CONFIDENTIAL

American Genomics, LLC

Clinical Study Protocol

AG-920-CS301

A Randomized, Double-Masked, Vehicle-Controlled, Parallel Evaluation of the Local Anesthetic Effect of [redacted] Sterile Topical Ophthalmic Solution

Protocol Number:	AG-920-CS301
IND Number:	IND # 145052
Investigational Product:	[redacted] Sterile Topical Ophthalmic Solution (AG-920)
Indication:	Topical anesthesia for intravitreal injection
Phase:	Phase 3
Sponsor:	[redacted]
Medical Monitor	[redacted] C.S.
Protocol Date:	15 September 2020
Protocol Version:	Amendment 1
Replaces:	Version 1.0, 9 June 2020

Contact Information and Protocol Authorization

Clinical Study Protocol

AG-920-CS301

Phase 3

Protocol Title: A Randomized, Double-Masked, Vehicle-Controlled, Parallel Evaluation of the Local Anesthetic Effect of [redacted] Sterile Topical Ophthalmic Solution

Protocol Number: AG-920-CS301 – Amendment 1

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory:

[redacted]

[redacted]

Signature:

09/16/2020

Date:

Protocol Amendment #1

15 September 2020

This study is ongoing with subjects randomized, treated, and completed. Enrollment is continuing. The changes in this amendment have no impact on subject safety, consent form, or electronic case report forms.

[redacted] The following edits were made with Amendment #1.

1. "Patient" was changed to "Subject" (Throughout)
2. "Vehicle" and "Placebo" were used as implied synonyms. This was clarified.
3. Table 1: Randomization was inadvertently listed as occurring at Visit 1 (Screening). It was moved to Visit 2 (Screening and Baseline).
4. IMP Treatment (Section 6.4.2):
    a. Clarified with the addition of the underlined text: "Administer a second drop of IMP to the same study eye <u>from the same vial</u>"
    b. Added this sentence: "Return used vial to foil pouch and retain used vial and remaining 4 unused vials for accountability"
5. Follow-up Phone Call (Day 2-5): Section 6.5: Changed for consistency and clarity:
    a. Section 3.4: Changed for consistency and clarity:
    From: "…a Follow-up Phone Call 2-5 days following Visit 2."
    To: "…a Follow-up Phone Call 1-4 days following Visit 2 (Day 2-5)."
    b. Section 6.5: Changed for consistency and clarity:
    From: "Subjects will receive a phone call from site staff 2-5 days following treatment with IMP. Patients will be asked about…"
    To: "Subjects will receive a phone call from site staff between Days 2-5, which is 1-4 days (24-96 hours post-dose) following treatment with IMP."
6. Statistics (Section 9):
    a. There was an error in numbering of sub-headings which was corrected.
    b. Per FDA comments, this section was changed in several places to reflect that the primary population for efficacy was changed FROM Per-protocol TO Intent-to-Treat.
    c. Additional changes were a clarification of the definition of population, an expansion on the description for accounting for missing, unused, or spurious data (Sections 9.2, 9.3, 9.4.3, 9.4.6, 9.4.8, and 9.5).
7. Typographical corrections including: "Two-tailed" was changed to "Two-sided" (several sections)

Abbreviations and Terms

Abbreviation	Full text
AE	Adverse event
AG-920	[redacted] sterile topical ophthalmic solution
BCVA	Best corrected visual acuity
BOCF	Baseline observation carried forward
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCl	Hydrochloride
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithmic Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
OD	Oculus dexter (Right eye)
OTC	Over the Counter
OS	Oculus sinister (Left eye)
PP	Per protocol
PPE	Personal protective equipment
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System/Order/Class
SOP	Standard Operating Procedures
TEAE	Treatment emergent adverse event
UPT	Urine Pregnancy Test
US	United States
VA	Visual acuity

Summary

Study Number	AG-920-CS301
Clinical Phase:	Phase 3
Type of study	Efficacy and Safety
Name of Investigational product:	[redacted] Sterile Topical Ophthalmic Solution (AG-920)
Duration of treatment per subject	1 day
Objectives and Endpoints:	**Primary Objective** / **Primary Endpoints** To evaluate anesthetic efficacy of AG-920 / The proportion of subjects with no pain at 5 minutes. **Secondary Objectives** / **Secondary Endpoints** To evaluate how long it takes one dose of AG-920 to anesthetize the eye / Mean time to no pain score (onset) To evaluate how long one dose of AG-920 anesthetizes the eye / Mean duration of anesthetic effect To evaluate the safety and tolerability of AG-920 / Visual acuity, biomicroscopy, AEs, TEAEs, SAEs, withdrawals due to TEAEs
Subject Population:	Healthy volunteers Exclusion criteria may be found in Section 4.2.
Design:	Randomized, placebo (vehicle) controlled, double-masked, parallel.
Visit Schedule:	Study visits will consist of a Screening Visit, a dosing and anesthesia testing visit, and a follow-up visit (by telephone)
Number of Investigational Sites:	1-2 US sites
Estimated Total Sample Size:	120/study; ~60/treatment group
Plan for Data Analysis:	With 60 subjects per treatment group and assuming 15% response in the vehicle group, this study will have 88% power to detect a treatment effect of at least 25% (α=0.05, two-sided).
Investigational/Comparator Product(s), Dose and Mode of Administration	Subjects will receive a single dose of IMP in one (study) eye. The IMP will be randomized as either AG-920 or Placebo. The study eye will be randomized as either right eye (OD) or left eye (OS). The single dose will be administered by the clinic staff as two drops in study eye 30 seconds apart.

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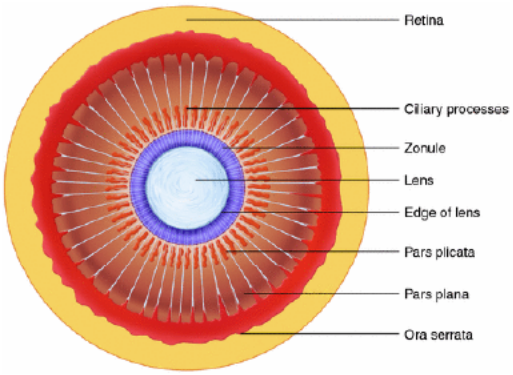
1 INTRODUCTION

American Genomics is evaluating the formulation of [redacted] an approved local anesthetic, for topical ocular use to provide local anesthesia for intravitreal injections. The Sponsor intends to develop [redacted] Sterile Topical Ophthalmic Solution (AG-920) for topical ocular use to induce local anesthesia for intravitreal injection. The systemic exposure to [redacted] after topical ocular instillation is not expected to be greater than that with [redacted] use of the marketed product, [redacted]® (Package Insert).

