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American Genomics, LLC

Clinical Study Protocol

AG-920-CS303

A Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Evaluation of the Ocular Safety of Articaine Sterile Topical Ophthalmic Solution

Protocol Number:	AG-920-CS303
IND Number:	IND # 145052
Investigational Product:	Articaine Sterile Topical Ophthalmic Solution (AG-920)
Indication:	Topical anesthesia for intravitreal injection
Phase:	Phase 3
Sponsor:	American Genomics, LLC 39 Sycamore Avenue Little Silver, NJ 07739 Phone (848) 444-0665
Medical Monitor	Lawrence Singerman, MD, FACS InFocus Clinical Research 205 Powell Place Brentwood, TN 37027 Phone (615) 944-0508
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Contact Information and Protocol Authorization

Clinical Study Protocol

AG-920-CS303

Phase 3

Protocol Title: **A Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Evaluation of the Ocular Safety of Articaine Sterile Topical Ophthalmic Solution**

Protocol Number: AG-920-CS303

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:

Martin Uram, M.D.
Chairman
American Genomics LLC

Signature:

04/22/22

Date:

Abbreviations and Terms

Abbreviation	Full text
AE	Adverse event
AG-920	Articaine sterile topical ophthalmic solution
BCVA	Best corrected visual acuity
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
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-CS303	
Clinical Phase:	Phase 3	
Type of study	Safety	
Name of Investigational product:	Articaine Sterile Topical Ophthalmic Solution (AG-920)	
Duration of treatment per subject	1 day	
Objectives and Endpoints:	**Primary Objective**	**Primary Endpoints**
	To evaluate the ocular safety of a single topical ocular administration of Articaine Sterile Topical Ophthalmic Solution (2 drops 30 seconds apart)	Visual acuity, intraocular pressure, biomicroscopy, AEs, TEAEs, SAEs, withdrawals due to TEAEs
	Secondary Objectives	**Secondary Endpoints**
	A subset of up to 20 subjects (with expectations that 12 receiving AG-920 and 6 receiving vehicle) will undergo specular microscopy prior to and 3 months after receiving masked study medication to evaluate the effect of AG-920 on corneal endothelial cell count (ECC).	Mean change from baseline in corneal endothelial cell density after treatment with AG-920
Subject Population:	Healthy volunteers Exclusion criteria may be found in Section 4.2.	
Design:	Randomized, placebo (vehicle) controlled, double-masked, parallel-group. Unequal randomization (2:1 Active:Placebo)	
Visit Schedule:	Study visits will consist of: • a 1-3 day Screening Period • a dosing visit (multiple timepoints over 90 minutes) • a follow-up phone call 1-4 days following dosing And • a follow-up visit at 90-95 days following dosing (**ONLY** for the subset of subjects participating in the ECC evaluation)	
Number of Investigational Sites:	Up to 5 US sites	
Estimated Total Sample Size:	240 total evaluable subjects; 160 AG-920; 80 Placebo.	

	A subset of up to 20 of subjects will have specular microscopy performed.
Plan for Data Analysis:	The size of this study is driven by the minimal safety exposure required for an eventual regulatory marketing application.
Investigational/Comparator Product(s), Dose and Mode of Administration	Subjects will receive a single dose of IMP (2 drops 30 seconds apart) 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 dose will be administered by the clinic staff.

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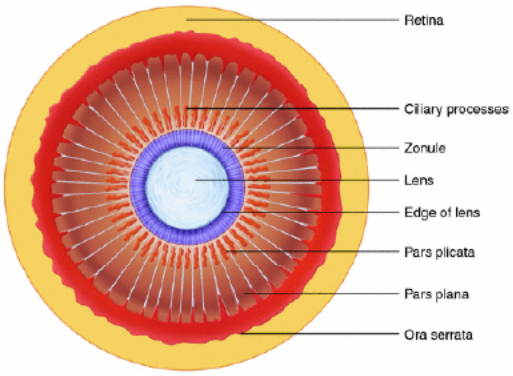
1 INTRODUCTION

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

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 articaine to penetrate the pars plana sufficiently to permit the intravitreal injection without undue discomfort. Articaine was selected for this procedure based upon its clinical use in dental procedures, which suggest it penetrates soft tissue and bone.

1.1 Findings from nonclinical and clinical studies

[redacted]

1.2 Potential Risks and benefits to human subjects

Minimal risks are expected with AG-920. Based upon clinical trials conducted to date, expected risks for subjects may include temporary, mild conjunctival/ocular hyperemia, eye pain, instillation site reaction (stinging/burning), and conjunctival hemorrhage. upon instillation of the investigational medicinal product (IMP). 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.

Any new, unexpected adverse events (AEs) 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)

[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 2:1 to AG-920 or Placebo.

2 OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To evaluate the ocular safety of a single dose of AG-920 after topical ocular administration of Articaine Sterile Topical Ophthalmic Solution (2 drops 30 seconds apart)	Visual acuity, intraocular pressure, biomicroscopy, AEs, TEAEs, SAEs, withdrawals due to TEAEs
Secondary Objectives	**Secondary Endpoints**
A subset of up to 20 subjects (with expectations that 12 receiving AG-920 and 6 receiving vehicle) will undergo specular microscopy prior to and 3 months after receiving masked study medication to evaluate the effect of AG-920 on corneal endothelial cell count (ECC).	Mean change from baseline in corneal endothelial cell density after treatment with AG-920

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-group design study in healthy subjects performed in the US. It is designed to evaluate the safety of one dose of Articaine 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 2:1 ratio to receive 2 drops of AG-920 or identical looking placebo into one (study) eye (2 drops 30 seconds apart).

