STATISTICAL ANALYSIS PLAN

Protocol No.:	**AG920-CS303**
Protocol Title:	**A Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Evaluation of the Ocular Safety of Articaine Sterile Topical Ophthalmic Solution**
Drug Name:	**[redacted] Sterile Topical Ophthalmic Solution (AG-920)**
Indication:	**Topical Ocular Anesthetics**
Sponsor:	**American Genomics, LLC** **[redacted]** **Phone (848) 444-0665**
Version:	**2.0**
Amendment(s):	**None**
Date:	**May 16, 2023**
Statistician	**[redacted]**

Approved by:	**[redacted]**
Title	**American Genomics, LLC**
Signature:	DocuSigned by: Gary Novack
Date:	Signer Name: Gary Novack Signing Reason: I approve this document Signing Time: 17-May-2023 | 12:40:06 PM PDT B7FA616659E4409EAE61D0329FA5D9F1 17-May-2023

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	Intraocular 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
SM	Specular Microscopy
TEAE	Treatment Emergent Adverse Event
WHODrug	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Trial Objectives

The primary objective of this study is to evaluate the ocular safety of a single dose of AG-920 after topical ocular administration (2 drops 30 seconds apart), with reference to placebo (vehicle), including visual acuity, intraocular pressure, biomicroscopy, and adverse events.

The secondary objective of this study is to evaluate a subset of subjects (approximately 12 subjects receiving AG-920 and 6 subjects receiving placebo) for the effect of AG-920 on corneal endothelial cell count (ECC) using specular microscopy.

This document describes the statistical analysis methods and data presentations for the data analyses of Protocol AG920-CS303. 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 [redacted].

The study database(s) includes all CRF-based clinical data. The original EDC database constructed by [redacted] will be converted into a CDISC SDTM version 3.1 and/or 3.1.1 database. [redacted] will provide the treatment code for treatment unmasking 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 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 product is developed for physicians to use in assisting the intravitreal injection.

For that purpose, [redacted] 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 [redacted] (coded named AG-920) for topical ocular use to induce local anesthesia for intravitreal injecti [redacted] .

In summary, AG-920 is a sterile topical ophthalmic solution made from [redacted] 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

Refer to Section 1.3 Design Justification of the study protocol (see Protocol No. AG-920-CS303).

2.2 Description of Trial Design

This is a Phase 3, randomized, placebo-controlled, double-masked, parallel-group design study of AG-920 topically administered versus placebo (vehicle) in healthy subjects. The study will evaluate the safety following one dose of [redacted] Sterile Topical Ophthalmic Solution (AG-920) in reference to placebo. Eligible subjects will be randomized in a 2:1 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 consists of 2 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 to Day 0 (Visit 1), one baseline/assessment visit on Day 1 (Visit 2), and one follow-up phone assessment on Day 2-5 (Phone Follow-Up). In addition, approximately 18 subjects from one site will be asked to return to the clinic for an additional visit (Visit 3) 90 days following Visit 2 to undergo specular microscopy and other safety evaluations.

Following the screening visit, eligible subjects will be randomly assigned a study eye (right eye=OD or left eye=OS) and study medication (active or placebo). Following dose administration, adverse events will be monitored. Safety assessments of BCVA, IOP, biomicroscopy, and external eye exam, will be performed on both eyes 60 to 90 minutes post dosing.

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. A subset of subjects will return to the clinic for Visit 3, which is 90 days following Visit 2, for specular microscopy with all of the safety assessments.

2.3 Schedule of Assessments

The complete schedule of assessments for this study is shown in Table 1 of the study protocol (see Protocol No. AG920-CS303 version 1.0, Page 11).

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 2:1 allocation ratio to receive AG-920 or matching placebo. Subjects will also be randomized to study eye (OD or OS).

Study medication will be packaged and labeled identically in order to maintain the integrity of the double mask. The appearance of the blow fill seal vials for the AG 920 and matching placebo dosage forms are indistinguishable.