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 (Figure 1).

Figure 1: Human Ocular Structure (coronal view)



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. The purpose of the AG-920 topical drop would be to allow a technician to apply the topical solution to the eye, allow the [redacted] to penetrate the pars plana sufficiently to permit the intravitreal injection without undue discomfort. [redacted] was selected for this procedure based upon its clinical use in [redacted] procedures, which suggest it penetrates soft tissue and bone.

1.1 Findings from nonclinical and clinical studies

Detailed information on nonclinical and clinical studies with [redacted] including AG-920 is provided in the Investigator's Brochure (2020).

1.2 Potential Risks and benefits to human subjects

Minimal risks are expected with AG-920. The most common risks associated with [redacted] ® ([redacted]) are headache and pain. The incidence of these adverse events occur in 4% and 13% of patients respectively. These adverse events of [redacted] are following [redacted] injection, where AG-920 is applied topically to the eye ([redacted] Package Insert).

Expected risks for subjects may include a temporary mild to moderate stinging or burning sensation upon instillation of the investigational medical product (IMP). Temporary mild hyperemia may also occur following instillation. For any additional information on AG-920 use, please refer to the Investigator's Brochure.

As this study is to be conducted in healthy subjects, there is no anticipated benefit other than the possibility that a subject's participation in the present study may help others in the future to have more options for local anesthesia before ophthalmic procedures.

Adverse events (AEs) not reported in previous clinical trials but present among subjects in this clinical trial will be communicated to Investigators and to ethics committees or Institutional Review Board (IRBs) in accordance with local regulations.

1.3 Design justification

Route of administration, dosage, dosage regimen, and treatment period(s)

The dose selected for this study is based clinical experience with this molecule by another route ([redacted] or from outside the United States, and preclinical safety studies. For more details, please refer to the Investigator's Brochure.

The selected dose of the investigational medicinal product AG-920 is [redacted] Sterile Topical Ophthalmic Solution which contains [redacted]

The intended route of administration for AG-920 is topical ocular in this study. Each dose will consist of two drops 30 seconds apart in the study eye. This study consists of a single treatment and subjects will be randomized 1:1 to AG-920 or Placebo.

2 OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**
To evaluate anesthetic efficacy of AG-920	The proportion of subjects with no pain at 5 minutes.
Secondary Objectives	**Secondary Endpoints**
To evaluate how long it takes one dose of AG-920 to anesthetize the eye	Mean time to no pain score (onset)
To evaluate how long one dose of AG-920 anesthetizes the eye	Mean duration of anesthetic effect
To evaluate the safety and tolerability of AG-920	Visual acuity, biomicroscopy, AEs, TEAEs, SAEs, withdrawals due to TEAEs

3 STUDY DESIGN

Randomized, placebo-controlled, double-masked, parallel.

3.1 Description and schedule of visits and procedures

This is a Phase 3, randomized, placebo-controlled, double-masked, parallel design study in healthy subjects performed in the US. It is designed to evaluate the safety and anesthetic efficacy of one dose of [redacted] Sterile Topical Ophthalmic Solution (AG-920). In this study, subjects who provide informed consent and fulfill all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive a single dose of AG-920 or identical looking placebo into one (study) eye (2 drops 30 seconds apart). Subjects will undergo a conjunctival pinch procedure and the pain associated with the pinch rated. IMP dosing and conjunctival pinch procedure will be performed by the study staff.

A schedule of assessments, including allowable visit windows, is displayed in Table 1.

Table 1: Schedule of Visits and Procedures

	Visit 1	Visit 2						Phone Follow-Up
	Screening Day -2 to 0/1 Pre-dose	Dose		[redacted]			5 m	15-60 m post last pinch	Day 2-5
Procedures		0 sec	30 sec						
Written Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Demographics, Systemic and Ocular Medical History	X								
Concomitant Medication Query	X	X	X						X
OTC Tear Tolerability	X								
BCVA	X							X	
Urine Pregnancy Test (if applicable)	X								
Biomicroscopy and External Eye Exam	X							X	
IOP Measurement	X								
Randomization		X							
IMP Administration[2]		X	X						
Conjunctival pinch[3]				X	X	X	X		
Assessment of Pinch Pain				X	X	X	X		
Adverse Event Assessment		X	X	X	X	X	X	X	X

BCVA = Best corrected visual acuity, IOP = Intraocular pressure, OTC = over the counter, IMP = investigational medicinal product.
See Section 6.4.3 for Windows in Day 1 timing.

[1] Screening may occur on the same day as Visit 2 (≥ 60 minutes) or up to 3 days previously. If on separate days, inclusion/exclusion criteria should be re-evaluated prior to dosing subject to ensure subject still qualifies.
[2] One dose is 2 drops. First drop administered at 0 seconds and the second drop administered at 30 seconds (2 drops 30 seconds apart).
[3] [redacted]

3.2 Measures taken to minimize/avoid bias

The Investigator(s), Sponsor, and the subject will be masked to treatment assignment throughout the conduct of the study. Exceptions to this are limited to one statistician at the Contract Research Organization (CRO) who will prepare the randomization code, and three people at the Sponsor who will review the batch records and release product. None of these masked persons will be involved in the day to day execution of the study. The masking will be broken after database lock.

3.3 Study medications

[redacted] Sterile Topical Ophthalmic Solution (AG-920) is a sterile, isotonic, non-preserved aqueous solution containing the active ingredient [redacted] HCl 8%, Boric Acid, Mannitol, Sodium Acetate Trihydrate, Glacial Acetic Acid, and Edetate Disodium Dihydrate. The product formulation is adjusted to pH 4.5 to 5.0.

Placebo ophthalmic solution is identical to the active product, with the exception of the active ingredient.