A subset of subjects will undergo endothelial cell count (ECC) evaluations at one site.

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

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

Articaine Sterile Topical Ophthalmic Solution (AG-920) is a sterile, isotonic, non-preserved aqueous solution [redacted]

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

Figure 2: Investigational Medicinal Product

	INVESTIGATIONAL PRODUCT	
PRODUCT NAME	Articaine Sterile Topical Ophthalmic Solution (AG-920)	Placebo (Vehicle)
ACTIVE INGREDIENT	[redacted]	[redacted]
INACTIVE INGREDIENTS	[redacted]	[redacted]
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	[redacted]	[redacted]

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.

[redacted]

[redacted] 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) and a Follow-up Phone Call 1-4 days following Visit 2 (Day 2-5). A subset of up to18 subjects will undergo specular microscopy prior to dosing, and approximately 90 days after dosing.
The total duration a subject can expect to be in the study is between 2-8 days. If they are in the specular microscopy group, they can expect to be in the study 85-99 days.

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 2:1 ratio to receive AG-920 or Placebo.

[redacted]

[redacted]

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. For those subjects participating in the specular microscopy group, they will not be considered completed until they have had their specular microscopy visit 90 ±5 days following treatment (Visit 3).

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 Medical Monitor. 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 records.

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.

For the subset of subjects participating in the specular microscopy who choose 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 3.

3.6.6 **Completed study**

The end of the study is defined as the date the last subject completes the specular microscopy visit (Visit 3).

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. Have provided 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) to be eligible for randomization.
3. Are healthy by clinical assessment (detailed medical history), including ocular examination, based on the judgement of the Investigator.
4. [redacted]
6. [redacted]
7. [redacted]
8. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study.
9. Have verbal communication skills adequate to participate.

Specular microscopy subset subjects only:

10. Have a central corneal endothelial cell density [redacted]

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. [redacted]
3. [redacted].
5. Have ocular surface disease requiring punctal plugs.
6. Have evidence of any current ocular inflammation.
7. Subject who must wear contact lenses on study visit days.
8. Current ocular allergy symptoms.
9. 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).
10. [redacted]

11. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved in the conduct of the study.
12. [redacted]
13. Previous participation in a clinical study of AG-920.
14. [redacted]

[redacted]

4.3 Subject replacement

Discontinued subjects may be replaced by enrollment of additional subjects until approximately 240 evaluable subjects have completed the study.

5 TREATMENT OF SUBJECTS

Subjects will receive a single dose of IMP (2 drops 30 seconds apart) 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 dose will be administered by the clinic staff.

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.

- [redacted]

As noted in the exclusion criteria (Section 4.2), individuals must refrain from contact lens wear on the Dosing 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 Medical Monitor.

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. There will be a subset of subjects (~18 at one site) who will participate in specular microscopy (Visit 3). These subjects only will have one additional visit 90 days following Visit 2.

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 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. Subjects participating in specular microscopy will have one additional visit on Day 90 (Visit 3).

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.

- [redacted]

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 60 to 90 minutes post dose.

6.4.1 [redacted]

6.4.2 [redacted]

6.4.3

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

- Assess for AEs
- Collect any changes to concomitant medications
- If they are in the specular microscopy group, they will be reminded of their visit at Day 90 (Visit 3) and appointment confirmed.

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.

For subjects NOT in the specular microscopy subset, subjects will be thanked for their participation and released to follow their normal standard of care.

6.6 Visit 3 - Specular microscopy (90 days) – subset of subjects ONLY

For subjects in the specular microscopy subset, 90 days ± 5 days after Visit 2, these subjects will return to the study site for the following assessments:

- Perform of specular microscopy in both eyes.
- Assess for AEs
- Collect any 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.

6.7 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.

6.8 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 the 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

The is no measure of efficacy in this study.

8 ASSESSMENT OF SAFETY

8.1 Specification of safety parameters

The assessment of safety and tolerability will be evaluated changes in by:

- BCVA (ETDRS)
- Intraocular pressure
- Biomicroscopy and external eye exam of anterior segment including evaluation of cornea, conjunctiva and anterior chamber.
- Heart rate and Blood pressure
- AEs (post treatment)
- AEs will be collected at every visit. See Section 8.3 for details on collection and reporting of AEs.
- (Subset only) Specular microscopy for assessment of corneal health.

Screening only:

- 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[1]

All AEs occurring after the first dose of IMP and throughout the remainder of the study period (Follow-up Phone Call; Visit 3 for subjects participating in specular microscopy)ill 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.

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).

[1] 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).

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 Dr. Lawrence Singerman (see address below). All SAEs must be reported to Dr. Singerman via phone or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug related. Send to:

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

As this is only a safety study, there is no planned inferential hypothesis in this study for efficacy.

9.2 Sample Size Considerations

The size of this study is driven by the minimal safety exposure required for an eventual regulatory marketing application.

9.3 Analysis populations

For this safety study, there is no Per-protocol (PP) population. Three other explicit populations are listed here, although they may the effectively synonymous in this single dose safety study.

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 . The ITT population will include subjects as randomized.

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.

[redacted]

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 WHODrug 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**

Not applicable.

9.4.7 **Analysis of Safety**

Intraocular pressure, slit lamp biomicroscopy, external eye exam, intraocular pressure and cardiovascular 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.

[redacted]

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

For this safety study, only observed data will be used. This is no planned method for imputation of missing data.

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

[redacted].

14 REFERENCES

14.1 Published references

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- 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.
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- 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, Articaine Sterile Topical Ophthalmic Solution Investigator's Brochure, 2021.