STATISTICAL ANALYSIS PLAN

Protocol No.:	**AG920-CS304**
Protocol Title:	**A Randomized, Single-Masked, Active-Controlled, Parallel-Group Evaluation of Safety and the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution (AG-920) in a Pediatric Population**
Drug Name:	**Articaine Sterile Topical Ophthalmic Solution (AG-920)**
Indication:	**Topical Ocular Anesthetics**
Sponsor:	**American Genomics, LLC** [redacted]
Version:	**Final (1.0)**
Amendment(s):	**None**
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Statistician	[redacted]

Approved by:	**Audrey Schupp**
Title	**American Genomics, LLC**
Signature:	Audrey Schupp Digitally signed by Audrey Schupp Date: 2022.06.03 15:31:18 -04'00'
Date:	

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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 in healthy pediatric subjects as compared to Proparacaine.

The secondary objective of this study is:

- To evaluate the safety and tolerability of AG-920 administered by topical ocular route in pediatric subjects.

This document describes the statistical analysis methods and data presentations for the data analyses of Protocol AG920-CS304. Related documents to this Statistical Analysis Plan (SAP) are the study protocol and electronic case report form (eCRF). Data analysis will be based on the final dataset(s) provided by Sponsor or designee Data Management group, which is InFocus Clinical Research.

[redacted]

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.

[redacted]

[redacted]

2 STUDY DESIGN

2.1 Rationale

The AG-920 topical drop would allow a technician to apply the topical solution to the eye, to allow the articaine to penetrate the pars plana sufficiently to permit the intravitreal injection without undue discomfort.

[redacted]

2.2 Description of Trial Design

This is a Phase 3, randomized, active-controlled, single-masked, parallel-group study of safety and anesthetic efficacy of AG-920 topical drop versus Proparacaine HCl Ophthalmic Solution (Proparacaine) in healthy pediatric subjects. The study will evaluate the safety and anesthetic efficacy following one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920), in comparison with Proparacaine (active-control). Eligible subjects will be randomized in a 1:1 ratio to receive a single dose of AG-920 or active-control into one eye, designated as subject's study eye. The application of one single dose of AG-920 or active control involves two drops of the study medication 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). The screening visit and baseline/assessment visit may be conducted on a single day.

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. Two to four minutes post the end of their dose (following second drop), subjects will undergo an eye exam for which the subject is seeing the ophthalmologist and the principal investigator (PI) will assess if they were able to conduct the eye exam or not. Dosing of the study medication and eye exam will be performed by the PI.

To assess the anesthetic effect of the study medication, PI will be queried if the subject has achieved adequate anesthesia for the PI to conduct the eye exam at 2 to 4 minutes post dose application by answering Yes or No. 15 to 60 minutes post dose application, the following eye exam or tests will be performed by the PI: visual acuity and external eye exam and, if needed, a slit lamp bio-microscopy test.

All subjects who are randomized and who receive a single dose of either AG-920 or Proparacaine HCl Ophthalmic Solution on Day 1 will be followed up with a phone call on Day 2-5 (1-4 days post treatment) 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. AG-920-CS304, Page 11).

The effect of anesthesia is assessed 2 to 4 minutes following the second drop of study medication by the PI on the study eye, prior to conducting the protocol-specified external eye exam or tests. The PI's response to whether adequate anesthesia was achieved to conduct the eye exam for which the subject is seeing the ophthalmologist will be recorded.

2.4 Randomization

As stated in the protocol, a 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 a single dose of AG-920 or Proparacaine according to the randomization schedule.

Study medication will be packaged with an investigational label. Marketed Proparacaine HCl Ophthalmic Solution will be "overwrapped" with an investigational label.

[redacted]

[redacted]

[redacted]

Each eligible subject will be assigned to one of the prepackaged packs available at a site. The study is single masked. Treatment assignments and study medication will be masked to the subjects and their parent/legal guardian only. The treatment randomization number or study medication kit number assigned to the subject will be recorded on the CRF at the site.

2.5 Sample Size Estimation

This study has an active-control treatment with the intention to compare the treatment of AG920 in reference to the active-control treatment of Proparacaine in healthy pediatric subjects in order to meet the regulatory requirements, rather than testing for superiority against the latter.

The study plans to randomize approximately 70 subjects in order to have at least 60 evaluable subjects, in a 1:1 allocation ratio for AG-920 and reference groups. [redacted]

2.6 Efficacy and Safety Measurements

In this study, primary efficacy endpoint will be assessed using the proportion of subjects with adequate local anesthetic effect assessed by the principal investigator (PI) so that the eye exam for which the subject is seeing the ophthalmologist can be conducted.

Two to four minutes following treatment of study medication, the PI will be asked "Did you achieve adequate anesthesia to conduct the eye exam?" The PI's response is recorded as "YES" for adequate anesthesia or "NO" for inadequate anesthesia.

Safety will be assessed through subject early terminations, adverse events, visual acuity, and external eye exam, and concomitant medications. Slit lamp bio-microscopy test will be conducted if needed (if an AE is suspected).

2.6.1 Primary efficacy measure

The primary efficacy endpoint for this study is the proportion of subjects with anesthetic effect assessed by the PI at 2-4 minutes post application of the dose.

2.6.2 Secondary efficacy measure

No secondary efficacy endpoint is defined in this study.

2.6.3 Safety measures

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

Age-appropriate visual acuity tests (including Teller acuity charts, Allen pictures, HOTV letters, Snellen acuity charts, or reaction to light) and external eye exam are performed pre- and post-dose at Visits 1 and 2. Abnormal visual acuity and eye exam findings will be recorded. Slit lamp bio-microscopy test will be conducted if needed.

2.6.4 Other measures

Concomitant medications associated with the treatment of study and fellow 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 anesthetic effect assessment will be assessed for each subject post dose. Missing values due to either invalid data or early termination will be considered as NO anesthetic effect for the subject.

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, unless stated otherwise.

2.9.1 Primary efficacy analysis

The primary efficacy endpoint for this study is the proportion of subjects with anesthetic effect that is adequate for eye exam as assessed by the PI at 2-4 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 and/or therapeutic equivalence in proportion of subjects with anesthetic effect at 2-4 minutes post dose between the active treatment group and active-control group.

In primary efficacy analysis, rather than to reject the null hypothesis when there is a difference ($P \leq 0.05$) between AG-920 and active-control treatments, this study is designed to accept the null hypothesis that there is no difference in anesthetic effect between AG-920 and active-control treatments ($P > 0.05$), indicating the therapeutic equivalence of AG-920 to Proparacaine without reference to a pre-defined non-inferiority margin.

To further measure the therapeutical equivalence of anesthetic effect of AG-920 to the active-control treatment, between-group difference and its 95% confidence interval (CI) as well as its 90% CI in the proportion of subjects with anesthetic effect (yes=1) vs. non-effect (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 conventional 90% CI of the between-group difference will be used to measure the extent of the equivalent margin or non-inferiority margin of anesthetic effect of AG-920 to Proparacaine. The conventional rule of the 90% CI of the between-group difference lying

within +/-20% of the reference treatment will be employed to claim the therapeutic equivalence or non-inferiority of AG-920 to Proparacaine.

The primary efficacy analysis will be performed for the ITT population, which will include all 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 effect for each study eye side.

Prior to the determination of the primary efficacy variable, handling of missing values that occur prior to eye exam 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

There are no secondary efficacy endpoints in this study.

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). AEs will be grouped into pre-treatment AEs, treatment-emergent AEs, and post-treatment AEs and will be reported separately, based upon the start date and time of the events compared to the start date and time of the treatment.

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

Frequency of 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.

Visual Acuity and External Eye Exam

Age-appropriate visual acuity tests and external eye exam will be summarized for abnormality by treatment for the screening (pre-dose) and Day 1 (post-dose), using frequency and percent. The analysis will be based on the safety population defined in Section 3.1.

Where applicable, for both study eye and fellow eye, abnormal findings of visual acuity and external eye exam at screening and post-dose will be analyzed, respectively, for differences between AG-920 and active-control groups, using a Chi-square test.

Bio-microscopy (Slit-Lamp)

Where available, total severity scores of bio-microscopy (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 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. Note that biomicroscopy is only performed if an Adverse Event is suspected by the Investigator. For those subjects with no bio-microscopy test performed on Day 1, the total severity scores will be set to zero for the purpose of the analysis.

For both study eye and fellow eye, the total severity score at post-dose will be analyzed for differences between AG-920 and active-control groups, using analysis of variance (ANOVA).

2.9.4 Other analysis

The concomitant medications, including those for study eye and fellow 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. fellow 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. fellow 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 or Randomized Population. The following subject populations are defined to assess the safety and efficacy of AG-920 in comparison with Proparacaine.

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 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 (2 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 treatment assignment is merged into the study database.

Per-Protocol (PP) Population

This population is defined as a 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 the investigator. 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.

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, treated, and completing 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 randomized into the study. The number of subjects treated with at least one drop of the dose 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 5-, 6 to 8, 9 to 10, and 11+), gender, race, and ethnicity. Demography will also be listed for all subjects enrolled (Listing 1).

3.4 Disease Characteristics and Prior Treatment

For the safety, ITT and PP populations, 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).

Visual acuity and other characteristics of the study and fellow 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 the ITT population (Table 1.5.1). Subjects who are randomized to receive single-masked treatment in the study and included in the ITT population but do not have two drops of IMP dosed and/or post-dose status of anesthetic effect 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. 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 (8- vs. 9+), 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 effect status, the primary efficacy measure of the ITT population in Table 1.6.1.

4.4 Baseline Measures

Medical history will be listed for individual subjects. Descriptive statistics of the study eye characteristics will be 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 effect assessed by the PI at 2 to 4 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 effect at 2 to 4 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 effect at 2 to 4 minutes post dose will be presented in Table 2.1.3.

The results of the proportion analysis on the number of subjects with anesthetic effect at 2 to 4 minutes post dose will be presented for the sub-populations of boys vs. girls in Tables 2.2.1 and 2.2.2; for 8 years or younger vs. 9 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., anesthetic effect) 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

There are no secondary efficacy endpoints defined in this study.

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 boys and girls, 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

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 AEs 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 fellow eye in Table 4.2.6.

Incidences of subjects reporting treatment-emergent AEs will also be tabulated by onset time (on-dosing day vs. post-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 the fellow 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 fellow eye.

Details of AEs associated with both study and fellow 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 Visual Acuity and External Eye Exam

Frequency and percent of visual acuity abnormality will be presented by treatment for the pre-dose (screening) and post-dose assessments in Table 5.1.1 for the study eye.

Frequency and percent of visual acuity abnormality will be presented by treatment for the pre-dose (screening) and post-dose assessments in Table 5.1.2 for the fellow eye.

Frequency and percent of eye exam abnormality will be presented by treatment for each category of iris, pupil, and lens at the pre-dose (screening) and post-dose assessments in Table 5.2.1 for the study eye.

Frequency and percent of eye exam abnormality will be presented by treatment for each category of iris, pupil, and lens at the pre-dose (screening) and post-dose assessments in Table 5.2.1 for the fellow eye.

5.5 Bio-microscopy

For those subjects with no bio-microscopy test performed on Day 1, the total severity scores will be set to zero for the purpose of the analysis.

Descriptive and inferential statistics of bio-microscopy (Slit-Lamp) total severity score will be presented by treatment for the post-dose assessments in Table 6.1.1 for the study eye.

Descriptive and inferential statistics of bio-microscopy (Slit-Lamp) total severity score will be presented by treatment for the post-dose assessments in Table 6.1.2 for the fellow 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 fellow eye.

6 REFERENCES

Study Protocal No. AG920-CS304.

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.

Table Title (SAP)	ICH E3 Title for Section 14 (TFL)
Table 1.1.1 Screen Summary	Table 14.1.1.1
Table 1.1.2 Enrollment Summary: Enrolled/Randomized population	Table 14.1.1.2
Table 1.1.3 Randomized Treatment Summary: Safety population	Table 14.1.1.3
Table 1.1.4 Randomized Complete Treatment Summary: ITT population	Table 14.1.1.4
Table 1.1.5 Randomized As-Treated Summary: PP population	Table 14.1.1.5
Table 1.2.1 Demography: Enrolled/Randomized population	Table 14.1.2.1.1
Table 1.2.2 Demography: Safety population	Table 14.1.2.1.2
Table 1.2.3 Demography: ITT population	Table 14.1.2.1.3
Table 1.2.4 Demography: PP population	Table 14.1.2.1.4
Table 1.3.1 Baseline Eye Characteristics: Safety population	Table 14.1.2.2.1
Table 1.3.2 Baseline Eye Characteristics: ITT population	Table 14.1.2.2.2
Table 1.3.3 Baseline Eye Characteristics: PP population	Table 14.1.2.2.3
Table 1.4.1 Disposition: Safety population	Table 14.1.3.1
Table 1.4.2 Disposition: ITT population	Table 14.1.3.2
Table 1.5.1 Protocol Deviations: ITT population	Table 14.1.6.1
Table 1.5.2 Treatment Compliance: Safety population	Table 14.1.6.2
Table 1.5.3 Treatment Compliance: ITT population	Table 14.1.6.3
Table 1.6.1 Summary of Missing Anesthetic Effect Status for the Study: ITT Population	Table 14.1.6.4
Table 2.1.1 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose (LOCF): ITT population	Table 14.2.1.1
Table 2.1.2 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose (Actual): PP population	Table 14.2.1.2
Table 2.1.3 By-Site Summary of Proportion of Subjects with Anesthetic Effect (LOCF)	Table 14.2.1.3
Table 2.2.1 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Boys	Table 14.2.2.1
Table 2.2.2 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Girls	Table 14.2.2.2
Table 2.2.3 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Subjects aged 8-	Table 14.2.2.3
Table 2.2.4 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Subjects aged 9+	Table 14.2.2.4
Table 2.2.5 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Caucasian	Table 14.2.2.5
Table 2.2.6 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Non-Caucasian	Table 14.2.2.6
Table 2.2.7 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Iris Color Dark Brown	Table 14.2.2.7
Table 2.2.8 Summary and Analysis of Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose: Iris Color Other	Table 14.2.2.8
Table 3.1.1 Treatment Exposure of All Applications: Safety population	Table 14.1.3.3
Table 4.1.1 Overall Summary of Adverse Events: Subjects Enrolled	Table 14.3.1.1

Table Title (SAP)	ICH E3 Title for Section 14 (TFL)
Table 4.1.2 Overall Summary of Adverse Events: Safety population	Table 14.3.1.2
Table 4.2.1 Incidence of Pre-Treatment AEs by Preferred Terminology	Table 14.3.1.3
Table 4.2.2 Incidence of Treatment-Emergent AEs by Preferred Terminology	Table 14.3.1.4
Table 4.2.3 Treatment-Emergent AEs with >5% Subjects Reporting by Preferred Terminology	Table 14.3.1.5
Table 4.2.4 Incidence of Subjects Reporting Post-Treatment AEs by Preferred Terminology	Table 14.3.1.6
Table 4.2.5 Incidence of Subjects Reporting Study-Eye Treatment-Emergent AEs by Preferred terminology	Table 14.3.1.7
Table 4.2.6 Incidence of Subjects Reporting Fellow-Eye Treatment-Emergent AEs by Preferred terminology	Table 14.3.1.8
Table 4.3.1 Incidence of Treatment-Emergent AEs and Onset Time	Table 14.3.1.9
Table 4.3.2 Incidence of Study-Eye Treatment-Emergent AEs and Onset Time	Table 14.3.1.10
Table 4.3.3 Incidence of Fellow-Eye Treatment-Emergent AEs and Onset Time	Table 14.3.1.11
Table 4.4.1 Treatment-Emergent AEs by Severity and Relationship to Study Treatment	Table 14.3.1.12
Table 4.4.2 Incidence of Treatment-Emergent AEs Associated with Discontinuations by Preferred Terminology	Table 14.3.2.3.1
Table 4.4.3 Incidence of Treatment-Emergent SAEs by Preferred Terminology	Table 14.3.2.2.1
Table 4.4.4 Incidence of Study-Eye Treatment-Emergent AEs Associated with Discontinuations and by Preferred Terminology	Table 14.3.2.3.2
Table 4.4.5 Incidence of Study-Eye Treatment-Emergent SAEs by Preferred Terminology	Table 14.3.2.2.2
Table 4.4.6 Incidence of Fellow-Eye Treatment-Emergent AEs Associated with Discontinuations and by Preferred Terminology	Table 14.3.2.3.3
Table 4.4.7 Incidence of Fellow-Eye Treatment-Emergent SAEs by Preferred Terminology	Table 14.3.2.2.3
Table 5.1.1 Summary of Visual Acuity Abnormalities: Study Eye	Table 14.3.4.1
Table 5.1.2 Summary of Visual Acuity Abnormalities: Fellow Eye	Table 14.3.4.2
Table 5.2.1 Summary of External Eye Exam Abnormalities: Study Eye	Table 14.3.5.1
Table 5.2.2 Summary of External Eye Exam Abnormalities: Fellow Eye	Table 14.3.5.2
Table 6.1.1 Summary and Analysis of Slit-Lamp Severity Scores: Study Eye	Table 14.3.6.1
Table 6.1.2 Summary and Analysis of Slit-Lamp Severity Scores: Fellow Eye	Table 14.3.6.2
Table 7.1.1 Summary of Pre-Randomization Concomitant Medication Use: Safety population	Table 14.1.5.1
Table 7.1.2 Summary of Post-Randomization Concomitant Medication Use: Safety population	Table 14.1.5.2
Table 7.1.3 Summary of Post-Treatment Concomitant Medication Use: Safety population	Table 14.1.5.3
Table 7.2.1 Summary of Pre-Randomization Study-Eye Concomitant Medication Use: Safety population	Table 14.1.5.4
Table 7.2.2 Summary of Pre-Randomization Fellow-Eye Concomitant Medication Use: Safety population	Table 14.1.5.5
Table 7.3.1 Summary of Post-Randomization Study-Eye Concomitant Medication Use: Safety population	Table 14.1.5.6
Table 7.3.2 Summary of Post-Randomization Fellow-Eye Concomitant Medication Use: Safety population	Table 14.1.5.7

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.

Listing Title (SAP)	ICH E3 Title for Section 14 (TFL)
Listing 1 Demography and Study Eye Baseline Characteristics	Listing 14.1.2.1
Listing 2 Early Termination Details	Listing 14.1.3.1
Listing 3 Randomization and Exposure Details	Listing 14.1.3.2
Listing 4 Subjects Randomized and Dosed But Have No Post-Dose Anesthetic Effect Data	Listing 14.1.1.2
Listing 5 Subjects Included in the ITT and PP Populations	Listing 14.1.1.1
Listing 6 ITT Population Efficacy Data of Study Eye and Associated Measures	Listing 14.2.1.1
Listing 7 Adverse Events Associated with Study and Fellow Eyes	Listing 14.3.1.1
Listing 8 Adverse Events Associated with Study Discontinuation	Listing 14.3.2.3
Listing 9 Serious Adverse Events (Including Deaths)	Listing 14.3.2.2
Listing 10 Abnormal Medical History	Listing 14.1.4.1

9 List of Figures

Treatment Histogram Plots or Line graphs for the following:
Proportion of Subjects with Anesthetic Effect at 2-4 Minutes Post Dose

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.

Data 1.1 (Listing 16.2.1.1) Inclusion/Exclusion Criteria and Eligibility Check
Data 2.1 (Listing 16.2.4.1) Demography
Data 2.2 (Listing 16.2.4.2) Medical History
Data 2.3 (Listing 16.2.2.1) Protocol Deviations
Data 3.1 (Listing 16.2.5.1) Dose Administration and Randomization
Data 4.1 (Listing 16.2.6.2) Visual Acuity
Data 4.2 (Listing 16.2.6.3) Bio-microscopy and External Eye Exam
Data 5.1 (Listing 16.2.7.1) Adverse Events
Data 6.1 (Listing 16.2.4.3) Concomitant Medication
Data 7.1 (Listing 16.2.1.2) Disposition (End of Study Information)
Data 8.1 (Listing 16.2.6.1) PI's Anesthetic Effect Assessment

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