*CONFIDENTIAL*

*American Genomics, LLC*

# Clinical Study Protocol

**AG-920-CS304**

## A Randomized, Single-Masked, Active-Controlled, Parallel-Group Evaluation of Safety and the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution (AG-920) in a Pediatric Population

| | |
|---|---|
| Protocol Number: | AG-920-CS304 |
| IND Number: | IND # 145052 |
| Investigational Product: | Articaine Sterile Topical Ophthalmic Solution (AG-920) |
| Comparator Product: | 0.5% Proparacaine Hydrochloride |
| Indication: | Topical anesthesia for intravitreal injection |
| Phase: | Phase 3 |
| Sponsor: | American Genomics, LLC [redacted] |
| Medical Monitor | Lawrence Singerman, MD, FACS [redacted] |
| Protocol Date: | 7 February 2022 |
| Protocol Version: | 1.0 |
| Replaces: | N/A |

## Contact Information and Protocol Authorization

# Clinical Study Protocol

AG-920-CS304

**Phase 3**

**Protocol Title:** A Randomized, Single-Masked, Active-Controlled, Parallel-Group Evaluation of Safety and the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution (AG-920) in a Pediatric Population

**Protocol Number:** AG-920-CS304

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:

02/09/22

Date:

## Abbreviations and Terms

| Abbreviation | Full text |
|---|---|
| AE | Adverse event |
| AG-920 | Articaine 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 |
| US | United States |
| VA | Visual acuity |

## Summary

| | | |
|---|---|---|
| **Study Number** | AG-920-CS304 | |
| **Clinical Phase:** | Phase 3 | |
| **Type of study** | Efficacy and Safety | |
| **Name of Investigational product:** | Articaine Sterile Topical Ophthalmic Solution (AG-920) | |
| **Name of Comparator product** | 0.5% Proparacaine Hydrochloride | |
| **Duration of treatment per subject** | 1 day | |
| **Objectives and Endpoints:** | **Primary Objective**<br>To evaluate anesthetic efficacy of AG-920 | **Primary Endpoints**<br>The proportion of subjects in which an eye exam was able to be performed |
| | **Secondary Objective**<br>To evaluate the safety and tolerability of AG-920 | **Secondary Endpoints**<br>Incidence of AEs, TEAEs, SAEs, withdrawals due to TEAEs |
| **Subject Population:** | Healthy pediatric volunteers<br>Exclusion criteria may be found in Section 4.2. | |
| **Design:** | Randomized, active-controlled, single-masked, parallel-group. | |
| **Visit Schedule:** | Study visits will consist of a Screening Visit, a dosing and eye exam visit, and a follow-up phone call | |
| **Number of Investigational Sites:** | 1-3 US sites | |
| **Estimated Total Sample Size:** | Enroll up to 70 subjects to result in 60 evaluable subjects; ~30 per treatment group | |
| **Plan for Data Analysis:** | The sample size is as directed by the U.S. FDA for a Pediatric Study Plan. | |
| **Investigational/Comparator Product(s), Dose and Mode of Administration** | Subjects will receive a single dose (two drops) of IMP in one (study) eye. The IMP will be randomized as either AG-920 or Proparacaine HCl Ophthalmic Solution. 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. | |

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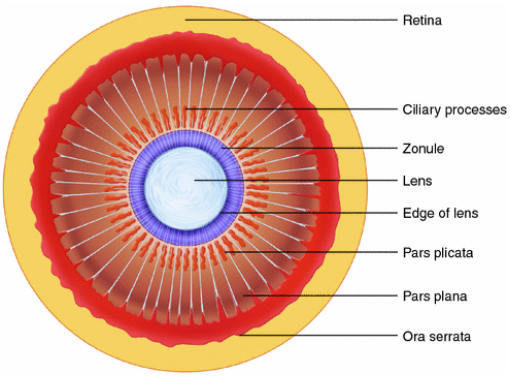
# 1 INTRODUCTION

American Genomics is evaluating the formulation of articaine, an approved local anesthetic, for topical ocular use to provide local anesthesia. The Sponsor intends to develop Articaine Sterile Topical Ophthalmic Solution (AG-920) for topical ocular use to induce local anesthesia. The systemic exposure to articaine after topical ocular instillation is not expected to be greater than that with oral (dental) use of the marketed product, Septocaine® (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 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*

Detailed information on nonclinical and clinical studies with articaine including AG-920 is provided in the Investigator's Brochure (2022).