Figure 2: Investigational Medicinal Product

	INVESTIGATIONAL PRODUCT	
PRODUCT NAME	[redacted] Sterile Topical Ophthalmic Solution (AG-920)	Placebo
ACTIVE INGREDIENT	[redacted] Hydrochloride	--
INACTIVE INGREDIENTS	Boric Acid Mannitol Sodium Acetate Trihydrate Glacial Acetic Acid Edetate Disodium Dihydrate Water for Injection	Boric Acid Mannitol Sodium Acetate Trihydrate Glacial Acetic Acid Edetate Disodium Dihydrate Water for Injection
UNIT DOSE	0.5 mL blow fill seal vial	0.5 mL blow fill seal vial
ROUTE OF ADMINISTRATION	Topical ocular	Topical ocular
DOSING REGIMEN	2 drops 30 seconds apart from a single vial into study eye	2 drops 30 seconds apart from a single vial into study eye
STORAGE REQUIREMENTS	Store at Room Temperature (15-25°C or 59-77°F)	Store at Room Temperature (15-25°C or 59-77°F)

3.3.1 **IMP Packaging and labeling**

Investigational Medical Product (IMP) 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. Each foil pouch will be labeled with an investigational label with the following minimal information: the study number, kit number, and storage statement, including a statement "Caution – New Drug – Limited by Federal (US) Law to Investigational Use" or equivalent. Each foil pouch will be individually placed into a single-unit carton and a similar investigational label will be applied to the carton. The IMP for each individual treatment assignment will be packaged into identical subject kits.

3.3.2 Storage of study medication

The IMP should be stored at room temperature (15-25°C or 59-77°F). Do not freeze the product. Prior to dispensing to the subject, all investigational material must be stored in a secure location with strictly limited access documented by signature of authorized persons who may dispense investigational materials.

3.3.3 Study medication accountability

Accountability of IMP kits will be conducted by a member of the site and verified by a study monitor. Accountability will be ascertained by performing reconciliation between the number of kits sent to the site and the amount used and unused at the time of reconciliation. Site staff will be queried about any discrepancies.

IMP kit shipment records will be verified, and accountability performed by comparing the shipment inventory sheet to the actual quantity of kits received at the site. In addition, receipt of kits will be confirmed by the study monitor. Accurate records of receipt and disposition of the kits (e.g., dates, quantity, subject number, kits used, kits unused, etc.) must be maintained by the Investigator or his/her designee.

At the end of the study and after the monitor has verified kit accountability, all IMP is to be returned to American Genomics (or designee) or destroyed at the site and documented per the site's standard process.

3.4 Expected duration of subject participation

Each subject is planned to participate in the study for up to 2 Visits (Screening and Treatment/Anesthesia testing) and a Follow-up Phone Call 1-4 days following Visit 2 (Day 2-5).

3.5 Randomization and procedure for breaking the code

A randomization code for allocating the treatments will be prepared by an independent biostatistician, who is not involved in the day-to-day conduct of the study. Subjects will be randomized in a 1:1 ratio to receive AG-920 or Placebo.

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.

If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator should contact the Sponsor Safety Officer or designee. Only after consultation with the Sponsor Safety Officer will a decision be made as to whether or not the treatment for the subject should be unmasked. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on the remaining subjects intact.

If there is an emergency situation in which treatment of an adverse event requires immediate decoding, and the Investigator is unable to contact the Sponsor Safety Officer, the Investigator should treat the subject as if they received active treatment (AG-920) and not placebo. The Investigator should contact the Sponsor immediately and document the AE.

3.6 Participant and Study completion

3.6.1 **Completed subject**

A completed subject is defined as one who completes all Visits (1 and 2) and the Follow Up Phone call.

3.6.2 **Non-completing subject/Subject Withdrawal**

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator and/or the Sponsor Safety Officer. Any subject may decide to voluntarily withdraw from the study at any time without prejudice and the reason will be documented. In the event that discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments. Every attempt should be made to keep subjects in the study and to perform the required study procedures, but if this is not possible, the subject may be withdrawn.

All reasonable efforts should be made to contact the subject who is lost to follow-up. These efforts must be documented in the subject's file.

Subjects may be withdrawn from the study for any reason at any time, including but not limited to the following reasons:

- Subject request
- Use of prohibited concomitant medication/therapy
- Lost to follow-up
- Occurrence of AEs that are not compatible with the continuation of the subject in the study, in the Investigator's opinion, or that make it unacceptable to the subject to continue
- Investigator judgment
- Sponsor request
- Randomization code broken prematurely
- Pregnancy

The reason for early discontinuation will be collected

3.6.3 **Discontinuation of the Study**

If the clinical study is prematurely terminated or suspended, the Sponsor or designee will inform the Investigators and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension. The Investigators should promptly notify their Independent Ethics

Committee (IEC) or Institutional Review Board (IRB) of the termination or suspension and of the reasons.

3.6.4 Discontinuation of a Clinical Site

The Sponsor reserves the right to close an investigational site or terminate the study in its entirety at any time, for reasonable cause. Reasons for the closure of any investigational site or termination of the study may include:

- Failure to accrue subjects into the study at an acceptable rate.
- Failure of the Investigator to comply with applicable regulations and Good Clinical Practice (GCP) guidelines.
- Submission of knowingly false information from the research facility to the Sponsor, Food and Drug Administration (FDA), or other regulatory authorities.
- Insufficient adherence to protocol requirements and procedures.

If the study is prematurely discontinued, all study data must be returned to the Sponsor or designee. Additionally, the site must conduct final disposition of all unused IMP in accordance with CRO procedures. Study termination and follow-up will be performed in compliance with the conditions set forth in regulatory guidelines.

Financial compensation to the Investigator and/or institution will be in accordance with the agreement established between the Investigator and the Sponsor or Sponsor designee.

3.6.5 Actions after discontinuation

All subjects who discontinue IMP due to a report of an AE **must** be followed-up and provided appropriate medical care until their signs and symptoms have remitted, stabilized, determined to be chronic, or until abnormal laboratory findings have returned to acceptable or pre-study limits.

For the subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to assure there is a final visit that includes all examinations listed for Visit 2.

3.6.6 Completed study

The end of the study is defined as the date the last subject completes the Follow-up Phone Call.

3.6.7 Procedure after the completion of the study

When the study is completed and the site has been closed out, the Investigator will be asked to notify the governing IRB.

