visual acuity (BCVA) and biomicroscopy (Slit-Lamp) and external eye exam are performed at each visit.

A urine pregnancy test will be performed at screening for all female subjects of child-bearing potential.

2.6.4 Other measures

Concomitant medications associated with the treatment of study and non-study eyes will be specifically noted as such.

2.7 Drug Concentration and PK Measurements

No drug concentration measures will be taken in this study.

2.8 Handling of Missing, Incomplete, and Repeat Data

For efficacy parameters, missing or invalid data for pinch pain assessment will be assessed for each assessment time point post dose. Missing values that occur either within 5 minutes (inclusive) post dose or after 5 minutes post dose, due to either invalid data or early termination, will be imputed with the method of last-observation-carried-forward (LOCF) for the planned assessment time points on Day 1.

For safety parameters, missing or invalid data will be treated as missing for the corresponding assessment of a visit.

All data records are identified by study visit and/or assessment time point. Should repeated data records exist within a study visit and/or assessment time point, the first valid data record will be utilized for any statistical analyses of the corresponding study visit and/or assessment time point. All existing data records including the repeat data records in the study database will be presented in data listings and CRF data tabulations.

Any resultant incomplete or missing data of either efficacy or safety parameters will be treated as missing in the statistical analyses involving these parameters.

2.9 Statistical Methods

Unless specified otherwise, SAS® Version 9.0 or higher will be utilized to perform the statistical analyses of efficacy and safety measures.

Categorical variables will be summarized in general using frequencies and percentages, whereas continuous variables will be summarized in general using descriptive statistics of number of observations (n), mean, standard deviation (SD), minimum (Min), median, and maximum (Max).

In both data listings and CRF domain data tabulations, subject ID will consist of site number plus the subject screening number in the format of XXX-YYY, where XXX denotes the site number and YYY the subject's screening number within the site.

Hypothesis testing, unless otherwise indicated, will be performed at the 5% significance level. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' in all tables. All group comparisons from analysis of variance (ANOVA) and/or analysis of covariance (ANCOVA) models will be based on Type III sums of squares. In the case of substantial non-normality, results from non-parametric tests will also be reported. All confidence intervals (CI) will be two-sided with 95% coverage.

2.9.1 Primary efficacy analysis

The primary efficacy endpoint for this study is the proportion of subjects with anesthetic response defined as no pain at 5 minutes post application of the dose. The definition of the primary efficacy endpoint is given in Section 2.6.1. The non-parametric Cochran-Mantel-Haenszel (CMH) test with adjustment for study eye side will be used to examine the difference in proportion of subjects with anesthetic response at 5 minutes post dose between the active treatment group and placebo group. If the proportion of subjects (expressed as a percentage) is higher in the AG-920 group and the *P* value is statistically significant ($P \leq 0.05$), then superiority of AG-920 over placebo will be claimed.

Between-group difference and its 95% confidence interval (CI) in the proportion of subjects with anesthetic response (yes=1) vs. non-response (no=0) will be calculated using a two-way analysis of variance (ANOVA) model with treatment (the effect of interest) and study eye side as the effects. The study-eye-side effect is used as a blocking factor in the model to control the potential treatment differences among the study eye sides.

The primary efficacy analysis will be performed for the ITT population, which will include all of the randomized subjects who received the complete application of one study dose (i.e., two drops). The analysis model adjusts for the effect of the study eye side. The study-eye-side by treatment interaction will be examined through the summary descriptive statistics of subjects with anesthetic response for each study eye side.

Prior to the determination of the primary efficacy variable, handling of missing values that occur prior to or at 5 minutes post dose is described in Section 2.8.

The primary efficacy endpoint will also be analyzed for the PP population as well as for subgroups of the ITT population, such as male vs. female, Caucasian vs. Non-Caucasian, age groups, and iris color dark brown vs. other colors.

2.9.2 Secondary efficacy analysis

The secondary efficacy endpoints include 1) the onset of anesthetic effect defined as the time to no pain by conjunctival pinch within 5 minutes post application of the dose; and, 2) the duration of anesthetic effect defined as the time from the onset of anesthetic effect to the time point when pinch pain resumes. Secondary efficacy endpoints will be analyzed for the ITT population and PP population.