The container-closure system to be used for the AG-920 and Placebo in this clinical study is a 0.5 mL low-density polyethylene (LDPE) resin blow fill seal vial. There are 5 vials inside an aluminum foil pouch. [redacted]

Each eligible subject will be assigned to one of the prepackaged cartons available at a site. The kit number associated with the prepackaged carton 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 enroll a total of 240 subjects in a 2:1 ratio of 160 subjects for AG-920 treatment and 80 subjects for placebo. This sample size is driven by the minimal safety exposure required for a regulatory marketing application.

2.6 Efficacy and Safety Measurements

Since this study is primarily a Phase 3 safety study, no efficacy assessments will be performed or defined.

Safety will be assessed through subject early terminations, adverse events, and changes in best corrected visual acuity (BCVA), IOP, biomicroscopy and external eye exam, heart rate and blood pressure, and concomitant medications. Changes in corneal health will be assessed through specular microscopy in a subset of patients.

2.6.1 Primary efficacy measure

Not applicable.

2.6.2 Secondary efficacy measure

Not applicable.

2.6.3 Safety measures

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

Best corrected visual acuity (BCVA), IOP, and biomicroscopy (slit lamp) and external eye exam are performed at each visit, including at Visit 3 for the subset of subjects who participate in the specular microscopy test. Specular microscopy will be collected for the subset of subjects at Screening and at Visit 3.

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 the 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

There are no efficacy parameters in this study.

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 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.

2.9.1 Primary efficacy analysis

Not applicable.

2.9.2 Secondary efficacy analysis

Not applicable.

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 by gender.

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 date, 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 AE, treatment-emergent AE, and post-treatment AE and will be reported separately, based upon the start date and time of the events and 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.

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 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 fellow 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. Any BCVA changes of >3 lines from baseline will be flagged.

Intraocular Pressure (IOP)

Mean or median IOP values observed at a time point will be summarized in mmHg units by treatment for the screening (pre-dose) and Day 1 (post-dose), using 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. Subjects who participated in the specular microscopy subset will also have IOP measured at Visit 3.

IOP measurements can be performed using a Tonopen® or Goldmann Tonometer. If a Goldmann tonometer is used, then two consecutive IOP measurements of each eye will be obtained. If the two measurements differ by more than 2 mm Hg, a third measurement should be obtained. IOP will be analyzed as the mean of two measurements or as the median of three measurements.

For both study eye and fellow eye, changes in IOP 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 and analyzed individually by treatment for the screening (pre-dose) and Day 1 (post-dose), and Visit 3 (for specular microscopy subjects) using 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 fellow 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.

Specular Microscopy

Endothelial cell count (and corneal morphology) will be summarized by continuous summaries. Mean and mean changes in data from the reading center from specular microscopy at baseline and 90 days post dosing from screening will be reported by treatment groups. The imaging parameters of Cell Density (CD), Coefficient of Variation (CV), Hexagonality (HEX) and Average Number of Cells (NUM) will all be reported variables from the central reading center.

2.9.4 Other analysis

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). 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 as defined in the study protocol. The following subject populations are defined to assess the safety of AG-920 in comparison with placebo.

Safety Population

The safety population is defined as all subjects were randomized and who have received at least one drop of the dose (2 drops) of the study medication. The safety population will be utilized as primary population 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. 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.

The ITT population is the secondary population for safety evaluation in this study if the ITT population is not identical to the safety population.

Specular Microscopy (SM) Population

The SM population includes those subjects who are randomized and treated and have had the specular microscopy findings for at least one visit.

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 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 subset population of subjects tested for specular microscopy (i.e., the SM population) will be summarized for each treatment group and overall (Table 1.1.5).

3.3 Population Demography

For subjects enrolled/randomized, safety, ITT, and SM 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 calculated age in years (continuous and categorical 18 to 29, 30 to 39, 40 to 49, 50 to 64, and 65+), gender, race, and ethnicity. Demography will also be listed for all subjects enrolled (Listing 1). Since this study collected only subject's birth year, rather than birth date, subject's age will be calculated as informed consent year minus birth year.