4 SUBJECT INCLUSION AND EXCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study. On criteria that involves the eyes, both eyes must qualify.

4.1 Subject inclusion criteria

1. Provide written informed consent prior to any study-related procedures being performed.
2. Is male or a non-pregnant, non-lactating female aged 18 years or older. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening (Visit 1) in order to be eligible for randomization.

3. Are willing and able to follow instructions and can be present for the required study visits and Follow-up Phone Call for the duration of the study.
4. Have an Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of 20/200 or better in each eye as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) at the screening visit. Note: previous refractive procedures allowed.
5. Have an Intraocular Pressure (IOP) between 7 and 30 mmHg.
6. Certified as healthy by clinical assessment (detailed medical history) including ocular examination.
7. Verbal communication skills adequate to participate.
8. Able to tolerate bilateral instillation of Over-The-Counter artificial tear product based on investigator judgement.

4.2 Subject exclusion criteria

Subjects who meet any of the following exclusion criteria are ineligible for this study:

1. Have participated in an investigational study (drug or device) within the past 30 days.
2. Have a contraindication to local anesthetics, [redacted]®, or any component of the IMP.
3. Have known decreased corneal or conjunctival sensitivity (e.g., sequelae of herpetic eye disease, corneal graft) or a diagnosed corneal pathology which might lead to decreased sensitivity.
4. Have had ocular surgery (intraocular, refractive, extraocular muscles, eyelid) or general surgery in either eye within the past 90 days (Note: [redacted] restorative work allowed)
5. Have had an intravitreal injection in either eye within 14 days of randomization.
6. Have ocular surface disease requiring punctual plugs.
7. Evidence of any current ocular inflammation.
8. Subject who must wear contact lenses on Study Day 1 (Visit 2).
9. Are currently using, or used within the past 30 days, a systemic opioid or opiate analgesic or topical Non-steroidal Anti-Inflammatory Drug (NSAID).
10. Subject who cannot withhold their intermittent over-the-counter (OTC) artificial tear lubricant products for one hour preceding or following study medication.
11. Any condition, including alcohol or drug dependency, that would limit the subject's ability to comply with the procedures of the protocol (per Investigator's judgment).

Note: Given the approval status and preclinical safety information on the molecule, and low chance of systemic exposure, other than the negative urine pregnancy test, there is no restriction on women of child-bearing potential.

4.3 Subject replacement

Discontinued subjects may be replaced by enrollment of additional subjects until approximately 120 subjects are enrolled.

5 TREATMENT OF SUBJECTS

Subjects will receive a single dose of IMP in one (study) eye. The IMP will be randomized as either AG-920 or Placebo. The study eye will be randomized as either right eye (OD) or left eye (OS). The single dose will be administered by the clinic staff as two drops in study eye 30 seconds apart.

5.1 Concomitant medications

5.1.1 Prohibited medications

The list of prohibited medications provided below may not be comprehensive. Investigators are encouraged to consult with the Medical Monitor for a decision about proceeding if they have any questions or concerns about any medication.

The following medications are prohibited.

- systemic opioids or opiate analgesics within 30 days of randomization and during the study treatment day
- topical NSAIDs within 30 days of randomization and during the study treatment day
- Over-the-counter (OTC) artificial tear lubricant products within one hour preceding or following study medication, other than the tolerability test

As noted in the exclusion criteria (Section 4.2), individuals must refrain from contact lens wear on the Dosing and Anesthesia Testing Day.

5.1.2 Allowed medications

Other than the agents and/or times noted above, systemic therapy with agents is allowed.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact the Sponsor for any questions regarding allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Sponsor.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in the CRF. The name of the drug, dose, route of administration, duration of treatment and indication will be recorded for each medication. For combination products (e.g., Contac®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (e.g., fluorescein and local anesthetic) will be allowed, and individual documentation not required.

5.2 Female Subjects

Female subjects of childbearing potential must not be pregnant or breastfeeding at Randomization. These subjects must have a negative urine pregnancy test at Screening in order to be eligible for the study.

Female subjects who are not of childbearing potential must meet at least one of the following criteria:

- At least 1 year since the last menstrual period
- Surgically sterile (tubal ligation, bilateral oophorectomy, salpingectomy, or hysterectomy)
- Congenitally sterile
- Diagnosed as infertile and not undergoing treatment to reverse infertility

6 STUDY PROCEDURES

6.1 General Procedures:

The study will consist of 1 or 2 clinic visits and 1 Follow-up Phone Call. All ocular assessments will be performed on both eyes. Subjects will be screened for entry (Visit 1) and randomized/treated at (Visit 2). Visit 1 and 2 may be on the same day. At randomization, subjects will receive a single dose of IMP (2 drops 30 seconds apart) in the study eye. Subjects will then have a safety Follow-up Phone Call 1-4 days (Days 2-5) following Visit 2.

6.2 Re-screening Procedures:

A subject who is first designated as a screen failure prior to being randomized will be allowed to rescreen one additional time 7-30 days later.

6.3 Visit 1 (Screening) – Day -2 to 0/1

Visit 1 may be combined with Visit 2 in order to accommodate clinic logistics. If both visits are combined, Visit 1 will last anywhere from 1-3 hours. If topical anesthetic drops are used to assess IOP, subject must wait at least 1 hour before IMP treatment. Topical anesthetic drops may cause a mild stinging or burning sensation upon instillation.

The following procedures will be performed in the following suggested order at Visit 1. All ocular tests at this and all visits will be performed in both eyes (with the exception of conjunctival pinching):

- Obtain written informed consent to participate before any study-required screening assessments have been conducted
- Collect demographics (sex, year of birth, race, ethnicity)
- Collect systemic medical history and ocular medical history
- Review of prior and concomitant medications (including ocular medications)
- Study technician to instill a drop of an Over-The-Counter artificial tear. At the opinion of the Investigator/Study Technician, only individuals who tolerate this drop, will be enrolled.
- Perform urine pregnancy test (UPT) on women of childbearing potential (see Appendix 1).
- Measure Best Corrected Visual Acuity (BCVA) (see Appendix 1)
- Perform slit lamp biomicroscopy and external eye exam (see Appendix 1)
- Measure IOP (see Appendix 1)
- Verify subject eligibility based on Inclusion/Exclusion requirements
- Schedule subject to return for Visit 2 if Visit 1 and 2 are not performed on the same day.