Prior to the determination of the secondary efficacy variables, handling of missing values that occur prior to or at 5 minutes post dose or after 5 minutes post dose on Day 1 is described in Section 2.8.

Onset of anesthetic effects

The secondary endpoint of the onset of anesthetic effect in minutes from time of dose application completion to no pain within 5 minutes post dose is defined in Section 2.6.2. This endpoint will be compared for between-group differences, using a 2-way ANOVA model with treatment (the effect of interest) and study eye side as the effects. The study-eye-side effect is used as a blocking factor in the model to control the potential treatment differences among the study eye sides. For the accuracy and appropriateness of the analysis, those subjects who are censored on (or not achieving) the onset of anesthetic effect will be excluded from statistical analysis.

Duration of anesthetic effects

The secondary endpoint of the duration of anesthetic effect in minutes from the onset of anesthetic effect to the time point when pinch pain resumes is defined in Section 2.6.2. This endpoint will be compared for between-group differences, using a 2-way ANOVA model with treatment (the effect of interest) and study eye side as the effects. The study-eye-side effect is used as a blocking factor in the model to control the potential treatment differences among the sites.

2.9.3 Safety analysis

Treatment Exposure

Frequencies of exposure to the study medication will be calculated based on the number of drops the subject has received over the course of the study. Frequencies of exposure will be categorized as the following: 1 drop and 2 drops. Frequencies of exposure will be summarized by treatment for the safety population defined in Section 3.1, as well as for each gender group.

Compliance rates will be calculated by dividing the number of drops received by the number of drops that should have been given during the application of dose. Compliance rates will be summarized.

Early Termination

Subject disposition will be summarized by treatment and will be listed for those subjects who are terminated early. This listing will include demographic variables, treatment assigned, number of drops received, termination time, and the primary reason for early termination.

Adverse Events

Adverse events will be coded for preferred terminologies using Medical Dictionary for Regulatory Activities (MedDRA). AE will be grouped into pre-treatment AE and treatment-emergent AE and post-treatment AE and will be reported separately, based upon the start date and time of the events, the start date and time of the treatment.

Adverse events will be defined as the pre-treatment AEs if they occur prior to the treatment start date and time; as the treatment-emergent AEs if they occur on or after the treatment start date and time and before the next day; and as the post-treatment AEs if they occur after the treatment date.

Frequency of the treatment-emergent AEs will be calculated for each body system, by preferred terminology, by treatment group, for number of subjects and percentage reporting the event. The severity of the adverse events and the relationship to the investigational product will be summarized for each body system and preferred terminology by treatment group. Withdrawals due to adverse events will be summarized for each body system and preferred terminology by treatment group and will be listed with demographic variables for individual subjects.

Serious adverse events (SAE) (including deaths) will be listed for individual events.

Narratives will be provided for all deaths, non-fatal serious adverse events, and subjects withdrawn due to adverse events.

Best Corrected Visual Acuity (BCVA)

BCVA will be summarized in logMAR units by treatment for the screening (pre-dose) and Day 1 (post-dose), using a number of observations, mean, standard deviation, minimum, median, and maximum values. The analysis will be based on the safety population defined in Section 3.1.

For both study eye and non-study eye, changes in BCVA at post-dose from screening (pre-dose) will be analyzed for differences between AG-920 and placebo groups, using analysis of covariance (ANCOVA), with the pre-dose measurement as the covariate.

Biomicroscopy (Slit-Lamp)

Total severity scores of Biomicroscopy (Slit-Lamp of seven items on grading scale, including lid erythema, lid edema, conjunctiva hyperemia, conjunctiva edema, corneal edema, anterior chamber cells, and anterior chamber flare) will be summarized by treatment for the screening (pre-dose) and Day 1 (post-dose), using a number of observations, mean, standard deviation, minimum, median, and maximum values. The analysis will be based on the safety population defined in Section 3.1.

For both study eye and non-study eye, changes in the total severity score at post-dose from screening (pre-dose) will be analyzed for differences between AG-920 and placebo groups, using analysis of covariance (ANCOVA), with the pre-dose measurement as the covariate.

2.9.4 Other analysis

The concomitant medications, including those for study eye and non-study eye, will be grouped into those taken pre-randomization and those taken post-randomization as well as those taken post-treatment, based upon the starting dates of the concomitant medication and the treatment.