### *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.

Minimal risks are expected with the comparator, Proparacaine HCl ophthalmic solution. Occasional temporary stinging, burning and conjunctival redness may occur with the use of Proparacaine. A rare, severe, immediate-type, apparently hyperallergic corneal reaction (characterized by acute, intense and diffuse epithelial keratitis, a gray, ground glass appearance, sloughing of large areas of necrotic epithelium, corneal filaments and, sometimes, iritis with descemetitis) has been reported. Allergic contact dermatitis from Proparacaine with drying and fissuring of the fingertips has also been reported. For any additional information on Proparacaine use, please refer to the Package Insert.

As this study is to be conducted in healthy pediatric 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)**

The dose selected for this study is based on clinical experience with this molecule by another route (dental) or from outside the United States, and preclinical safety studies. The positive-control design is as discussed with the U.S. FDA for ethically and scientifically appropriate investigation in the pediatric population. For more details, please refer to the Investigator's Brochure.

The selected dose of the investigational medicinal product AG-920 is 8% Articaine Sterile Topical Ophthalmic Solution which contains 80 mg/mL of Articaine Hydrochloride (HCl).

The intended route of administration for AG-920 (testing treatment) and Proparacaine HCl Ophthalmic Solution (active-control or reference treatment) is topical ocular in this study. Each dose of AG-920 or Proparacaine HCl 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 Proparacaine HCl Ophthalmic Solution.

## 2 OBJECTIVES AND ENDPOINTS

| **Primary Objective** | **Primary Endpoints** |
|---|---|
| To evaluate anesthetic efficacy of AG-920 | The proportion of subjects in which an eye exam was able to be performed |

| Secondary Objectives | Secondary Endpoints |
|---|---|
| To evaluate the safety and tolerability of AG-920 | Incidence of AEs, TEAEs, SAEs, withdrawals due to TEAEs |

# 3 STUDY DESIGN

Randomized, Active-Controlled, single-masked, parallel.

## *3.1 Description and schedule of visits and procedures*

This is a Phase 3, randomized, active-controlled, single-masked, parallel-group design study in healthy pediatric subjects performed in the US. It is designed to evaluate the safety and anesthetic efficacy of one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920) compared to Proparacaine HCl Ophthalmic Solution (Proparacaine). In this study, parent/legal guardians will provide informed consent (and where applicable, subjects will provide assent). Subjects who 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 Proparacaine into one (study) eye.

Each dose of AG-920 or Proparacaine HCl will consist of two drops 30 seconds apart in the study eye. Two to 4 minutes after the completion of dosing, subjects will undergo an eye exam, and the ability to conduct that eye exam will be documented. IMP dosing 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** | | | | **Follow-Up** |
|---|---|---|---|---|---|---|
| | ***Screening*** | ***Screening & Baseline*** | | | | ***Phone call*** |
| | **Day -2 - 0/1 Pre-dose** | **Day 1[1]** | | | | **Day 2-5** |
| **Procedures** | | **Dose** | | **2 -4 min post last drop** | **15-60 min post eye exam** | |
| | | **0 sec** | **30 sec** | | | |
| Written Assent/Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria[2] | X | X[2] | | | | |
| Demographics, Systemic and Ocular Medical History | X | | | | | |
| Concomitant Medication Query | X | ----------X---------- | | | | X |
| Visual Acuity[3] | X[3] | | | | X[3] | |
| External Eye Exam | X | | | | X | |
| Biomicroscopy [4] | | | | | X[4] | |
| Randomization | | X[1] | | | | |
| IMP Administration[5] | | X | X[1] | | | |
| Eye Exam Procedure | | | | X | | |
| Adverse Event Assessment | ----------X---------- | | | | | X |

IMP = investigational medicinal product

[1] Screening may occur on the same day as Visit 2 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] If Visit 1 and 2 are not performed on the same day, these assessments must be performed prior to dosing at 0 seconds.
[3] Age appropriate optotype (if capable) with clinically appropriate test (either Teller acuity charts, Allen pictures, HOTV letters, or Snellen acuity, per standard of care), or reaction to light (if not).
[4] Biomicroscopy only performed if necessary for a suspected AE
[5] One dose is 2 drops. First drop administered at 0 seconds and the second drop administered at 30 seconds (2 drops 30 seconds apart).