6.4 Visit 2 (Randomization/Treatment) – Day 1

Visit 2 must occur within 3 days of Visit 1 (Screening) if it is not performed on the same day as Visit 1. As noted in Section 6.3, Visit 1 and Visit 2 may be performed on the same day for clinic logistics. If a topical anesthetic is used to measure IOP at Screening (Visit 1), there must be at least a 1-hour interval post-anesthetic drops prior to treatment with IMP. At Visit 2, subjects are expected to be in the clinic for approximately 60 minutes post dose.

6.4.1 **Pre-dose**

The following procedures will be performed in the following order at Visit 2, if Visit 1 was <u>not</u> performed on the same day:

- Re-verify subject eligibility based on Inclusion/Exclusion requirements.
- Review of any changes in health (medical history and AEs) or concomitant medications (including ocular medications) if Visit 2 is not combined with Visit 1

6.4.2 IMP Treatment

- Once qualification is confirmed, subject will be randomized.
  - Subject will be randomly assigned to receive a single dose of either AG-920 or Placebo
  - Subject will be randomly assigned to receive the IMP dose into one eye only (study eye)
  - [redacted]
- Retrieve IMP kit number assigned and confirm study eye
- Remove foil pouch from kit and remove 1 vial from foil pouch
- Open vial top
- Administer 1 drop of IMP to the study eye
- Wait 30 seconds
- Administer a second drop of IMP to the same study eye from the same vial
- Assess for adverse events
- [redacted]

6.4.3 Post Treatment and Pinch Test

- A [redacted] forceps will be used to "pinch" the inferior bulbar conjunctiva of the study eye [redacted]. Details on the pinching method will be provided separately:
  - [redacted]

As soon as the subject does not experience pain [redacted] pinching will stop until the 5-minute timepoint. [redacted]

If the subject experiences pain [redacted], pinching will be concluded [redacted]

Within 15-60 minutes after the last pinch test, the following examinations will be performed

- BCVA
- Perform slit lamp biomicroscopy and external eye exam

- Assess for adverse events
- Schedule Follow-up Phone Call between Day 2-5.

[redacted]

6.5 Follow-Up Phone Call (Day 2-5)

Subjects will receive a phone call from site staff between Days 2-5, which is 1-4 days (24-96 hours post-dose) following treatment with IMP. Subjects will be asked about

- AEs
- Changes to concomitant medications

If there are any ongoing adverse events, the subject will be instructed to return to the investigator's office for appropriate evaluation. If there are no ongoing adverse events, the subject will be considered completed.

Subjects will be thanked for their participation and released to follow their normal standard of care.

6.6 Unscheduled visits

To ensure subject safety during the trial, any subject who requires additional follow-up during the study for any reason (that does not fall on a scheduled study visit) should have that visit recorded as an Unscheduled Visit.

6.7 COVID-19 Pandemic Accommodations

This study may be conducted during the COVID-19 pandemic. As a result, American Genomics is providing guidance to Investigators on how to modify the current protocol based on guidance documents from the FDA and other regulatory authorities. The objective of these potential modifications is to ensure the safety of trial participants and clinic staff, maintain compliance with good clinical practice (GCP), and minimize the risks to trial integrity during the COVID-19 pandemic.

To ensure the safety of trial participants and to minimize or eliminate hazards as a result of COVID-19 pandemic, the following alternative processes and procedures may be implemented when necessary:

1. Depending on local COVID-19 prevalence and prevailing local ordinances and guidances, some screening visit procedures may be conducted by telephone, by video conferencing, or by remote staff in the subject's home.
2. The Randomization/Treatment Visits cannot be done by telephone or video conferencing and must be completed at the investigative site, if it is safe and feasible, per Investigator's judgment.
3. Site specific accommodations should be implemented per state and local guidances possibly including social distancing or personal protective equipment (PPE) requirements.
4. Remote monitoring visits of clinical trial data may be implemented.

7 ASSESSMENT OF EFFICACY[1]

Assessments of efficacy will be as follows:

- **Assessment of pain questionnaire following conjunctival pinch.**

The timing of this assessment is provided in Section 6.4.3.

8 ASSESSMENT OF SAFETY

8.1 Specification of safety parameters

The assessment of safety and tolerability will be evaluated by:

- BCVA (ETDRS)
- Biomicroscopy and external eye exam of anterior segment including evaluation of cornea, conjunctiva and anterior chamber.
- AEs (post treatment)
- AEs will be collected at every visit. See Section 8.3 for details on collection and reporting of AEs.

Screening only:

- Intraocular pressure
- Urine pregnancy test for females of childbearing potential

8.2 The methods and timing for assessing, recording, and analyzing safety parameters

Methods may be found in Table 1 and Appendix 1.

8.3 Adverse events[2]

All AEs occurring after the first dose of IMP and throughout the remainder of the study period (Follow-up Phone Call) will be considered TEAEs and must be documented on the relevant Electronic Data Capture (EDC) pages and in the source documents. Whenever possible, the diagnosis, if available, and not the symptoms should be reported as the AE. AEs and Serious Adverse Events (SAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Documentation of adverse events/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

8.3.1 **Adverse Event (AE) definitions**

An *AE* is any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

[2] Note: This section is referenced to 21 CFR 312.32 (IND safety reports), updated as per "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (Fed Reg 2010: 75 (188): 59935-59963).

Note: An AE can therefore be any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research will be documented.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- Signs, symptoms, or clinical sequelae of a suspected interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do **not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not significantly worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless rescue medication or other medical treatment is required.

8.3.1.1 Life-threatening adverse event or life-threatening suspected adverse reaction.

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.3.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.3.1.3 Unexpected adverse event or unexpected suspected adverse reaction.

An adverse event or suspected adverse reaction is considered ''unexpected'' if it is not listed in the Investigator brochure or is not listed at the specificity or severity that has been observed; or, if

an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Note: Any medical condition present prior to administration of the masked study medication which remains unchanged or improved should not be recorded as an adverse event at subsequent visits.

