U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 218643
Supplement #:	Original
Drug Name:	CYKLX (Articaine Sterile Topical Ophthalmic Solution 8%)
Indication(s):	Local anesthetic indicated for ocular surface anesthesia prior to ocular procedures and/or intraocular injections
Applicant:	American Genomics, LLC
Date(s):	Submission Date: October 16, 2024 Primary Review Date: July 8, 2025 PDUFA goal date: August 16, 2025
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Biometrics Division:	DBIV
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Keywords: local anesthesia, superiority, pediatrics

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1 EXECUTIVE SUMMARY

This original NDA seeks the approval of CYKLX (Articaine Sterile Topical Ophthalmic Solution 8%, also known as AG-920 topical ophthalmic solution or AG-920 throughout this review) for local anesthetic indicated for ocular surface anesthesia prior to ocular procedures and/or intraocular injections.

The Applicant (American Genomics, LLC) formulated articaine, an approved local anesthetic for dental use, for topical ocular use to provide local anesthesia prior to ocular procedures and/or intraocular injections. The Applicant is relying on the Agency's prior findings of safety for the reference product Septocaine® (articaine and epinephrine, NDA No. 020971) and does not have the right of reference for those data. Articaine Sterile Topical Ophthalmic Solution is intended to be administered to human subjects in the clinic as a single dose to a single eye, via ocular surface instillation of two drops of approximately (b) (4) µL each, 30 seconds apart.

To achieve regulatory approval, the Applicant conducted three efficacy studies: AG-920-CS301, AG-920-CS302, and AG-920-CS304. Studies AG-920-CS301 and AG-920-CS302 were similarly designed, double-masked, vehicle-controlled studies conducted in healthy adult subjects. Study AG-920-CS304 was single-masked, active-controlled study conducted in a pediatric population aged 10 years or younger (pre-pubescent with no childbearing potential) undergoing eye exams; a marketed proparacaine HCl ophthalmic solution 0.5% was selected as the active control.

Both studies AG-920-CS301 and AG-920-CS302 demonstrated superiority of AG-920 to the vehicle for the primary endpoint (**Error! Reference source not found.**) in adults. Therefore, the Statistical Reviewer recommends the approval of articaine sterile topical ophthalmic solution 8% as a local anesthetic for ocular surface anesthesia prior to ocular procedures and/or intraocular injections in adults.

Table 1: Summary of the Primary Efficacy Results (ITT)

	Study AG-920-301		**Study AG-920-302**	
	AG-920 (N=60) n (%)	**Vehicle (N=60) n (%)**	**AG-920 (N=60) n (%)**	**Vehicle (N=60) n (%)**
Responders	41 (68.3)	2 (3.3)	50 (83.3)	11 (18.3)
Difference (95% CI)		65 (52.4, 77.6)[1]		65 (51.4, 78.6)[1]
p-value		<0.001*		<0.001+

Note: ITT = Intent-to-Treat; AG-920 = articaine sterile topical ophthalmic solution 8%; CI = Confidence Interval
* p-value was from the Pearson's Chi-Square test to compare treatment groups.
+ p-value was from the Cochran-Mantel-Haenszel (CMH) test with adjustment for study eye (right [OD] vs. left [OS]).
[1] The estimated 95% CI was based on normal approximation.
Source: Tables 13 and 14 of Study 301 Clinical Study Report (CSR), Tables 13 and 14 of Study 302 CSR, and the reviewer's calculation.

For the pediatric Study 304, the investigators were able to perform the planned eye examination without additional local anesthetic for all subjects (100%) in each treatment group (30 subjects in AG-920 and 30 subjects in proparacaine HCl ophthalmic solution 0.5%). The examinations performed included slit lamp examination, dilated ophthalmoscopy, and scleral depression. However, prior to conducting the examination, the sub-investigators' response to the question

"Did you achieve adequate anesthesia to conduct the eye exam?" (Yes or No) at 2-4 minutes post application of study treatment was not consistent with the eye examination measure: the proportion of subjects with the "Yes" response by the investigator was 8/30 (26.7%) in the AG-920 group, and 28/30 (93.3%) in the proparacaine group; the difference was -66.6% (95% CI: [-82.5%, -50.7%]). According to the Applicant, sub-investigators utilized multiple concepts and indicators to complete the assessment of anesthetic effect in this population of subjects from <1 year of age to 10 years of age; nonetheless, the conclusive anesthetic metric is conjunctival touch and this was achieved in 100% of patients. Without knowing the clinical criteria for deciding local anesthetic effect in pediatrics or the clinical applicability of extrapolating the anesthetic effects from adults to pediatrics, the Statistical Reviewer would like to defer the efficacy conclusion for pediatric subjects to the clinical review team.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

The Applicant (American Genomics, LLC) formulated articaine, an approved local anesthetic, for topical ocular use to provide local anesthesia for intravitreal injections.

Articaine was approved by FDA as articaine hydrochloride 4% with epinephrine 1:100,000 or with epinephrine 1:200,000 combination for intraoral submucosal infiltration use of the indication: for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures in adults and pediatric patients 4 years of age and older.