### *3.2 Measures taken to minimize/avoid bias*

The subject and parent/legal guardian will be masked to treatment assignment throughout the conduct of the study by use of an "overwrap" label of the marketed product (Proparacaine). A randomization code will be generated by an independent statistician and will assign study drug (AG-920 or Proparacaine) to be received as well as the study eye to be used for each subject.

### *3.3 Study medications*

Articaine Sterile Topical Ophthalmic Solution (AG-920) [redacted]

The comparator product, 0.5% Proparacaine Hydrochloride (NDC number 24208-0730-06, manufactured by Bausch & Lomb), is packaged in 15 mL dropper bottles.

**Figure 2: Investigational Medicinal Product**

| | **INVESTIGATIONAL PRODUCT** | |
|---|---|---|
| **PRODUCT NAME** | **Articaine Sterile Topical Ophthalmic Solution (AG-920)** | **Proparacaine HCl Ophthalmic Solution, 0.5%** |
| **ACTIVE INGREDIENT** | Articaine Hydrochloride | Proparacaine HCl |
| **INACTIVE INGREDIENTS** | [redacted] | Glycerin<br>Purified water<br>Benzalkonium chloride 0.01% |
| **UNIT DOSE** | [redacted] | 15 mL dropper bottle |
| **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 bottle into study eye |
| **STORAGE REQUIREMENTS** | [redacted] | Store bottles under refrigeration at 2° to 8°C (36° to 46°F) |

#### 3.3.1 **IMP Packaging and labeling**

Investigational Medicinal Product (IMP) will be packaged with an investigational label. Marketed Proparacaine HCl Ophthalmic Solution will be "overwrapped" with an investigational label.

The container-closure system to be used for the AG-920 in this clinical study [redacted] vial. [redacted] 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 comparator product, 0.5% Proparacaine Hydrochloride [redacted], is packaged [redacted]. The bottles will be stored in a kit comprised of an individually labeled carton containing 1 bottle. [redacted] Each kit 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.

### 3.3.2 Storage of study medication

[redacted]

The Proparacaine should be stored refrigerated (2 – 8°C or 36 – 46°F).

Prior to administering 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 and comparator bottles will be conducted by a member of the site and verified by a study monitor. Accountability will be completed 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 and bottle 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/Eye Exam) 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 and study eye 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 Proparacaine HCl Ophthalmic Solution. The site will have a randomization list that will assign each subject to treatment and study eye.

The study is single masked. Treatment assignments will be masked to the subjects and their parent/legal guardian only so there is no reason to break the code.

## *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, by decision of their parent/legal guardian, 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 or parent/legal guardian 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

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.

### 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 if performed as part of the AE assessment.

For the subject who chooses to withdraw consent or who is non-compliant, every possible effort should be made by the Investigator to perform 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 of study closure.

# 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 involve the eyes, both eyes must qualify.

## *4.1 Subject inclusion criteria*

1. Male or female aged 10 years or less (pre-pubescent with no childbearing potential)
2. Capable of undergoing an eye exam per investigator judgement
3. Subject's legally appointed and authorized representative willing to sign and date an informed consent form (ICF) and, where appropriate, the subject willing to sign an assent form prior to any study-related procedures being performed.
4. Parent/legal guardian and subject 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.
5. Have a healthy, normal cornea.
6. Have a planned ophthalmic examination.

## *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 known contraindication to local anesthetics, Septocaine®, any component of the Investigational Medical Product (IMP) or Proparacaine HCl Ophthalmic Solution.
3. Children with known autism spectrum disorders or known to have heightened sensitivity.
4. Corneal pathology that would make the corneal sensitivity lower/higher or make the test hard to perform or interpret (e.g., central corneal scar, clinically apparent corneal edema, etc.).
5. Have low visual acuity
   (Optotype capable): Corrected acuity in either eye worse than 20/200 Snellen (0.1 ETDRS) or equivalent
   (Not optotype capable): No demonstrable reaction to light.
6. Manifest nystagmus
7. Have had ocular surgery (intraocular, refractive, extraocular muscles, eyelid) or general surgery in either eye within the past 45 days (Note: dental restorative work allowed).
8. Have had an intravitreal injection in either eye within 14 days of randomization.
9. Have ocular surface disease requiring punctal plugs, or evidence of current ocular inflammation.
10. Subject who must wear contact lenses on Study Day 1 (Visit 2).
11. Are currently using, or used within the past 7 days, a systemic or topical Non-steroidal Anti-Inflammatory Drug (NSAID).
12. Are currently using, or used within the past 30 days, a systemic opioid or opiate analgesic.
13. The subject's parent(s) or legal guardian(s) is a study team member (i.e., has direct involvement in this study or other studies under the direction of the Investigator or the study center) or is a family member of either the Investigator or other team members.

### *4.3 Subject replacement*

This study will enroll up to 70 subjects in order to obtain at least 60 evaluable subjects. No replacement of withdrawn subjects is allowed.

# 5 TREATMENT OF SUBJECTS

Subjects will receive a single dose (two drops) of IMP in one (study) eye. The IMP will be randomized as either AG-920 or Proparacaine HCl Ophthalmic Solution. 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.

### *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]

- [redacted]

As noted in the exclusion criteria (Section 4.2), individuals must refrain from contact lens wear on the Dosing and Eye Exam Day (Day 1).

#### 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 study monitor for escalation to the Medical Monitor (if necessary) 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 if known. 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*

As all subjects are pre-pubescent, typical language regarding women of childbearing potential is not required.

## 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 (Visit 2). Visit 1 and 2 may be on the same day. At randomization, subjects will receive a single dose of IMP in the study eye and have an eye exam 2-4 minutes post the end of their IMP dose. The PI will assess if they were able to conduct the eye exam or not. Subjects and/or parent/legal guardians 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 after initial screening.

### *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 1-2 hours. 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:

- Obtain written informed consent from parent/legal guardian, and, where appropriate, written assent from the subject, to participate before any study-required procedures have been conducted
- Collect demographics (sex, year of birth, race, ethnicity, iris color)
- Collect systemic medical history and ocular medical history
- Review of prior and concomitant medications (including ocular medications)
- Measure Visual Acuity (VA) [redacted]
- Perform external eye exam
- 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. At Visit 2, subjects are expected to be in the clinic for up to 60 minutes post dose for observation.

#### 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)

#### 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 Proparacaine HCl Ophthalmic Solution
    - Subject will be randomly assigned to receive the IMP dose into one eye (OD or OS) only (study eye)
    - Subjects and parent/legal guardian should be reminded that instillation of study drug, like other topical anesthetic drops, may cause a mild stinging or burning sensation upon instillation.
- Retrieve IMP kit number assigned and confirm study eye.
- For AG-920:
    - [redacted]
    - 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

- [redacted]

- For Proparacaine:
  - Remove dropper bottle from kit (carton)
  - Open bottle 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
  - Recap bottle and retain used bottle in the carton (kit) for accountability
- Assess for adverse events

### 6.4.3 Post Treatment and Eye Exam

#### *6.4.3.1 2-4 minutes Post Treatment*

- At the 2-4 minutes time point (after the last drop of study drug is administered), the eye exam for which the subject is seeing the ophthalmologist will be conducted.
- PI is queried [redacted]

#### *6.4.3.2 15-60 minutes Post Treatment*

Fifteen (15) to 60 minutes after the eye exam, the following examinations will be performed

- Visual Acuity
- External eye exam
- Slit lamp biomicroscopy ONLY if necessary for a suspected AE
- Assess for adverse events and changes in medications
- Schedule Follow-up Phone Call between Days 2-5 (1-4 days following dosing).

*Windows: Times will be measured to the nearest minute*

### 6.4.4 Follow-Up Phone Call (Day 2-5)

Subjects/parent/legal guardian 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/parents/legal guardians 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 and parents/legal guardians will be thanked for their participation and released to follow their normal standard of care.

## *6.5 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.

### *6.6 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 guidelines, 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 guidance 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

Assessments of efficacy will be a determination by the investigator as to whether there was adequate local anesthetic effect to perform the eye exam for which the subject is seeing the ophthalmologist.

[redacted]

## 8 ASSESSMENT OF SAFETY

### *8.1 Specification of safety parameters*

The assessment of safety and tolerability will be evaluated by:

- Visual Acuity
- External eye exam
- Slit lamp biomicroscopy ONLY if necessary for a suspected AE
- AEs (post treatment)
- AEs will be collected at every visit. See Section 8.3 for details on collection and reporting of AEs.