8.3.2 **Serious Adverse Event (SAE) definitions**

An *SAE* is an AE that:

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. Complications occurring during hospitalization are AEs or SAEs if they cause prolongation of the current hospitalization. Hospitalization or prolonged hospitalization for elective treatment of a pre-existing non worsening condition is not, however, considered an AE.
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This can include an AE that suggests any significant hazard, contraindication, adverse event, or precaution that may be associated with the use of the IMP.

8.3.2.1 Recording an AE and/or SAE including Onset Date, End Date

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the CRF.

If an AE starts but does not end before the final visit, the Investigator must make a reasonable effort to establish the outcome and the end date of the AE. If this is not possible (e.g., because the AE is still ongoing) or the subject is lost to follow-up, there will be no end date for the AE and the status will be recorded as "ongoing." For all AEs that resolve, resolve with sequelae, or have a fatal outcome, an end date must be provided.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

8.3.2.2 Assessment of Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the IMP. Causality should be assessed as unrelated or related using the categories defined in Table 2.

Table 2: AE Assessment of Causality

Unrelated:	• Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP, **or** • Clinical event whose time relationship to IMP makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Related:	• Clinical event with a reasonable time relationship to IMP, but that could also be explained by concurrent disease or other drugs or chemicals, **or** • Clinical event with a reasonable time relationship to IMP and is unlikely to be attributed to concurrent disease or other drugs or chemicals, **or** • Clinical event with plausible time relationship to IMP, and that cannot be explained by concurrent disease or other drugs or chemicals.

Abbreviations: AE=Adverse Event; IMP=investigational medicinal product

8.3.2.3 Assessment of Severity (Intensity)

The severity of an adverse event is defined as a qualitative assessment of the level of discomfort of an adverse event as is determined by the Investigator or reported to him/her by the subject. The assessment of intensity is made irrespective of study medication relationship or seriousness of the event. The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: and should be evaluated according to the scale in Table 3.

Table 3: Assessment of Severity (Intensity)

Mild	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate	An event that causes sufficiently discomfort and interferes with normal everyday activities.
Severe	An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Please note: the term "severe" is used to describe the intensity (severity, see above) of an event/reaction; the event/reaction itself may be of relatively minor medical significance (such as severe headache). This is not the same as a "Serious" Adverse Event, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to the

subject's life or vital functions. "Serious" (NOT severity) serves as a guide for defining regulatory reporting obligations. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

8.3.3 Expedited reporting of Serious and Unexpected Adverse Events

Safety reports

An investigator must immediately report to the Sponsor or Sponsor representative any serious adverse event, whether or not considered drug-related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor. The investigator must record non-serious adverse events and report them to the Sponsor according to the timetable for reporting specified in the protocol. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

This requirement applies to occurrences observed during the course of the study and within four (4) weeks of last administration of the study medication.

In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (i.e., not in the Clinical Investigator's Brochure) and judged related to the investigational product, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE.

SAEs must be reported to the IRB/EC according to the IRB/EC requirements.

The Investigator/designee will forward all source documents (redacted, if necessary, to maintain the blind) related to the SAE to the Medical Monitor. For each SAE and follow-up to an SAE, the site should ensure that an SAE Narrative and critical baseline CRFs are completed as of the onset date for the SAE (e.g. demographics, concomitant medications, and medical history) and emailed to [redacted] (see address below). The site shall ensure all source documents are redacted for subject private information prior to emailing to [redacted] All SAEs must be reported to [redacted] via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug related. Send to:

[redacted]

8.3.4 Follow-up of subjects after adverse events

If an adverse event/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a non-serious adverse event/adverse reaction is unresolved at the time

of the last visit, efforts will be made to follow up until the adverse event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

9 Statistics

9.1 Primary Hypotheses

H_{01}: The percentage of subjects with no pain within 5 minutes is NOT different between subjects treated with AG-920 and Placebo.

H_{11}: The percentage of subjects with no pain within 5 minutes is different between subjects treated with AG-920 and Placebo.

9.2 Sample Size Considerations

Efficacy:
With 60 subjects per treatment group and assuming 15% response in the vehicle group, this study will have 88% power to detect a treatment effect of at least 25% between AG-920 and vehicle (α=0.05, two-sided).

9.3 Analysis populations

Randomized Population: The randomized population will include all subjects who were randomized to treatment. Baseline (screening) variables and demographic characteristics will be summarized for this population.

Intent-to-Treat Population (ITT): The ITT population will include all randomized subjects who have received at least one dose (2 drops) of study medication. This population will be the primary population for the efficacy analyses and all efficacy variables will be summarized using this set of subjects. The ITT population will include subjects as randomized.

Per-protocol population (PP): The PP population is a subset of the ITT population, which will include those subjects (and their visits) who do not have 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. This population will be the secondary population for efficacy analyses and all efficacy variables will be summarized using this set of subjects. If the PP and ITT populations are exactly the same and there are no missing data, then additional efficacy analyses on the PP population will not be performed. The PP population will include subjects as treated.

Safety Population: The safety population will include all randomized subjects who have received at least one dose (2 drops) of study medication. This population will be used to summarize the safety variables and will summarize subjects as treated.

9.4 Statistical methods to be employed

9.4.1 General Considerations

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages.

Hypothesis testing, unless otherwise indicated, will be performed at a two-sided 0.05 significance level. Where applicable, two-sided 95% confidence intervals will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. Difference between [redacted] Sterile Topical Ophthalmic Solution (AG-920) and Placebo will be calculated as [redacted] Sterile Topical Ophthalmic Solution –Placebo.

All study data will be listed by treatment, subject, time point, and eye (as applicable).

Statistical methods will be more fully described in a separate document (Statistical Analysis Plan).

9.4.2 Interim analyses

There is no planned interim analysis.

9.4.3 Analysis of Baseline Data

Demographic and baseline characteristics such as age, sex, ethnicity, race, and iris color will be summarized and listed. Depending upon the extent of medical and ocular history and concomitant medications in these healthy subjects, coding systems such as MedDRA and WHO will be used, and these data will be summarized and listed.

9.4.4 Subject Disposition

Subject enrollment and exit status (completed or discontinued) will be summarized and listed.

9.4.5 Protocol Deviations

Important protocol deviations are deviations from the protocol that potentially could have a meaningful impact on study conduct, or on the primary efficacy or key safety outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unmasking to confirm exclusion from analysis sets. Further details will be provided in the SAP.