Ophthalmic anesthetics are eye drops, gels, or ointments that contain a local anesthetic and can be administered directly into the eye. Ophthalmic anesthetics block the transmission of pain signals from the nerve endings of the eye to the brain, numbing the eye. Ophthalmic anesthetics are used to numb the eye or eyes before surgery, after injury, or before certain tests or procedures. FDA approved local ophthalmic anesthetics include lidocaine, proparacaine, chloroprocaine, and tetracaine.

According to the Applicant, 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. According to the Applicant, 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.

2.1.2 History of Drug Development

The product was developed under IND145052.

The first meeting was a pre-IND meeting held between the FDA and the Sponsor on September 27, 2019. Regarding the clinical development plan for the product, the Agency recommended that a masked, randomized vehicle-controlled study of pain following conjunctival pinching be acceptable to demonstrate efficacy of ocular anesthesia. The Division clarified that the primary efficacy analysis could be a categorical analysis of subjects who did not report any pain. The Division proposed the Sponsor consider including 30 subjects (healthy volunteers or patients receiving intravitreal injection). The Division stated that two adequate and well-controlled studies would be required to demonstrate efficacy in an NDA submission.

On October 23, 2023, the Applicant and the Agency had pre-NDA meeting to discuss the NDA submission plan. Based on the meeting minutes, the Agency agreed the Applicant's proposal of NDA submission in general.

2.1.3 Studies Reviewed

Table 2 summarized the three Phase 3 studies (AG-920-CS301, AG-920-CS302, and AG-920-CS304), which are the focus of this statistical review.

Table 2: Summary of Efficacy Studies to be assessed in the Statistical Review

Study No	Design	Objective	Treatment / Sample Size	Study Population	Primary Endpoint
AG-920-CS301 & AG-920-CS302	Single center, randomized, double-blinded, parallel group, vehicle-controlled	To evaluate the safety and anesthetic efficacy of one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920) compared with Vehicle	AG-920 / 60 Vehicle / 60	Healthy adult subjects	Primary: Proportion of subjects with no pain at 5 minutes after dose administration of the investigational product. Subjects underwent a conjunctival pinch procedure and the pain associated with the pinch assessed.
AG-920-CS304	Single center, randomized, double-blinded, parallel	to evaluate the safety and anesthetic efficacy of one dose of	AG-920 / 30 Vehicle / 30	Healthy pediatric subjects aged 10 years or less (pre-pubescent with	Primary: Proportion of subjects in which an eye exam was able to be performed.

	group, active-controlled	Articaine Sterile Topical Ophthalmic Solution (AG-920) compared to proparacaine HCl Ophthalmic Solution (proparacaine)		no childbearing potential)	

Source: Statistical Reviewer's Summary.

2.2 Data Sources

The data sources for this review include clinical study reports, protocols, statistical analysis plan (SAP), and datasets. All data sources were electronic submitted and located at \\CDSESUB1\evsprod\NDA218643\0001.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be verified by the statistical reviewer with minor data manipulation. The statistical reviewer's analyses were primarily based on the analysis datasets.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of the three Phase 3 studies. Sections 3.2.1 and 3.2.2 summarize the study design, endpoints, and statistical methods. Section 3.2.3 summarizes subject disposition as well as demographic and baseline characteristics. Section 3.2.4 discusses the primary analysis and supporting evidence.

3.2.1 Study Design and Endpoints

3.2.1.1 Studies AG-920-CS301 and AG-920-302

The efficacy of AG-920 was evaluated in two nearly identically designed Phase 3 pivotal clinical trials in healthy adults: AG-920-CS301 (referred to as Study 301), and AG-920-CS301 (referred to as Study 302).

Both studies were single-center, randomized (1:1 ratio), double-masked, vehicle-controlled, parallel-group studies, evaluating the safety and anesthetic efficacy of one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920). Study 301 was conducted by Dr. David L. Wirta from Newport Beach, CA; and Study 302 was conducted by Dr. Victor H. Gonzalez from McAllen, TX.

In both studies, eligible subjects were randomized in a 1:1 ratio to receive a single dose of AG-920 or identical looking vehicle into one (study) eye (2 drops 30 seconds apart). Subjects underwent a conjunctival pinch procedure and the pain associated with the pinch rated. Investigational Medicinal Product (IMP) dosing and conjunctival pinch procedure were performed by the study staff. Both studies consisted of a Screening Visit, a treatment and anesthesia testing visit, and a follow-up visit (by telephone). A schedule of assessments, including allowable visit windows, is displayed in the following table.

Table 3: Schedule of Visits and Procedures (Studies 301 and 302)

	Visit 1	**Visit 2**							**Phone Follow-Up**
	Screening **Day -2 to 0/1**	***Screening & Baseline*** **Day 1[1]**							**Day 2-5**
	Pre-dose	**Dose**		**20 s post 2nd drop**	**40 s post 2nd drop**	**60 s post 2nd drop**	**5 m**	**15-60 m post last pinch**	
Procedures		**0 sec**	**30 sec**						
Written Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Demographics, Systemic and Ocular Medical History	X								
Concomitant Medication Query	X	X	X						X
OTC Tear Tolerability	X								
BCVA	X							X	
Urine Pregnancy Test (if applicable)	X								
Biomicroscopy and External Eye Exam	X							X	
IOP Measurement	X								
Randomization		X							
IMP Administration[2]		X	X						
Conjunctival pinch[3]				X	X	X	X		
Assessment of Pinch Pain				X	X	X	X		
Adverse Event Assessment		X	X	X	X	X	X	X	X

BCVA = Best corrected visual acuity, IOP = Intraocular pressure, OTC = over the counter, IMP = investigational medicinal product.
[1] Screening may occur on the same day as Visit 2 (≥ 60 minutes) or up to 3 days previously. If on separate days, inclusion/exclusion criteria should be re-evaluated prior to dosing subject to ensure subject still qualifies.
[2] One dose is 2 drops. First drop administered at 0 seconds and the second drop administered at 30 seconds (2 drops 30 seconds apart).

[3] Verbal question: As soon as the subject does not experience pain (at 20, 40 or 60 second timepoints), pinching will stop until the 5-minute timepoint. This subject will be considered "anesthetized." Pinching of anesthetized subjects will resume at 5 minutes and pinching will continue EVERY FIVE MINUTES for up to 30 minutes or until pain resumes. If the subject experiences pain at 20, 40, 60 seconds AND 5 minutes, pinching will be concluded and this subject will be considered to NOT have reached anesthesia.
Source: Table 1 of Study 301 Clinical Study Report (CSR).

The key inclusion criteria in the two studies were:

- Adult subjects who 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.
- Had an Early Treatment of Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) of 20/200 or better in each eye as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) at the screening visit. Note: previous refractive procedures allowed.
- Had an Intraocular Pressure (IOP) between 7 and 30 mmHg.
- Certified as healthy by clinical assessment (detailed medical history) including ocular examination.

The primary assessment of efficacy was the assessment of pain questionnaire following conjunctival pinch. When performing the conjunctival pinch assessment, a 0.3 mm forceps was used to "pinch" the inferior bulbar conjunctiva of the study eye, with instructions to site as follows:

1. Retract lower lid
2. Ask subject to look upward
3. Explain to the subject that they may feel some pressure and you are going to ask them about pain. Explain to the subject that the feeling of pressure is NOT to be judged as pain. In addition, any burning or stinging sensation experienced upon instillation of study medication was NOT to be judged as conjunctival pinch pain.
4. Take your 0.3 mm sterilized 0.3 mm fixed forceps and prepare for pinch
5. Quickly pinch inferior bulbar conjunctiva with forceps and release
6. Ask subject, "Was that painful"
7. Record response as "Yes" or "NO"

The timepoints were:

- 20 seconds following complete dose administration (second drop of IMP)
- 40 seconds following dose administration
- 60 seconds following dose administration
- 5 minutes following dose administration

Per the protocol, as soon as the subject does not experience pain (at 20, 40 or 60 second timepoints), pinching was to stop until the 5-minute timepoint. This subject was considered "anesthetized." Pinching of anesthetized subjects was to resume at 5 minutes and pinching was to continue EVERY FIVE MINUTES for up to 30 minutes or until pain resumed. If the subject experienced pain at 20, 40, 60 seconds AND 5 minutes, pinching was to be concluded and this subject was considered to NOT have reached anesthesia.

For Study 301, a protocol deviation occurred, and all subjects were pinched at all timepoints up to 5 minutes; therefore, all 120 subjects were pinched and assessed for pain at 20, 40, 60 seconds and 5 minutes. For Study 302, the investigator followed the protocol.

3.2.1.2 Study AG-920-CS304

Study AG-920-CS304 (referred to as Study 304) was a single-center, randomized (1:1 ratio), active-controlled, single-masked, parallel-group design study in healthy pediatric subjects performed in the US. It was 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). Study AG-920-CS304 was conducted by Dr. Victor H. Gonzalez from McAllen, TX, note that he was the same doctor conducted Study 302.

In this study, parent/legal guardians provided informed consent (and where applicable, subjects will provide assent). Subjects who fulfilled all the inclusion criteria and none of the exclusion criteria were 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 consisted of two drops 30 seconds apart in the study eye. Two to 4 minutes after the completion of dosing, the investigator judged whether the local anesthesia was adequate to conduct an examination, and then the subject was to undergo an eye examination. Investigational Medicinal Product (IMP) dosing was performed by the study staff. A schedule of assessments, including allowable visit windows, is displayed in the following table.

Table 4: Schedule of Visits and Procedures (Study 304)

	Visit 1	**Visit 2**				**Follow-Up**
	Screening	***Screening & Baseline***				***Phone call***
	Day -2 -	**Day 1[1]**				**Day 2-5**
Procedures		**Dose**		**2 -4 min**	**15-60 min**	
		0 sec	**30 sec**			
Written Assent/Informed Consent	X					
Inclusion/Exclusion Criteria[2]	X	X[2]				
Demographics, Systemic and Ocular	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[2]				
IMP Administration[5]		X	X[5]			
Eye Exam Procedure				X		
Adverse Event Assessment	----------X----------					X

IMP = investigational medicinal product

[1] Screening may occur on the same day as Visit 2 (≥ 60 minutes) or up to 3 days previously. If on separate days, inclusion/exclusion criteria should be re-evaluated prior to dosing subject to ensure subject still qualifies.

[2] 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).

Source: Table 1 of Study AG-920-CS304 CSR.

The key inclusion criteria for Study 304 were:

- Male or female aged 10 years or less (pre-pubescent with no childbearing potential).
- Capable of undergoing an eye exam per investigator judgement.
- 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.
- Parent/legal guardian and subject was willing and able to follow instructions and could be present for the required study visits and Follow-up Phone Call for the duration of the study.
- Had a healthy, normal cornea.
- Had a planned ophthalmic examination.

In this study, primary efficacy endpoint would be assessed using the proportion of subjects with adequate local anesthetic effect assessed by the principal investigator (Pl) so that the eye exam for which the subject is seeing the ophthalmologist can be conducted. Based on the protocol, two to four minutes following treatment of study medication, the Pl was asked "Did you achieve adequate anesthesia to conduct the eye exam?" The Pl's response was recorded as "YES" for adequate anesthesia or "NO" for inadequate anesthesia.

According to the clinical study report (CSR), after dosing and evaluation was completed, in reviewing the data, the Applicant noted inconsistencies in the investigator (and sub-investigator) judgement of "adequate anesthesia to conduct an examination" and the actual conduct of that examination. In response, the investigator provided a letter of explanation. The investigator noted that "…These assessments of anesthetic adequacy included conjunctival touch (100% of subjects achieved this metric according to my staff and sub investigators) and sensitivity to light (more than 60% of subjects achieved this metric according to my staff and sub investigators). While some investigators used sensitivity to light to document lack of complete anesthesia, this is not a conclusive metric and is subjective. The conclusive anesthetic metric is conjunctival touch and this was achieved in 100% of patients."

Therefore, based upon the change in the conduct of the study noted above, according to the Applicant, the statistical analysis plan (SAP)-defined primary efficacy measure "investigator judgement as to whether adequate anesthesia was achieved to conduct an examination" was inappropriately applied. The actual conduct of an examination was identified as the primary efficacy measure **post-hoc** by the Applicant after dosing and evaluation was completed.

3.2.2 Statistical Methodologies

3.2.2.1 Studies AG-920-CS301 and AG-920-CS302

For both studies, the primary analysis set was the Intent-to-Treat (ITT) population, which consisted of all randomized subjects who have received at least one dose (drop) of study medication. Subjects were analyzed according to the treatment assignment at randomization.

Primary efficacy analyses were also performed using the PP population as a sensitivity analysis. The Per-Protocol (PP) population consisted of all subjects in the ITT population who did 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.

The corresponding null and alternative hypotheses to be tested in this study are the following:
H_0: The proportion of subjects with no pain at 5 minutes is NOT different between subjects treated with AG-920 and vehicle.
H_A: The proportion of subjects with no pain at 5 minutes is different between subjects treated with AG-920 and vehicle.

For Study 301, a Pearson chi-square test was used for the comparison of the proportions from the two treatment groups. In addition, a two-sided 95% confidence interval (CI) for the difference in proportions between the two treatment groups was calculated. If the proportion of subjects (expressed as a percentage) is higher in the AG-920 group and the P value is statistically significant ($P \leq 0.05$), then superiority of AG-920 over vehicle was claimed.

In Study 302, a Cochran-Mantel-Haenszel (CMH) test with adjustment for study eye (OD vs. OS) was used for the comparison of the proportions from the two treatment groups. In addition, a two-sided 95% confidence interval (CI) for the difference in proportions between the two treatment groups was calculated.

The secondary efficacy endpoints Study 301 include the proportion of subjects with no pain within 5 minutes, defined as that a subject needs to report no pain at two or more consecutive time points within the first 5 minutes to be counted (at a minimum, this would be at either 20 and 40 seconds, 40 and 60 seconds, or 60 seconds and 5 minutes), the mean time to no pain score (onset of anesthesia Effect in Minutes), and the duration of anesthetic effect. The secondary efficacy endpoints in Study 302 include 1) the onset of anesthetic effect defined as the time to no pain by conjunctival pinch within 5 minutes post application of the dose; and, 2) the duration of anesthetic effect defined as the time from the onset of anesthetic effect to the time point when pinch pain resumes. However, the Applicant didn't specify any statistical procedure for controlling Type I error in testing multiple secondary endpoints.

The sample size estimation (120 total with 60 subjects per group) for both studies was based on the following assumptions:

- A 15% response in the vehicle group for the primary endpoint
- A treatment effect of at least 25% (40% vs. 15%) between AG-920 and vehicle
- 88% power
- Two-sided Type I error rate (α) of 0.05 based on a two-sample chi-square test

3.2.2.2 Study AG-920-CS304

For Study AG-920-CS304, the primary analysis set was the Intent-to-Treat (ITT) population, which includes all subjects who are randomized to treatment and have received at least one dose (2 drops) of the study medication. Subjects were analyzed according to the treatment assignment at randomization.

The primary efficacy endpoint was the proportion of subjects in which an eye exam was able to be performed (without additional local anethetic). The corresponding null and alternative hypotheses to be tested in this study are the following:
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.

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. Without pre-specifying the non-inferiority margin, from statistical perspective, the test product (AG-920) could be claimed as therapeutical equivalent to active control (proparacaine) even the outcomes show it is inferior to the active control.

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 Applicant plans to enroll up to 70 subjects in order to obtain at least 60 evaluable subjects.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

Studies 301, and 302 each randomized 120 subjects. Study 304 screened 61 subjects, of which 60 were randomized and treated. As single-visit, short-duration studies enrolled healthy subjects, all randomized subjects completed the studies without any treatment or study discontinuation; and were included in the safety, ITT, and PP populations.

Table 5 is a summary of number of subjects in each analysis population by study and by treatment.

Table 5: Summary of Analysis Population (All Randomized)

	Study 301		Study 302		Study 304	
	AG-920 (N=60)	Vehicle (N=60)	AG-920 (N=60)	Vehicle (N=60)	AG-920 (N=30)	Vehicle (N=30)
ITT	60 (100%)	60 (100%)	60 (100%)	60 (100%)	30 (100%)	30 (100%)
Safety	60 (100%)	60 (100%)	60 (100%)	60 (100%)	30 (100%)	30 (100%)
PP	60 (100%)	60 (100%)	60 (100%)	60 (100%)	30 (100%)	30 (100%)

Source: Table 4 of Study 301 CSR, Table 5 of Study 302 CSR, and Table 2 of Study 304 CSR.

3.2.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics were generally balanced between treatment groups in the two studies (301 and 302) for adults (**Error! Reference source not found.**). In Study 301, there were more females than males, the mean age was 31.3 (± 12.6) years (range 18-65 years), and the majority of subjects were white. In Study 302, there were more females than males, the mean age was 35.9 (± 15.0) years (range 18-74 years), and the majority of subjects were white and Hispanic/Latino.

Table 6: Demographic and Baseline Characteristics (Studies 301 and 302, ITT)

	Study 301		Study 302	
	AG-920 (N=60)	Vehicle (N=60)	AG-920 (N=60)	Vehicle (N=60)
Age				
Mean (SD)	32.6 (13.7)	30.0 (11.3)	34.9 (15.6)	37.0 (14.4)
Median	27.0	27.0	28.0	33.0
Min, Max	18, 64	19, 65	18, 74	18, 63
≥ 65	0	1 (1.7%)	4 (6.7)	0
Gender				
Female	33 (55.0)	34 (56.7)	31 (51.7)	36 (60.0)
Male	27 (45.0)	26 (43.3)	29 (48.3)	24 (40.0)
Race				
American Indian or Alaska Native	1 (1.7%)	1 (0.5%)		
Asian	10 (16.7%)	10 (16.7%)	1 (1.7)	1 (1.7)
Black or African American	18 (9.9%)	27 (3.7%)		
Native Hawaiian or Pacific Islander	0	1 (1.7)		
White	49 (81.7%)	49 (81.7%)	58 (96.7)	58 (96.7)
Other	0	0	1 (1.7)	1 (1.7)
Ethnicity				
Hispanic or Latino	13 (21.7%)	14 (23.3%)	59 (98.3)	59 (98.3)
Not Hispanic/Latino	47 (78.3%)	47 (78.3%)	1 (1.7)	1 (1.7)
Iris Color				
Blue	12 (20.0)	14 (23.3)	0	2 (3.3)
Brown	33 (55.0)	28 (46.7)	56 (93.3)	50 (83.3)
Green	4 (6.7)	5 (8.3)	0	2 (3.3)
Hazel	11 (18.3)	13 (21.7)	4 (6.7)	6 (10.0)
Study Eye				

OD (right)	29 (48.3)	31 (51.7)	24 (40.0)	37 (61.7)
OS (left)	31 (51.7)	29 (48.3)	36 (60.0)	23 (38.3)

Source: Table 11 of Study 301 CSR, and Table 11 of Study 302 CSR.

In Study 304, there were similar proportions of female and males, the mean age was 5.8 (± 2.9) years (range 7 months to <11 years), and the majority of subjects were white and Hispanic/Latino.

Table 7: Demographic and Baseline Characteristics (Study 304, ITT)

	AG-920 (N=30)	**Vehicle (N=30)**
Age		
Mean (SD)	5.2 (3.1)	6.3 (2.5)
Median	5.3	6.8
Min, Max	0.6, 10.8	1.7, 9.8
< 2 years	7 (23.3)	2 (6.7)
Gender		
Female	17 (56.7)	16 (53.3)
Male	13 (43.3)	14 (46.7)
Race		
Black or African American	0	1 (3.3)
White	30 (100.0)	29 (96.7)
Ethnicity		
Hispanic or Latino	30 (100.0)	29 (96.7)
Not Hispanic/Latino	0	1 (3.3)
Iris Color		
Brown	30 (100.0)	28 (93.3)
Green	0	2 (6.7)
Study Eye		
OD (right)	15 (50.0)	15 (50.0)
OS (left)	15 (50.0)	15 (50.0)

Source: Table 6 of Study 304 CSR.

3.2.4 Results and Conclusions

3.2.4.1 Studies AG-920-CS301 and AG-920-CS302

The primary assessment of efficacy was the assessment of pain questionnaire following conjunctival pinch. Post IMP instillation, subjects underwent a conjunctival pinch procedure and the pain associated with the pinch rated:

- At 20, 40, 60 second, or 5 minutes timepoints
- As soon as the subject does not experience pain (at 20, 40 or 60 second timepoints), pinching will stop until the 5-minute timepoint. This subject will be considered "anesthetized."
- Pinching of anesthetized subjects will resume at 5 minutes and pinching will continue EVERY FIVE MINUTES for up to 30 minutes or until pain resumes

- If the subject experiences pain at 20, 40, 60 seconds AND 5 minutes, pinching concluded and this subject was considered to NOT have reached anesthesia.

However, for Study AG-920-CS301, a protocol deviation occurred, and all subjects were pinched at all timepoints up to 5 minutes; therefore, all 120 subjects were pinched and assessed for pain at 20, 40, 60 seconds and 5 minutes.

In both studies, AG-920 demonstrated statistically significant response compared with vehicle:

- In Study 301, 68.3% (41/60) in the AG-920 group achieved the primary efficacy endpoint of "no pain at 5 minutes", compared to 3.3% (2/60) in the vehicle group. The treatment difference of 65% with 95% CI of (52.4%, 77.6%).
- In Study 302, 83.3% (50/60) in the AG-920 group achieved the primary efficacy endpoint of "no pain at 5 minutes", compared to 18.3% (11/60) in the vehicle group. This difference between groups of 65% with 95% CI of (51.4%, 78.6%).

Table 8: Summary of Proportion of Subjects with No Pain at 5 Minutes (Studies 301 and 302, ITT Population)

	Study 301		Study 302	
	AG-920 (N=60) n (%)	**Vehicle (N=60) n (%)**	**AG-920 (N=60) n (%)**	**Vehicle (N=60) n (%)**
Responders	41 (68.3)	2 (3.3)	50 (83.3)	11 (18.3)
Difference (95% CI)		65 (52.4, 77.6)		65 (51.4, 78.6)
p-value		<0.001		<0.001

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3 of Study 301 CSR, and Table 14.2.3 of Study 302 CSR.

In addition, the Applicant reported the response to the pinch test at each time point post IMP instillation (20, 40, 60 second, or 5 minutes). At each of the time point in both studies, the response rate for the AG-920 group was greater than the vehicle group (Table 9); hence these results were supportive of the primary efficacy findings.

Table 9: Responses Over Time (Studies 301 and 302, ITT)

	Study 301			Study 302		
Time Post Dosing	**AG-920 (N=60) n (%)**	**Vehicle (N=60) n (%)**	**Diff (95% CI)***	**AG-920 (N=60) n (%)**	**Vehicle (N=60) n (%)**	**Diff (95% CI)***
20 Seconds	53 (88.3)	5 (8.3)	80.0 (69.3, 90.7)	54 (90.0)	18 (30.0)	60.0 (46.1, 73.9)
40 Seconds	58 (96.7)	1 (1.7)	95.0 (89.4, 100.0)	57 (95.0)	11 (18.3)	76.7 (65.4, 87.9)
60 Seconds	59 (98.3)	2 (3.3)	95.0 (89.4, 100.0)	54 (90.0)	6 (10.0)	80.0 (69.3, 90.7)
5 Minutes	41 (68.3)	2 (3.3)	65 (52.4, 77.6)	50 (83.3)	11 (18.3)	65.0 (51.4, 78.6)

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3.1 of Study 301 CSR, Table 14.2.1.6 of Study 302 CSR, and the statistical reviewer's calculation.

For the endpoint of "no pain within 5 minutes", defined by the Applicant as that a subject needs to report no pain at two or more consecutive time points within the first 5 minutes to be counted (at a minimum, this would be at either 20 and 40 seconds, 40 and 60 seconds, or 60 seconds and 5 minutes):

- In Study 301, 98.3% (59/60) achieved "no pain within 5 minutes" in the AG-920 group, compared to 3.3% (2/60) in the vehicle group.

- In Study 302, 98.3% (59/60) achieved “no pain within 5 minutes” in the AG-920 group, compared to 35.0% (21/60) in the vehicle group.

These results are also supportive of the primary efficacy results.

3.2.4.2 Study AG-920-CS304

The primary efficacy endpoint defined in the SAP was the proportion of subjects with adequate local anesthetic effect assessed by the principal investigator (Pl) so that the eye exam for which the subject is seeing the ophthalmologist can be conducted. Two to four minutes following treatment of study medication, the Pl will be asked "Did you achieve adequate anesthesia to conduct the eye exam?" The Pl's response is recorded as "YES" for adequate anesthesia or "NO" for inadequate anesthesia. After reviewing the data as noted in Section 3.2.1.2, the primary efficacy endpoint was revised post-hoc to whether the investigator was able to perform the eye examination.

For the primary endpoint defined in the SAP, the sub-investigators’ response to the question “Did you achieve adequate anesthesia to conduct the eye exam?” (Yes or No) at 2-4 minutes post application of study treatment showed that AG-920 was statistically significant worse: the proportion of subjects with the “Yes” response by the investigator was 8/30 (26.7%) of subjects in the AG-920 group, and 28/30 (93.3%) of subjects in the proparacaine group; the difference was -66.6% (95% CI: [-82.5%, -50.7%]). However, the sub-investigators were still able to proceed performing the planned eye examinations without additional local anesthetic in 100% (30/30) subjects treated with AG-920, the same as for subjects treated with the marketed product, proparacaine. The examinations performed included slit lamp examination, dilated ophthalmoscopy, and scleral depression.

Table 10: Summary of Study 304 Results

	AG-920 (N=30) n (%)	**Proparacaine (N=30) n (%)**
No Anesthetic Response	8 (26.7)	28 (%)
Difference (95% CI)*		-66.6 (-82.5, -50.7)
p-value		<0.0001
Planned Examination Performed	30 (100)	30 (100)

* The estimated 95% CI was based on normal approximation.
Source: Tables 8 and 14.2.1.1. of Study 301 CSR, and the statistical reviewer’s calculation.

The following is the Applicant’s explanation for this inconsistency:

> *“After dosing and evaluation was completed, in reviewing the data, the Sponsor noted inconsistencies in the investigator (and sub-investigator) judgement of “adequate anesthesia to conduct an examination” and the actual conduct of that examination. In response, the investigator provided a letter of explanation (in Appendix 16.1.9 of the CSR). The investigator noted that “…These assessments of anesthetic adequacy included conjunctival touch (100% of subjects achieved this metric according to my staff and sub investigators) and sensitivity to light (more than 60% of subjects achieved this metric*

according to my staff and sub investigators). While some investigators used sensitivity to light to document lack of complete anesthesia, this is not a conclusive metric and is subjective. The conclusive anesthetic metric is conjunctival touch and this was achieved in 100% of patients."

Based on the protocol, assessments of efficacy were a determination by the investigator as to whether there was adequate local anesthetic effect to perform the eye exam for which the subject was seeing the ophthalmologist. The investigator was asked "Did you achieve adequate anesthesia to conduct the eye exam?" two to four minutes following treatment (the second drop) of IMP. The response was recorded as "YES" or "NO." In addition, the investigator was also asked "Was the Scheduled Post-IMP Eye Exam performed?" It was expected that the investigator would not perform the eye exam if they did not consider a subject to be anesthetized enough to do the exam. However, some clinicians also used photophobia in their judgement of local anesthesia, which was an inappropriate criterion according to the Applicant and the clinical review team; additionally, the investigator reported that conjunctival touch was achieved in 100% of patients.

3.2.4.3 Conclusion

Both Study 301 and Study 302 demonstrated statistical superiority of AG-920 to the vehicle in the primary efficacy endpoint of "no pain at 5 minutes"; with consistent treatment effect in both studies. Additional sensitivity analyses by the Applicant and the reviewer also support the primary efficacy results. Therefore, the statistical reviewer concludes that there is substantial evidence to support the aesthetic effect of AG-920 in adults.

For Study 304, although the response to the question "Did you achieve adequate anesthesia to conduct the eye exam?" (Yes or No) at 2-4 minutes post application of study treatment showed that AG-920 was statistically significant worse than the active comparator proparacaine, the sub-investigators were able to perform the planned eye examination without additional local anesthetic in all pediatric subjects aged 10 years or less for both groups.

3.3 Evaluation of Safety

As presented in the following table, based on the pooled safety analysis, the AG-920 group had higher percentage of subjects experiencing AEs, ocular AEs, and treatment-related AEs in both studies 301 and 302. There was no severe AE reported in both clinical studies.

Table 11: Summary of Number of Subjects Experiencing Adverse Events (Safety Population)

	Study 301		Study 302	
Category	**AG-920 (N=60)**	**Vehicle (N=60)**	**AG-920 (N=60)**	**Vehicle (N=60)**
Any AEs	34 (56.7%)	13 (21.7%)	10 (16.7%)	4 (6.7%)
Ocular AEs	32 (53.3%)	13 (21.7%)	9 (15.0%)	4 (6.7%)
Severe AEs	0	0	0	0

AEs Related to Treatment	34 (56.7%)	13 (21.7%)	9 (15.0%)	4 (6.7%)

Source: Table 11 of Study 301 CSR, and Table 18 of Study 302 CSR.

In Study 301, the most frequently reported adverse event was instillation site pain, seen in 53% (32/60) subjects in the AG-920 group and 7% (4/60) subjects in the vehicle group. Dysgeusia was reported in 7% (4) subjects in the AG-920 treatment group and none of the subjects in the vehicle group. In Study 302, the most frequently reported AE was conjunctival hyperaemia, seen in 11.7% (7/60) and 3.3% (2/60) subjects in the AG-920 and vehicle groups, respectively. The only systemic AE was a single report of headache in the AG-920 group.

Table 12: Safety Analysis: Treatment-emergent ocular adverse events associated with ≥ 1.0% in the study eye (Safety Population)

System Organ Class Preferred Term	Study 301		Study 302	
	AG-920 (N=60)	Vehicle (N=60)	AG-920 (N=60)	Vehicle (N=60)
Eye Disorders	5 (8.3%)	10 (16.7%)	9 (15.0%)	4 (6.7%)
Conjunctival haemorrhage	0	0	1 (1.7%)	1 (1.7%)
Conjunctival hyperaemia	4 (6.7%)	9 (15.0%)	7 (11.7%)	2 (3.3%)
Eye pain	0	1 (1.7%)	0	1 (1.7%)
Ocular hyperaemia	1 (1.7%)	0	0	0
Vision blurred	0	0	1 (1.7%)	0
Gastrointestinal Disorders	4 (6.7%)	0	6 (3.3%)	1 (0.5%)
Dysgeusia	4 (6.7%)	0	6 (3.3%)	1 (0.5%)
General Disorders And Administration Site Conditions	32 (53.3%)	4 (6.7%)		
Instillation Site Pain	32 (53.3%)	4 (6.7%)		
Nervous system disorders	0	0	1 (1.7%)	0
Headache	0	0	1 (1.7%)	0

Source: Table 12 of Study 301 CSR, and Table 19 of Study 302 CSR.

The Applicant reported no adverse events in Study 304.

For a comprehensive review of safety, please refer to Dr. Shilpa Rose's clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Subgroup analyses based on gender, race, age, iris color for each study were performed (see results in below) by the statistical reviewer. In both studies, the subgroup analyses results were similar to those seen for the overall population for each demographic subgroup.

Table 13: Subgroup Analyses for Proportion of Subjects with No Pain at 5 Minutes (Studies 301 and 302, ITT)

	Study 301		Study 302	
	AG-920 (N=60) n (%)	Vehicle (N=60) n (%)	AG-920 (N=60) n (%)	Vehicle (N=60) n (%)

Overall Response	41 (68.3)	2 (3.3)	50 (83.3)	11 (18.3)
Age				
<65	41/60 (68.3)	2/59 (3.4)	46/56 (82.1)	11/60 (18.3)
≥ 65	0/0	1/1 (100.0)	4/4 (100.0)	0/0
Sex				
Female	23/33 (69.7)	0/34	27/31 (87.1)	8/36 (22.2)
Male	18/27 (66.7)	2/26 (7.7)	23/29 (79.3)	3/24 (12.5)
Race				
White	33/49 (67.4)	2/49 (4.1)	49/58 (84.5)	11/58 (19.0)
Other	8/11 (72.7)	0/11	1/2 (50.0)	0/2
Iris Color				
Blue	8/12 (66.7)	1/14 (7.1)	n/a	n/a
Brown	23/33 (69.7)	0/28	46/56 (82.1)	8/50 (16.0)
Green	2/4 (50.0)	0/5	0/0	2/2 (100.0)
Hazel	8/11 (72.7)	1/13 (7.7)	4/4 (100.0)	2/6 (33.3)

Note: ITT = Intent-to-Treat, Diff = Difference, CI = Confidence Interval.
Source: Statistical reviewer's analysis based on ADQS and ADSL datasets of Study 301, ADEFF and ADSL datasets of Study 302.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for this NDA submission.

5.2 Collective Evidence

Both Study 301 and Study 302 in adults demonstrated superiority of the AG-920 to the vehicle for the primary efficacy endpoint of "no pain at 5 minutes". Sensitivity analyses demonstrated the robustness of the primary analysis results. Subgroup analyses showed a consistent treatment effect of the AG-920 across subgroups of sex, age, race, and iris color.

In the pediatric study 304, although the response to the question "Did you achieve adequate anesthesia to conduct the eye exam?" (Yes or No) at 2-4 minutes post application of study treatment showed that the proportion with "Yes" response in AG-920 group (8/30 (26.7%)) was statistically significant worse than in the active comparator proparacaine group (28/30 (93.3%)), the sub-investigators were able to perform the planned eye examination without additional local anesthetic in all pediatric subjects aged 10 years or less for both groups.

5.3 Conclusions and Recommendations

In conclusion, the two Phase 3 studies in adults (Studies 301 and 302) provided statistically substantial evidence that AG-920 (Articaine Sterile Topical Ophthalmic Solution 8%) is superior to vehicle in providing ocular surface anesthesia prior to ocular procedures. Therefore, the statistical reviewer recommends the approval of AG-920 for adults.

In the pediatric study, all the sub-investigators were able to perform the planned eye examination without additional local anesthetic in all pediatric subjects aged 10 years or less for both AG-920 group and the active comparator proparacaine group, with the caveat noted in the above Section 5.2. Without knowing the clinical criteria for deciding local anesthetic effect in pediatrics or the clinical applicability of extrapolating the local anesthetic effects from adults to pediatrics, the statistical reviewer would like to defer the efficacy conclusion for pediatric subjects to the clinical review team.

5.4 Labeling Recommendations

In the proposed label, the Applicant doesn't include the efficacy results of Study AG-920-CS304 in Section 14 CLINICAL STUDIES; but made the claim "(b) (4) ." in Section 8.4 Pediatric Use. The statistical reviewer would like to defer the label claim of efficacy in pediatric subjects to the clinical review team.

Since the Applicant didn't specify any statistical procedure for controlling Type I error in testing multiple secondary endpoints, the statistical reviewer doesn't recommend that the results of the secondary endpoints include in Section 14 Clinical Studies.

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