Number and percent of subjects in the safety population who take pre-randomization concomitant medications will be reported. Number and percent of subjects in the safety population who take post-randomization concomitant medications will be reported by treatment and by study eye vs. non-study eye. Number and percent of subjects in the safety population who take post-treatment concomitant medications will be reported by treatment and by study eye vs. non-study eye.

3 STUDY POPULATION

3.1 Definition of Subject Populations

All subjects who have the randomization procedure completed at Day 1 are considered study participants. The following subject populations are defined to assess the safety and efficacy of AG-920 in comparison with placebo.

Safety Population

The safety population is defined as all subjects who are randomized and who have received at least one drop of the dose (2 drops) of the study medication. The safety population will be utilized for comparative safety analyses among treatment groups.

Intention-to-treat (ITT) Population

This population is defined as all subjects who are randomized to treatment and have received at least one dose (two drops) of the study medication. The ITT population is the primary population for efficacy evaluation in this study. Treatment identification is defined in the ITT population by treatment assignment. The ITT population will be identified and finalized before the database is locked and the study is unmasked.

Per-Protocol (PP) Population

This population is defined as sub-population of the ITT population. The PP population is the secondary population for efficacy evaluation in this study and will be defined as all randomized subjects who completed the study treatment with no major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. In case there is a difference between treatment assigned and received, treatment actually received will be utilized to define the treatment identification in the PP population. In case there are missing data in efficacy measures, the analysis of the PP population will be based on observed or actual data only (without imputation). The PP population will be identified and finalized before the database is locked and the study is unmasked.

3.2 Screening and Enrollment

A screening summary including the number of subjects screened for study participation will be presented by site (Table 1.1.1).

An enrollment summary including the number of subjects enrolled, randomized, and completed the study will be presented for all enrolled subjects and by site (Table 1.1.2). Enrolled subjects include those individuals who are screened and returned to the clinic on Day 1 and randomized into the study. The number of subjects treated with at least one drop of the dose (2 drops) of the study medication (i.e., the safety population) will be summarized for each treatment group and overall (Table 1.1.3). The number of subjects treated with at least one dose (2 drops) of the study medication (i.e., the ITT population) will be summarized for each treatment group and overall (Table 1.1.4). The number of subjects in the PP population will be summarized for each treatment group and overall (Table 1.1.5).

3.3 Population Demography

For subjects enrolled, safety, ITT, and PP populations, descriptive summaries of demography and baseline characteristics will be presented for each subject group and overall to establish baseline comparability (Tables 1.2.1 to 1.2.4).

Demography includes age in years (continuous and categorical 18 to 29, 30 to 39, 40 to 49, 50 to 64, and 65+), gender, race, ethnicity, weight, and height. Demography will also be listed for all subjects enrolled (Listing 1).

3.4 Disease Characteristics and Prior Treatment

For the safety, ITT and PP population, descriptive summaries of baseline study eye characteristics will be presented for each treatment group and overall to establish baseline comparability (Tables 1.3.1 to 1.3.3).

BCVA and other characteristics of the study and non-study eye will be listed for all subjects enrolled (Listing 1).

3.5 Medical History

Medical history will be listed in listing and CRF data tabulation.

3.6 Disposition of Study Participants

Subject disposition including completion and discontinuation along with CRF-based termination reason will be summarized for safety and ITT populations (Tables 1.4.1 to 1.4.2). Subjects' early termination details will be listed for all subjects enrolled (Listing 2).

Subjects' randomized treatment, randomization (or kit) number, and randomization date as well as actual treatment received will be listed for all subjects randomized (Listing 3).

3.7 Protocol Deviations and Violations

A summary of protocol deviation and violations will be provided for ITT population (Table 1.5.1). Subjects who are randomized to receive double-masked treatment in the study and included in the ITT population, but do not have two drops dosed and/or post-dose status of pinch pain assessment will be listed for subjects randomized (Listing 4).

Subjects who are included in the ITT population, but not included in the PP population due to either protocol violations or other reasons will be listed for all subjects excluded from the PP population (Listing 5).

4 EFFICACY EVALUATION

4.1 Datasets Analyzed

The ITT population is defined as the primary efficacy population, and the PP population as the secondary efficacy population. Both populations will be identified and finalized before the database is locked and the study is unblinded. The definitions of the two populations are provided in Section 3.1.

In addition, sub-population datasets may be defined as the ITT subjects in each gender group (male vs. female), each age group (18-34 vs. 35+), each racial group (Caucasian vs. Non-Caucasian), and each color of the eye iris (dark brown vs. other colors).

4.2 Treatment Compliance

The compliance rate during treatment will be summarized by treatment group and demographic parameters for the safety and ITT populations (Tables 1.5.2 and 1.5.3).

4.3 Data Missing and Imputation

A summary of the observed data missing and imputation performed will be reported for study eye anesthetic response status, the primary efficacy measure, of the ITT population in Table 1.6.1.

4.4 Baseline Measures

As the participants of this study are normal subjects, rather than patients, there is no prior medical condition involved in this study. Descriptive statistics of the study eye characteristics are presented in Section 3.4.

4.5 Efficacy Results and Tabulations

4.5.1 Results of primary efficacy analysis

Descriptive and inferential statistics on the ITT population of the proportion of subjects with anesthetic response at 5 minutes post dose will be presented in Table 2.1.1.

For the PP population, the results of the same proportion analysis on the number of subjects with anesthetic response at 5 minutes post dose will be presented in Table 2.1.2.

The by-site summary of descriptive statistics of the number of subjects with anesthetic response at 5 minutes post dose will be presented in Table 2.1.3.

The results of the proportion analysis on the number of subjects with anesthetic response at 5 minutes post dose will be presented for the sub-populations of men vs. women in Tables 2.2.1 and 2.2.2; for 34 years or younger vs. 35 years or older in Tables 2.2.3 and 2.2.4; for Caucasian vs. Non-Caucasian in Tables 2.2.5 and 2.2.6; and, for iris color dark brown vs. other colors in Tables 2.2.7 and 2.2.8.

Individual subjects' primary efficacy data (i.e., pinch pain response) assessed post dose on Day 1 by Investigator, with and without imputation, will be listed by treatment for the ITT population (Listing 6).

4.5.2 Results of secondary efficacy analyses

Descriptive and inferential statistics of the anesthetic response onset in minutes post dose will be presented in Table 2.3.1 for the ITT population and in Table 2.3.2 for the PP population.

Descriptive and inferential statistics of the anesthetic response duration in minutes from the onset to pinch pain return will be presented in Table 2.4.1 for the ITT population and in Table 2.4.2 for the PP population.

5 SAFETY EVALUATION

For safety evaluation, the safety population as defined in Section 3.1 will be utilized to conduct safety analyses among treatment groups.

5.1 Extent of Drug Exposure

Exposure to study medication will be tabulated by treatment in Table 3.1.1 for number of drops received, using the following categories: 1 drop and 2 drops. The tabulations will be done for the safety population, and for man and woman, separately.

Individual subjects' treatment exposure (drops) will be listed by treatment for the safety population (Listing 3).

5.2 Early Termination

Early termination will be categorically summarized for the safety population in Table 1.4.1, and for the ITT population in Table 1.4.2. Subjects' study termination details will be listed (Listing 2).

5.3 Adverse Events

An overall summary of AEs reported in this study will provided in Table 4.1.1 for study participants and in Table 4.1.2 for the safety population. The incidences of subjects reporting pre-treatment AE will be reported in Table 4.2.1 for the pre-randomization period and in Table 4.2.2 for the treatment-emergent AEs by treatment. Those treatment-emergent AE by preferred terminology that are reported by more than 5% of subjects in any treatment will be tabulated in Table 4.2.3.

Incidences of subjects reporting treatment-emergent AEs (TEAEs) will also be tabulated by treatment for the TEAEs associated with the study eye in Table 4.2.5 and for the TEAEs associated with non-study eye in Table 4.2.6.

Incidences of subjects reporting treatment-emergent AEs will also be tabulated by onset time (on-dosing day vs. off-dosing day) in Table 4.3.1 for all TEAEs, and in Table 4.3.2 for the TEAEs associated with the study eye, and in Table 4.3.3 for the TEAEs associated with non-study eye.

The severity of the treatment-emergent AEs and the relationship to the investigational product will be summarized in Table 4.4.1.

Treatment-emergent AEs associated with early terminations and serious AEs will be summarized by preferred term, respectively, in Table 4.4.2 and Table 4.4.3 for all TEAEs, in Table 4.4.4 and Table 4.4.5 for the TEAEs associated with the study eye, and in Table 4.4.6 and 4.4.7 for the TEAEs associated with the non-study eye.

Details of AEs associated with both study and non-study eyes will be listed for each subject (Listing 7)

Details of AEs associated with early terminations will be listed for each subject (Listing 8). SAEs, including deaths, will be listed for each event (Listing 9).

Narratives will be presented for all deaths, non-fatal serious adverse events, and subjects withdrawn due to adverse events.

5.4 Best Corrected Visual Acuity

Descriptive and inferential statistics of BCVA will be presented by treatment for the pre-dose (screening) and post-dose assessments and their changes in post-dose assessment from pre-dose in Table 5.1.1 for the study eye.

Descriptive and inferential statistics of BCVA will be presented by treatment for the pre-dose (screening) and post-dose assessments and their changes in post-dose assessment from pre-dose in Table 5.2.1 for the non-study eye.

5.5 Biomicroscopy and External Eye Exam

Descriptive and inferential statistics of Biomicroscopy (Slit-Lamp) total severity score will be presented by treatment for the pre-dose (screening) and post-dose assessments and their changes in post-dose assessment from pre-dose in Table 6.1.1 for the study eye.

Descriptive and inferential statistics of Biomicroscopy (Slit-Lamp) total severity score will be presented by treatment for the pre-dose (screening) and post-dose assessments and their changes in post-dose assessment from pre-dose in Table 6.2.1 for the non-study eye.

5.6 Concomitant Medication

Number and percent of subjects who take pre-randomization concomitant medications will be reported in Table 7.1.1. Number and percent of subjects who take post-randomization concomitant medications will be reported by treatment in Table 7.1.2. Number and percent of subjects who take post-treatment concomitant medications will be reported by treatment in Table 7.1.3.

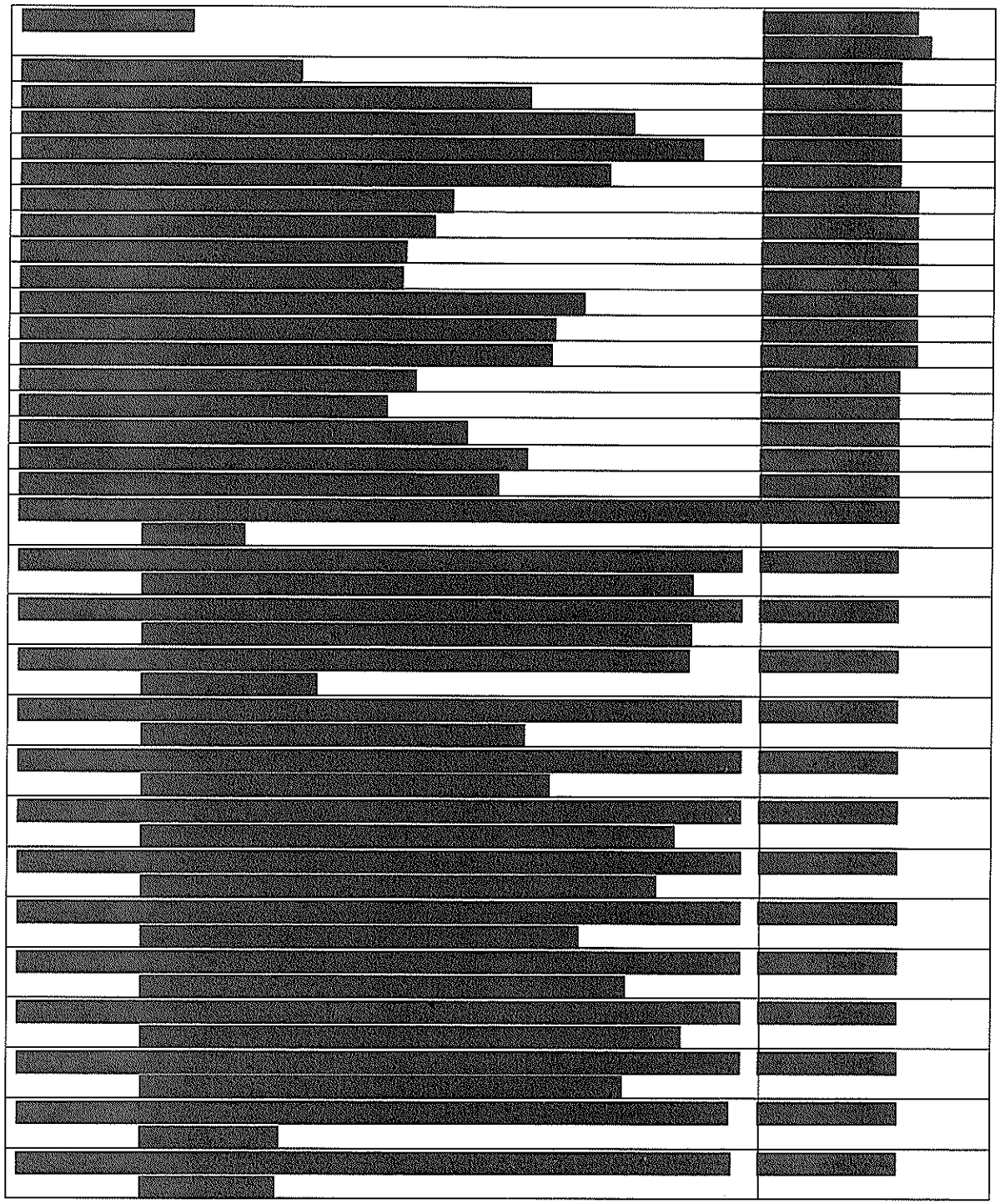
Number and percent of subjects who take post-randomization concomitant medications for eye treatment will be reported in Table 7.2.1 for study eye and in Table 7.2.2 for non-study eye.

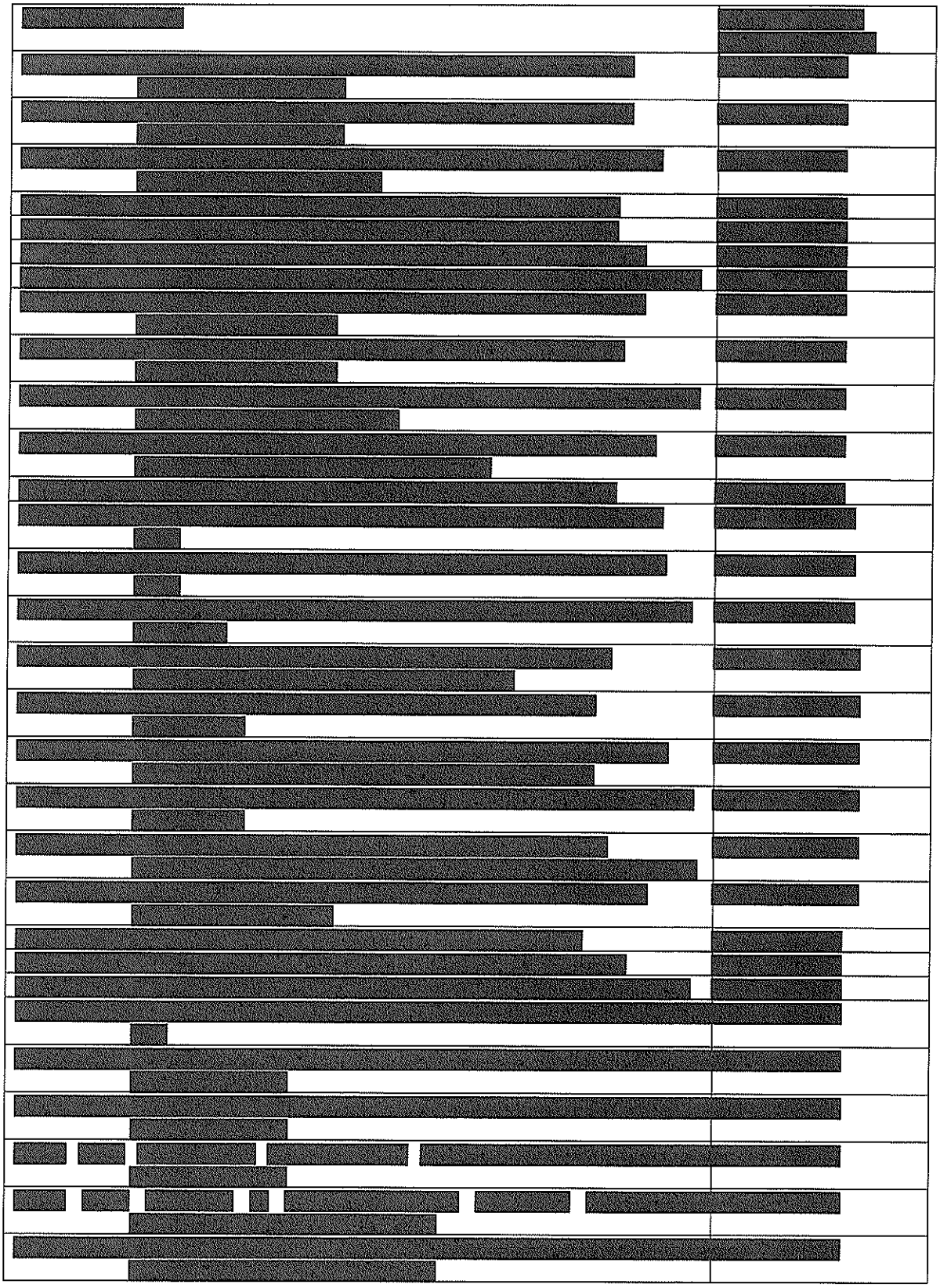
6 REFERENCES

Study Protocal No. AG920-CS302 Amendment 1.

7 List of Statistical Table Shells

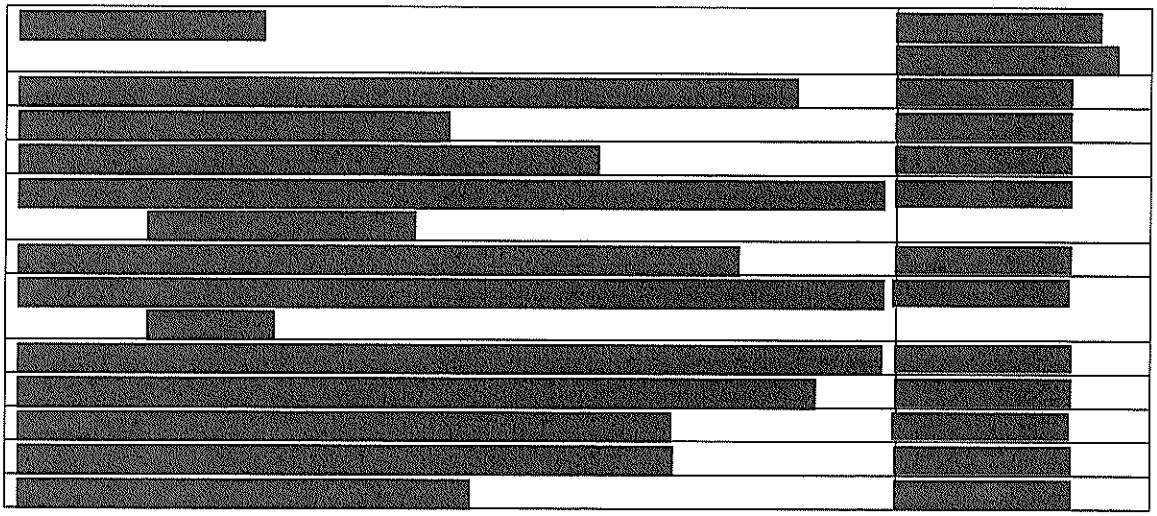
Statistical table shells are provided after the text portion. Table shells are presented only for those tables with a unique format. Tables with duplicate formats are indicated in the list of tables below. Final TFL sets will be numbered with the ICH E3 title as listed below.





8 List of Key Listing Shells

Listing shells are provided after the statistical table shells. Final TFL sets will be numbered with the ICH E3 title as listed below.



9 List of Figures

Treatment Histogram Plots or Line graphs for the following:

[redacted]

10 List of Other CRF Data Tabulations (ICH E3 Title for Section 16)

Final CRF data listings will be numbered with the ICH E3 title as listed below.

[redacted]

(Table and Listing Shells will be provided upon request.)