9.4.6 Analysis of Efficacy

Analyses will be performed primarily on the ITT population and will be repeated on the PP population to determine robustness of results. For the primary efficacy endpoint of the proportion of subjects with no pain at 5 minutes, a Pearson chi-square test will be used for the comparison of the two proportions from the two treatment groups. In addition, a two-sided 95% confidence interval for the difference in response rates between the two treatment groups will be calculated. If the lower limit of the 95% confidence interval is greater than 0 and the *P* value is statistically significant ($P<0.05$), then superiority of AG-920 over the vehicle will be claimed.

Sub-group analyses based upon pre-study characteristics such as sex, iris color, age, and race may be completed to further investigate the efficacy and safety measures.

9.4.7 Analysis of Safety

Slit lamp biomicroscopy and external eye exam measures will be summarized at each measured time point using discrete summary statistics.

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.

9.4.8 Adverse Events

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of study medication, will be summarized by treatment group using frequency counts and percentages for each system organ class (SOC) and preferred term (PT) within each SOC. Summaries will be presented separately for ocular and non-ocular AEs. These summaries will also be presented by the relationship to the Investigational Medical Product (related, unrelated) and by severity of the AE (mild, moderate, severe). Fisher's exact test will be used to test the difference in proportions of subjects with each AE between treatment groups (SOC and PT).

9.5 Procedure for accounting for missing, unused, or spurious data

A minimal amount of missing data is expected in this study because of the short duration and the subjects being in the clinic on Day 1. For the ITT population, any missing data on Day 1 will be imputed using the method of last observation carried forward (LOCF), where the closest non-missing value prior to the missing value will be carried forward and imputed for the missing value. The PP and Safety populations will be based on observed data only (without imputation). Any missing, unused, or spurious data will be noted and explained in the final statistical report.

9.6 Procedure for reporting deviations from the statistical plan

Any deviations from the statistical plan will be described and a justification given in the final statistical report.

9.7 Data listings

Data listings will be prepared for all data on the database.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audits during the study by the Sponsor or its designee. In addition, inspections may be conducted by regulatory authorities at their discretion.

10.2 Direct Access to Source Data Documents

Authorized representatives of the Sponsor, a regulatory authority, an IEC or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines, and any applicable

regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.3 Clinical Monitoring

Data for each subject will be recorded in a source document and in EDC for each subject who signs an informed consent form (ICF) and is administered IMP.

In accordance with current GCP and International Conference of Harmonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in EDC are accurate and reliable.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within EDC.
Due to the COVID-19 Pandemic, remote monitoring visits may replace some of the onsite monitoring visits. It will still be the responsibility of the monitor to discuss the study and any issues with the Principal Investigator via telephone or videoconference.

10.4 Data Management and Coding

The CRO will be responsible for data management per their SOPs. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of the CRO.

All data for subjects who sign an ICF and receive a dose of IMP will be recorded via EDC. Subjects who are screened but found ineligible for the study and who do not receive IMP will be considered screen failures. The reason for exclusion from the study will be recorded.

Study centers will enter data directly into the EDC via a secure internet connection. Data entered into EDC must be verifiable against source documents at the study center. Data recorded directly into EDC, if any, will be identified and the EDC will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA Code of Federal Regulations (CFR) 21 Part 11 compliant.

MedDRA will be used to code AEs. Medications will be coded by WHODrug. Missing or inconsistent data will be noted within the EDC system and queried with the Investigator for clarification. Subsequent modifications to the database will be documented.

11 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

11.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subject, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IMP released to the Investigator. Any

necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

11.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.3 Ethical Conduct of the Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

11.4 Written Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, inconveniences, and potential benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. The subject will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject. The Principal Investigator(s) must maintain the original, signed ICF.

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the subject has given written informed consent to participate in the study.

It should be emphasized that the subject may decline to participate in the study and may withdraw from the study at any time without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled.

If new information becomes available that may be relevant to the willingness of the subject to continue in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The subject will be informed about this new information and reconsent will be obtained.

11.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, as well as that of any other applicable agency, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

12 DATA HANDLING AND RECORD KEEPING

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and U.S. Food and Drug Administration (FDA) guidelines for the handling and analysis of data for clinical trials.

12.1 Data quality control and reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. The study database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

12.2 Inspection of Records

American Genomics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, IMP stocks, drug accountability records, subject charts and study source documents, and other records pertaining to study conduct.

12.3 Records retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years from the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor or its representatives to inform the study center when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12.4 Amendments to the protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by American Genomics, LLC and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

13 PUBLICATION

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

14 REFERENCES

14.1 Published references

- Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Opt 1976;53:740-5.
- Ferris FL, Freidlin V, Kassoff A, et al. Relative letter and position difficulty on visual acuity charts from the Early Treatment Diabetic Retinopathy Study. Am J Ophthalmol 1993;116:735-40.
- [redacted]® package insert, 2018.
- Sherwood MB, Craven ER, Chou C, DuBiner HB, Batoosingh AL, Schiffman RM, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006;124(9):1230-8.
- FDA Guidance on Conduct of Clinical Trials of Medicinal Products during COVID-19 Public Health Emergency, March 2020; https://www.fda.gov/media/136238/download.

14.2 Internal references

- American Genomics, LLC, [redacted] Sterile Topical Ophthalmic Solution Investigator's Brochure, 2020.

Appendix 1: Procedures

Procedures: Best Corrected Visual Acuity

Introduction: Best corrected visual acuity (Distance) will be measured at Visit 1 and at the end of Visit 2. Visual acuity will be measured using Bailey Lovie charts, ETDRS charts, or their equivalents. Accepted charts are those designed according to the following principles described by Bailey and Lovie (1976), Ferris et al (1993) and the National Academy of Science-National Research Council (NAS-NRC) Committee on Vision 1980 (1980): 1) letters of equal legibility; 2) combine the letters so that each line is of approximately equal difficulty (as described by Ferris et al, 1993); 3) present five letters at each acuity level; 4) space rows by the height of the smaller letter 5) space letters by the width of same-sized letters and 6) use a logarithmic progression of letter size from logMAR (Minimum Angle of Resolution to base 10) -0.3 (20/10) to 1.0 (20/200).

Rationale: Best corrected acuity taken at follow-up visits as a measure of ocular function. Best corrected visual acuity will be measured at screening and frequently throughout the study.