3.4 Disease Characteristics and Prior Treatment

For the safety, ITT and SM 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).

BCVA 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 (Listing 10) and CRF data tabulation. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

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 safety population (Table 1.5.1). Subjects who are randomized to receive double-masked treatment in the study and included in the safety population, but do not have two drops of the dose will be listed for subjects randomized (Listing 4).

4 EFFICACY EVALUATION

Not applicable.

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. Subjects included in the safety population will be listed in Listing 5.

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 be 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 individual treatment group 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-treatment day vs. off-treatment 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 6)

Details of AEs associated with early terminations will be listed for each subject (Listing 7). SAEs, including deaths, will be listed (Listing 8).

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

Female pregnancy results will be listed (Listing 9).

5.4 Best Corrected Visual Acuity

Visual Acuity data will be summarized at each time point using both continuous summaries (Logarithmic Minimum Angle of Resolution, logMAR), including change from baseline, and discrete summaries, including change from baseline in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline.

Descriptive and inferential statistics of BCVA in logMAR will be presented by treatment for the pre-dose (screening) and post-dose assessments and changes in post-dose assessment from pre-dose in Table 5.1.1 for the study eye and in Table 5.1.2 for the fellow eye.

5.5 Intraocular Pressure

Descriptive and inferential statistics of IOP will be presented by treatment for the pre-dose (screening) and post-dose assessments and changes in post-dose assessment from pre-dose in Table 5.2.1 for the study eye and in Table 5.2.2 for the fellow eye.

5.6 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 and in Table 6.1.2 for the fellow eye.

5.7 Specular Microscopy

Mean and mean changes in data from the reading center from specular microscopy at baseline and 90 days post dosing from screening will be reported by treatment groups in Table 6.2.1 for the study eye and in Table 6.2.2 for the fellow eye.

5.8 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 pre-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 pre-randomization concomitant medications for eye treatment will be reported in Table 7.2.1 for study eye and in Table 7.2.2 for the fellow eye.

Number and percent of subjects who take post-randomization concomitant medications for eye treatment will be reported in Table 7.3.1 for study eye and in Table 7.3.2 for the fellow eye.

6 REFERENCES

Study Protocol No. AG920-CS303 version 1.0.

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 Screening Summary	Table 14.1.1.1
Table 1.1.2 Enrollment Summary: 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 Specular Microscopy (SM) Summary: SM population	Table 14.1.1.5
Table 1.2.1 Demography: 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: SM 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: SM 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: Safety population	Table 14.1.6.1
Table 3.1.1 Treatment Exposure of All Applications (including active and placebo): Safety population	Table 14.1.3.3
Table 4.1.1 Overall Summary of Adverse Events: Randomized population	Table 14.3.1.1
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 Title (SAP)	**ICH E3 Title for Section 14 (TFL)**
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 and Analysis of BCVA Scores: Study Eye	Table 14.3.4.1
Table 5.1.2 Summary and Analysis of BCVA Scores: Fellow Eye	Table 14.3.4.2
Table 5.2.1 Summary and Analysis of IOP Measures: Study Eye	Table 14.3.4.3
Table 5.2.2 Summary and Analysis of IOP Measures: Fellow Eye	Table 14.3.4.4
Table 6.1.1 Summary and Analysis of Biomicroscopy (slit lamp) Severity Scores: Study Eye	Table 14.3.5.1
Table 6.1.2 Summary and Analysis of Biomicroscopy (slit lamp) Severity Scores: Fellow Eye	Table 14.3.5.2
Table 6.2.1 Summary of Specular Microscopy Test: Study Eye	Table 14.3.5.3
Table 6.2.2 Summary of Specular Microscopy Test: Fellow Eye	Table 14.3.5.4
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 and Fellow 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 Complete Dose of Two Drops	Listing 14.1.1.2
Listing 5 Subjects Included in the Safety, ITT, and SM Populations	Listing 14.1.1.1
Listing 6 Adverse Events Associated with Study and Fellow Eyes	Listing 14.3.1.1
Listing 7 Adverse Events Associated with Early Termination	Listing 14.3.2.3
Listing 8 Serious Adverse Events (Including Deaths)	Listing 14.3.2.2
Listing 9 Female Subjects' Pregnancy Test Results	Listing 14.3.6.1
Listing 10 Abnormal Medical History	Listing 14.1.4.1

9 List of Figures

Treatment Histogram Plots or Line graphs for the following:
None

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) BCVA
Data 4.2 (Listing 16.2.6.3) Biomicroscopy and External Eye Exam
Data 4.3 (Listing 16.2.6.4) IOP
Data 4.4 (Listing 16.2.6.5) Specular Microscopy
Data 5.1 (Listing 16.2.7.1) Adverse Events
Data 6.1 (Listing 16.2.4.3) Concomitant Medication
Data 7.1 (Listing 16.2.8.1) Pregnancy Data
Data 8.1 (Listing 16.2.1.2) Disposition (End of Study Information)

Meeting Minutes of the Technical Review Meeting held on 30 May 2023

Table of Contents

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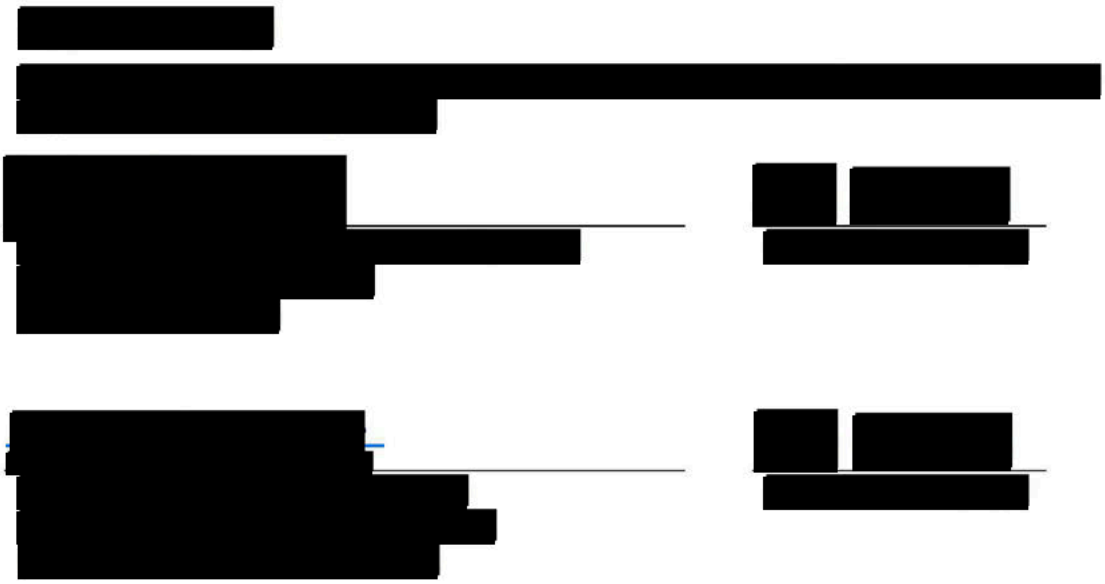

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Appendix 2 – SAP Version Note to File

Clarification Note to File explaining why SAP is Version 2 and there is no Version 1.0.

INFOCUS CLINICAL RESEARCH

MEMO

Date: 31-May-2023

To: AG-920-CS303 Trial Master File

From: Ken Milstead, VP Biostatistics and Data Management

RE: AG-920-CS303 SAP Versioning

Version 1.0 of the Statistical Analysis Plan for AG920-CS303 was drafted but never finalized.

Version 2.0 was the first implemented version and was dated 16-MAY-2023.

DocuSigned by:
Kenneth Milstead
Signer Name: Kenneth Milstead
Signing Reason: I am the author of this document
Signing Time: 31-May-2023 | 11:38:11 PM PDT
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