### *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) 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.

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

[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).

- 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 (e.g., 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**<br>• 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**<br>• Clinical event with a reasonable time relationship to IMP and is unlikely to be attributed to concurrent disease or other drugs or chemicals, **or**<br>• 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:

Lawrence Singerman, MD, FACS
[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 positive outcomes is NOT different between subjects treated with AG-920 and Proparacaine.

$H_{11}$: The percentage of subjects with positive outcomes is different between subjects treated with AG-920 and Proparacaine.

The primary hypotheses outlined above are based on a controlled trial design for superiority of testing. The current study has an active-control treatment with the intention to compare the treatment of AG-920 in reference to the active-control treatment of Proparacaine, rather than testing for superiority against the latter.

The experimental hypothesis of this study focuses thus on the primary null hypothesis ($H_{01}$) outlined above and intends, for simplicity, to accept the null hypothesis ($H_{01}$) without a pre-defined non-inferiority margin should the null hypothesis ($H_{01}$) is NOT rejected at a statistically significant level of 0.05 (2-sided).

## *9.2 Sample Size Considerations*

The sample size of approximately 70 subjects to be randomized in a 1:1 allocation ratio for AG-920 and reference groups is as directed by the U.S. FDA for a Pediatric Study Plan, rather than being estimated based on a pre-defined non-inferiority margin commonly used for the trial design of therapeutical equivalence. The Sponsor plans to enroll up to 70 subjects in order to obtain at least 60 evaluable subjects.

### *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 (two 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 drop 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 Articaine Sterile Topical Ophthalmic Solution (AG-920) and Proparacaine will be calculated as Articaine Sterile Topical Ophthalmic Solution – Proparacaine, with the 95% CI of the difference being reported for the reference of the treatment therapeutical equivalence.

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

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 in whom there was adequate local anesthetic effect to perform an eye exam for which the subject is seeing the ophthalmologist, 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 difference in response rates is around zero and the *P* value is NOT statistically significant (i.e., $P>0.05$), then the therapeutical equivalence of AG-920 to the Proparacaine will be claimed, without reference to a pre-defined non-inferiority margin. The 95% CI of the difference in response rates will be reported to measure the extend or margin of the efficacy equivalence of AG920 to Proparacaine.

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

External eye exam measures and slit lamp biomicroscopy (if applicable) will be summarized at each measured time point using discrete summary statistics.

Visual Acuity data will be summarized at each time point organized by the age and clinically appropriate test, which may be continuous, categorical or both.

### 9.4.8 Adverse Events

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and 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 Medicinal 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 has had a parent/legal guardian sign an informed consent form (ICF)/assent.

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/assent 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.

Data entered into EDC must be verifiable against source documents at the study center. 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 Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the parent(s)/legal guardian(s) have given written informed consent for their child to participate in the study.

The Investigator or designated personnel will inform the parent(s)/legal guardian(s) of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The parent(s)/legal guardian(s) should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the parent(s)/legal guardian(s) will be given ample time to consider the study. The parent(s)/legal guardian(s) 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's authorized representative.

It should be emphasized that the parent(s)/legal guardian(s) may refuse permission for their child to enter the study or may withdraw their child 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. Children of parents(s)/legal guardian(s) who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the willingness of the subject's parent(s)/legal guardian(s) to allow continuation of their child's participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The parent(s)/legal guardian(s) of the study subjects 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. Queries are entered directly into the eCRF page and are answered by the sites. They are then reviewed by the data manager and/or monitor. All database changes (and the query history) is documented automatically in the audit trail of the eCRF system.

### *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*


- Septocaine® package insert, 2018.
- Proparacaine Hydrochloride package insert, 2020
- 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.

## Appendix 1: Procedures

### Procedures: Visual Acuity

[redacted]

### Procedures: External Eye Exam and Biomicroscopy

[redacted]

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 |

## Appendix 2: Investigator Signature Page

**Protocol Title:** **A Randomized, Single-Masked, Active-Controlled, Parallel-Group Evaluation of Safety and the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution (AG-920) in a Pediatric Population**

**Protocol Number:** AG-920-CS304

### 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