Procedure: Distance visual acuity must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) or equivalent chart. Visual acuity testing should precede intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment.

Distance visual acuity will be measured with best correction.

The visual acuity chart may be either retro-illuminated ("back-lit"), or reflectance illuminated. If the latter, then the illumination must be checked at regular intervals to be consistent with ETDRS guidelines. Standard charts for a distance from subject to chart of 10 feet to 20 feet must be used. Ideally, the subject should be seated. The right eye should be tested first. Sites are directed to refer to the instructions on the commercial ETDRS charts. If there is any question, contact the Sponsor's monitor.

The subject should attempt to read each letter, line by line, left to right, beginning with line 1 at the top of the chart (20/200 line). The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subjects should be asked to read slowly, about one letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, he/she should be encouraged to guess. If the subject identified two letters (e.g., A or B), he/she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted. Repeat with left eye.

In order to provide standardized and well-controlled assessment of visual acuity during the study, all visual acuity assessments for a subject must be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) during the entire study.

The number of letters missed is multiplied by 0.02 and added to the baseline value to determine the logMAR visual acuity. Baseline is defined as the last line for which the subject reads at least one letter.

logMAR units VA = Baseline value + (n x 0.02)

If refraction was used at the screening or baseline, then this refraction should be used in the phoropter or trial frame for subsequent examinations. A repeated refraction is not required at these subsequent examinations.

A priori, a change of three lines (ETDRS) in visual acuity in either eye is considered clinically significant.

For comparison with Snellen, a chart of the Snellen ratio that best corresponds with LogMAR is provided in Table 4. This is provided for convenience only. Visual Acuity is not to be measured by Snellen Acuity charts in this study.

Table 4: Comparison of Snellen ratio and logMAR units

Snellen ratio	*logMAR*
20/200	+1.0
20/160	+0.9
20/125	+0.8
20/100	+0.7
20/80	+0.6
20/62.5	+0.5
20/50	+0.4
20/40	+0.3
20/32	+0.2
20/25	+0.1
20/20	+0.0
20/16	-0.1
20/12.5	-0.2
20/10	-0.3

Procedures: Measurement of intraocular pressure:
Local anesthetic may be applied in order to facilitate IOP measurements with Tonopen® or Goldmann Tonometer.

If a Goldmann tonometer is used, then two consecutive IOP measurements of each eye are to be obtained. If the 2 measurements differ by more than 2 mm Hg, a third measurement should be obtained. IOP will be analyzed as the mean of 2 measurements or as the median of 3 measurements (Sherwood et al 2006).

If local anesthetic is applied in order to facilitate IOP measurements, there must be at least a 1-hour interval post-anesthetic drops prior to treatment with IMP. Subjects should be reminded that

topical local anesthetics may cause a mild stinging or burning sensation upon instillation. This should not be considered as "pain" when conjunctival pinching is conducted.

If a Goldmann Tonometer is used, it must be regularly calibrated per manufactures recommendations.

Procedures: Biomicroscopy and External Eye Exam
The subject will be seated while being examined.

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice.

The clinician will examine and grade the eyelid. Observations will be documented on the appropriate CRF. The clinician will examine the conjunctiva, cornea, anterior chamber, iris, pupil and lens of the eye with the aid of a slit lamp, which is a table-mounted binocular microscope.

The Sponsor recommends that the same examiner should conduct all biomicroscopy examinations at each time point and at each visit for a given subject.

Biomicroscopic grading will be done as follows:

LID
Erythema

None (0)=	Normal, without any redness, or less than mild
Mild (+1)=	A low grade flushed reddish color
Moderate (+2)=	Diffused redness encompassing the entire lid margin
Severe (+3)=	Deep diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0)=	Normal, no swelling of the lid tissue, or less than mild
Mild (+1)=	Slight diffuse swelling above normal
Moderate (+2)=	General swelling
Severe (+3)=	Extensive swelling of the eyelid(s), with or without eversion of upper and/or lower lids.

CONJUNCTIVA
Hyperemia

None (0)=	Normal. Appears white with a small number of conjunctival blood vessels easily observed.
Mild (+1)=	Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva;
Moderate (+2)=	Bright, scarlet red color of the bulbar and palpebral conjunctiva
Severe (+3)=	"Beefy Red" with petechiae --- Dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage

Edema

None (0)=	Normal, no swelling of the conjunctiva or less than mild
Mild (+1)=	Slight diffuse or regional swelling of the conjunctiva
Moderate (+2)=	General swelling of the conjunctiva
Severe (+3)=	Extensive swelling of the conjunctiva

CORNEA
Edema

None (0)=	Transparent and clear or less than mild

Mild (+1) =	Dull glassy appearance
Moderate (+2)=	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3) =	Stromal edema, localized or diffuse, with stromal striae

ANTERIOR CHAMBER
Cells

None (0)=	No cells seen or less than mild
Mild (+ 1) =	+ cells
Moderate (+2) =	++ cells
Severe (+3) =	+++ cells
Hypopyon (+4)=	++++ cells, Hypopyon Formation (indicate size of hypopyon)

Flare

None (0)=	No Tyndall effect or less than mild
Mild (+1) =	Tyndall beam in the anterior chamber has a mild intensity
Moderate (+2) =	Tyndall beam in the anterior chamber is of strong intensity
Severe (+3) =	Tyndall beam is very intense. The aqueous has a white, milky appearance

Procedures: Urine

Urine pregnancy tests will be performed on all women of childbearing potential at Visit 1 (prior to treatment).

Appendix 2: [redacted]

[redacted]

Appendix 3: [redacted]

[redacted]

Appendix 4: Investigator Signature Page

Protocol Title: **A Randomized, Double-Masked, Vehicle-Controlled, Parallel Evaluation of the Local Anesthetic Effect of [redacted] Sterile Topical Ophthalmic Solution**

Protocol Number: AG-920-CS301

Confidentiality and Current Good Clinical Practice Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of American Genomics, LLC and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to American Genomics, LLC and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' name will be disclosed. All subjects will be identified by assigned numbers on all EDC, laboratory samples, or source documents forwarded to American Genomics, LLC. Clinical information may be reviewed by American Genomics, LLC or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by American Genomics, LLC, to other clinical Investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution