Summary Review of NDA 218643

Cross Discipline Team Leader, Deputy Division Director Memo

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, MD, William Boyd, MD
Subject	Summary Review
NDA #	216843
Applicant	American Genomics, LLC
Received Date(s)	October 16, 2024
PDUFA Goal Date	August 15, 2025
Proprietary Name	Cyklx
Established Name	articaine ophthalmic solution, 8%
Dosage Form(s)	Topical ophthalmic solution
Proposed Indication(s)/ Population(s)	For ocular anesthesia prior to ocular procedures and/or intraocular injections in adults and pediatric patients
Applicant Proposed Dosing Regimen	Two drops applied 30 seconds apart to the ocular surface
Regulatory Action	**APPROVAL**

NDA 218643 Review Team Role	**Reviewer**
OND RPM	Nick Connis
CDTL	Rhea Lloyd
Clinical Reviewer	Shilpa Rose
Pharmacology/Toxicology Reviewer	Erin Ruhland
Statistical Reviewer	Yunfan Deng
Clinical Pharmacology Reviewer	Youssef Mousa
OND Labeling Reviewer	Derek Alberding
OPQ Application Technical Lead	Chunchun Zhang
RBPM	Shazma Aftab
Drug Substance	Sa Wang/ Sithamalli Chandramouli
Drug Product	Milton Sloan/ Chunchun Zhang
Manufacturing	Dhamara Gunawardana/ Nathan Davis
Microbiology	Dustin Thomas/ Yuansha Chen
CDRH Reviewers	No review needed
DMEPA Team Lead / Reviewer	Valerie Vaughn / Sofanit Getahun
OSI CSO	Roy Blay
OPDP Reviewer	David Foss
Deputy Division Director	William Boyd
Deputy Office Director/ Office Director	Alexander Gorovets/ Charles Ganley

1. Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OAG	open angle glaucoma
OCS	Office of Computational Science
OHT	ocular hypertension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report

PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

2. Summary

American Genomics, LLC has submitted a New Drug Application (NDA) for Articaine Sterile Topical Ophthalmic Solution for ocular surface anesthesia prior to ocular procedures and/or intraocular injections. American Genomics submits this NDA pursuant to section 505(b)(2) of the Food, Drug, and Cosmetics (FD&C) Act and intends to rely on the Agency's previous findings of systemic safety for the approved listed drug (LD), Septocaine® (articaine HCl and epinephrine, NDA 20-971).

Articaine hydrochloride is an amide local anesthetic. Local anesthetics block the generation and conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of the affected nerve fibers.

In both Phase 3 studies, AG-920-CS301 and AG-920-CS302, when compared with placebo, CYKLX (articaine ophthalmic solution) 8% met the primary efficacy endpoint. A statistically significant treatment group difference compared to placebo for the primary endpoint, the proportion of subjects with no pain at 5 minutes. The endpoint refers to a conjunctival pinch performed with forceps given 5 minutes after dose administration of the study drug.

AG-920-CS304 was conducted in pediatric patients aged 0-10 years. This study met its primary endpoint, the ability to perform the eye examination without additional local anesthetic. AG-920 was therapeutically equivalent to proparacaine. Safety in the pediatric population was also demonstrated.

CYKLX (articaine ophthalmic solution) 8% is aseptically filled into 0.5 mL low-density polyethylene (LDPE) blow-fill-seal (BFS) vials separated into cards of 5 vials each and packaged into an aluminum foil overwrap (pouch) (b) (4) Each vial contains 0.40 ± (b) (4) mL of DP and produces a drop size of approximately (b) (4) µL. Each individual vial is embossed with the lot number (b) (4) Each pouch is inkjet coded with the lot number for identification.
The most common adverse events reported with CYKLX were instillation site pain seen in 24.5% (70/286) of subjects, dysgeusia (2.4%), conjunctival hyperemia (1.4%).

The results of the submitted clinical trials support the safety and efficacy of CYKLX (articaine ophthalmic solution) 8% for ocular surface anesthesia prior to ocular procedures and /or intraocular injections in adult and pediatric patients.

3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The adequate and well-controlled Phase 3 studies (AG-920-CS301 and AG-920-CS302) contained in this submission establish the efficacy of articaine sterile topical ophthalmic solution 8%, dosed two drops applied 30 seconds apart to the ocular surface prior to ocular procedures and/or intraocular injections. Five studies, AG-920-CS301, AG-920-CS302, AG-920-CS303, AG-920-CS304 and AG-920-CS101 were completed in healthy adult and pediatric subjects. Both AG-920-CS301 and AG-920-CS302 met their primary efficacy endpoints, the proportion of subjects with no pain at 5 minutes measure by conjunctival pinch given 5 minutes after dose administration of the study drug. The treatment effect (difference from placebo) was 65% in both studies ($P<0.0001$). In both studies, subjects treated with AG-920 achieved clinically and statistically significance on the following secondary endpoints -- anesthesia within 5 minutes (98.3% in both studies), a rapid mean onset of anesthesia in less than 30 seconds in both studies, and a mean duration of anesthesia of 4.8 minutes in AG-920- CS301 and 12.8 minutes in AG-920-CS302.

AG-920-CS304 was a pediatric efficacy and safety study The primary efficacy endpoint was whether the investigator was able to perform the eye examination. In all subjects in each treatment group, the investigator was able to perform the eye examination without additional local anesthetic. AG-920 was therapeutically equivalent to proparacaine. AG-920-CS101 was a Pharmacokinetic study and AG-920-CS303 was a safety study.

The safety of articaine sterile topical ophthalmic solution 8% was assessed in over 330 subjects exposed to Articaine Sterile Topical Ophthalmic Solution, all at the 8% strength across 5 trials. The most common adverse event with Articaine was instillation site pain seen in 24.5% (70/286) of subjects, compared to 6.9% (14/203) in subjects in the placebo group.

The benefit of Articaine single dose (2 drops 30 seconds apart) in adults and children ages 0-17 for ocular surface anesthesia prior to ocular procedures and/or intraocular injections is expected to outweigh the risks associated with its use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The cornea and conjunctiva have numerous touch and pain receptors which are triggered with ocular or periocular touch. There are multiple ophthalmic procedures which require a patient to remain still and not blink or respond to touch or pain in the eye.	Corneal and conjunctival anesthesia are required for patients to be able to hold still during ophthalmic procedures.
Current Treatment Options	Tetracaine ophthalmic solution, lidocaine ophthalmic solution and proparacaine ophthalmic solution will provide corneal and conjunctival anesthesia	Topical corneal and conjunctival anesthetics have been used for decades to provide corneal anesthesia.
Benefit	The intended procedure can be completed.	• Two trials, AG-920-CS301 and AG-920-CS302 demonstrated that articaine was effective in providing ocular surface anesthesia prior to ocular procedures and/or intraocular injections. One trial, AG-920-CS304 demonstrated that articaine was therapeutically equivalent to proparacaine in pediatric patients
Risk and Risk Management	• Corneal and conjunctival anesthesia inhibits self-protective reflexes and healing mechanism of the cornea and conjunctiva. • The most common adverse events experienced with articaine were instillation site pain seen in 24.5% (70/286) of subjects, compared to 6.9% (14/203) in subjects in the placebo group.	• The short-term efficacy duration and the localized area of effect limit potential injuries. • The risk-benefit profile of treatment with Articaine Sterile Ophthalmic Solution 8.0 for providing ocular surface anesthesia prior to ocular procedures and/or intraocular injections favors its use for the intended indication.

4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed
	☒	Clinical outcome assessment (COA) data, such as		Section 6
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.1 Clinical Primary Endpoints
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
☐	Patient experience data was not submitted as part of this application.			

5. Product Quality

Application/Product Information

From the Integrated Quality Assessment finalized on 7/22/2025:

NDA Number.	218643
Applicant Name	American Genomics, LLC
Drug Product Name	CYKLX (Articaine ophthalmic solution)
Dosage Form.	Solution/drops
Proposed Strength(s)	8%
Route of Administration	Ophthalmic
Maximum Daily Dose	(b) (4)
Rx/OTC Dispensed	Rx
Proposed Indication	Local anesthetic indicated for ocular surface anesthesia prior to ocular procedures and/or intraocular injections
Drug Product Description	Articaine ophthalmic solution is a clear, colorless, sterile, preservative-free aqueous solution and packaged in single dose blow-fill-seal vias
Co-packaged product information	NA
Device information:	Single dose vials; CDRH consult was determined to be not necessary on 10/25/2024.
Storage Temperature/ Conditions	20-25 °C

1. **Final Overall Recommendation - Approval**
2. **Action Letter Information**

   a. **Expiration Dating:** An expiration-dating period of 36 months for the commercial product is granted for Articaine ophthalmic solution, 8% stored in a single dose vial at 20 °C to 25 °C (68 °F to 77 °F).

   b. **Additional Comments for Action:** NA

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process and quality microbiology aspects.

The product is regulated as a drug and device combination product per the Genus decision. CDRH confirmed that no CDRH consult was necessary on Oct 25, 2024.

OPMA issued an overall recommendation of "approval" on Jul 6, 2025. Therefore, NDA 218643 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - N/A
Microbiology - Adequate
Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No Comments: NA

Comparability Protocols (PACMP): No Comments: NA

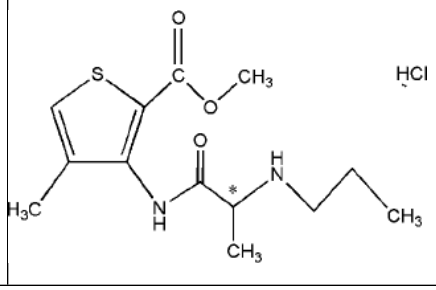
Additional Lifecycle Comments: NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph. D., Jul 22, 2025

Articaine Hydrochloride Drug Substance Specifications

Summary of information

INN/USP Name	Articaine Hydrochloride
Chemical name	Methyl 4-methyl-3-[[(2RS)-2-(propylamino) propanoyl] amino] thiophene-2-carboxylate hydrochloride
Other non-proprietary names	1. 3-propylamino-α-propionylamino-2-carbomethoxy-4-methylthiophene hydrochloride 2. Methyl 4-methyl-3-(2-propylaminopropionamido) thiophene-2-carboxylate hydrochloride 3. Carticaine Hydrochloride
Company or laboratory code	(b) (4)
CAS registry number	23964-57-0

Structural Formula	

	* Chiral center
Molecular Formula	C13H21ClN2O3S
Molecular Weight	320.8 g/mol

Physical and Chemical Properties of Articaine Hydrochloride

Physical/Chemical Properties	**Description**
Appearance	Crystalline powder. White or almost white
Odor	Odor free
Specific rotation	0.0° (Racemic mixture)
Solubility Profile	Freely soluble in water, in alcohol and methanol; slightly soluble in acetone and methylene chloride
Hygroscopicity	Not hygroscopic
Polymorphs	(b) (4)
Chiral centers	One chiral center located at * marked carbon atom
UV Spectrum	UV absorbance maximum at 272 nm

Facility Information

Name/Address/Contact	*Responsibility*
(b) (4)	DMF Holder

(b) (4)	Manufacturing, Packaging and Testing site (b) (4)
	Contract testing laboratory (microbial limits and endotoxin)
Woodstock Sterile Solutions 2210 Lake Shore Drive, Woodstock, IL 60098, USA DUNS Number: 117895702 FEI Number: 1419377 Contact Person: Sheila Moran, Senior Vice President of Quality Telephone No.: +1 (b) (4) Email: Sheila.moran@wssterile.com	Testing of incoming Drug Substance for release to Drug Product manufacturing
(b) (4)	Testing of incoming Drug Substance for release to Drug Product manufacturing

S.4 Control of Drug Substance

Current Specification of Drug Substance Provided by the Drug Product Manufacturer (Dated 10/16/2024)

Attribute	Test Procedure	Specification
Description	STW-MIA-0030[1]	White or almost white, crystalline powder
Identification: [redacted] (b) (4)		Conforms
Impurities: Inorganic Impurities 4. Residue on Ignition 5. Organic Impurities 6. Articaine related compound A 7. Articaine acid 8. Ethylarticaine 9. Articaine related compound E 10. Articaine Acid-propionamide 11. Butylarticaine 12. Dipropylarticaine 13. 3-Aminoarticaine	USP <281> Current USP Monograph	NMT[2] 0.1% NMT 0.2% NMT 0.1% NMT 0.1% NMT 0.1% NMT 0.1% NMT 0.1% NMT 0.1% NMT 0.1%
- Articaine isopropyl ester - Bromo compound - Any other individual impurity - Total impurities (excluding Articaine related compound A)		NMT 0.1% NMT 0.1% NMT 0.10% NMT 0.5%
Specific Tests: pH Loss on Drying	 USP <791> USP <731>	 (b) (4) NMT (b) (4)%
Assay: Potentiometric titration (on dried basis)	Current USP Monograph	(b) (4)%
Additional Tests: Residual Solvents (GC) (b) (4) Endotoxin Microbial Limits Total Aerobic Microbial Count (TAMC) Total Combined Yeasts/Molds (TYMC)	PDR-ATM-AXK-0011[2] PDR-ATM-AXK-0012[2] USP <85> USP <61> USP <61>	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) EU/mg NMT (b) (4) CFU/g NMT (b) (4) CFU/g

[1] Woodstock In-house method

2 (b) (4)

Drug Product Specification

Table 2: Drug Product Composition

Component	Function	Target Concentration (% w/v)	Amount (g/L)
Articaine Hydrochloride (USP)	Active Ingredient	9.02[1]	90.20 ± (b) (4)
Boric Acid (NF)	(b) (4)		
D-Mannitol (USP)			
Sodium Acetate Trihydrate (USP)			
Glacial Acetic Acid (USP)			
Edetate Disodium Dihydrate (USP)			
Water for Injection (USP)			
(b) (4)			

[1]Equivalent to 8.0% of Articame, as free base

(b) (4)

Table 1: Drug Product Release and Stability Specifications

Analytical Test	Test Procedure	Acceptance Criteria	Stability Y/N
Appearance (including color and clarity)[1, 3]	(b) (4)-0104[1, 2] Visual[3] USP <790>	Clear, colorless solution; Solution visibly free of foreign material	Yes
Appearance of Packaging[1, 3]	(b) (4)-0104[1, 2] Visual[3] USP <790>	Foil free of damage, scuffs, and discoloration	Yes
Identification by UV[1, 3]	ATM-AXK-J0001[1] PDR-ATM-AXK-0003[3]	The sample UV spectrum exhibits absorption maxima at wavelengths within ± 2 nm of corresponding spectrum of the standard	No
Identification by HPLC[1, 3]	ATM-AXK-J0001[1] PDR-ATM-AXK-0003[3]	Retention time of peak corresponding to Articaine in the sample conforms to that of the standard	No
Uniformity of Dosage by Weight[1, 3]	USP <905>	According to Current USP	No
Fill Volume / Minimum Fill[1, 3]	USP <755>	(b) (4) mL	No
Assay[1, 3]	ATM-AXK-J0001[1] PDR-ATM-AXK-0003[3]	95.0 – 105.0% LC	Yes
Impurities[1, 3]	Impurities by HPLC: ATM-AXK-J0001[1] PDR-ATM-AXK-0003[3] Impurities by GC-MS: PDR-ATM-AXK-0009[1]	**Impurities by HPLC:** Report any peak: ≥ (b) (4)% Impurity (b) (4) ≤ (b) (4)% Unknown RRT (b) (4)% Any individual unspecified: ≤ (b) (4)% **Impurities by GC-MS:** **Limit ≤** (b) (4) **ppm:** • (b) (4) • **Limit ≤** (b) (4) **ppm:** (b) (4)	Yes

Analytical Test	Test Procedure	Acceptance Criteria	Stability Y/N
		(b) (4) Total Impurities ≤ (b) (4)%	
pH[1, 3]	ATM-AXK-J0002[2] PDR-ATM-AXK-0004[3] USP <791>	4.5 – 5.0	Yes
Osmolality[3]	PDR-ATM-AXK-0005[3] USP <785>	(b) (4) mOsm/kg	Yes
Particulate Matter[3]	USP <789>, <788>	NMT (b) (4) particles/mL > 10 µm NMT particles/mL > 25 µm NMT particles/mL > 50 µm	Yes
Water Loss/Gain[1,3]	Per Protocol[5]	< (b) (4)%	Yes
Sterility[3]	USP <71>	No Growth	Yes (Annually)
Leak Detection (Foil Pouch)[4]	ASTM F1140	No leaks	Yes

1 Testing performed by (b) (4)
2 Procedure available at
3 Testing performed by
4 Testing performed by
5 Reference Module 3.2 P.5.2

NMT = not more than
NFPI = no first pass identification leachable

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)		Drug Master File Holder Only || 356h Status: Pending NEC	No Evaluation Necessary
		Manufacturing, Packaging and Testing site (b) (4) || 356h Status: Pending CSN	Approve - Based on Previous History
		Contract testing laboratory (microbial limits and endotoxin) || 356h Status: Pending LMN	Approve - Based on Previous History

Woodstock Sterile Solutions 2210 Lake Shore Drive n/a, Woodstock, IL, USA, 60098	1419377	Testing of incoming Drug Substance for release to Drug Product manufacturing. Manufacturing, In-process control, packaging, secondary packaging, labelling and distribution of Drug Product, sterility testing for release and stability || 356h Status: Pending SLQ	Approve - Based on Previous History
		MIS	No Evaluation Necessary
(b) (4)		Testing of incoming Drug Substance for release to Drug Product manufacturing. Release and stability testing of Drug Product || 356h Status: Pending	Approve - Based on Previous History
		LCP LMS	
		Sponsor. Batch Release and Disposition || 356h Status: Pending MIS NEC	No Evaluation Necessary
		Release and stability testing of Drug Product || 356h Status: Pending LCP	Approve - Based on Previous History
		Release and stability testing (Leak detection – Drug Product Foil Pouch) || 356h Status: Pending LCP	Approve - Based on Previous History

6. Nonclinical Pharmacology/Toxicology

From the Nonclinical Pharmacology/ Toxicology review finalized on July 9, 2025:

> Note: A previously proposed tradename, [redacted] (b) (4) is used by Pharmacology/ Toxicology in this review section instead of CYKLX. Both represent the articaine ophthalmic solution, 8% product.

Brief Discussion of Nonclinical Findings

505(b)(2) Bridge:

The maximum approved dose of Septocaine is up to 7 mg/kg of articaine (i.e., 420 mg articaine for a 60 kg adult) administered by submucosal or "nerve block" injection. The proposed dose of [redacted] (b) (4) is 4.8 mg/eye/day (9.6 mg/day bilateral dose). The approved injected dose of Septocaine® exceeds the dose of [redacted] (b) (4) by a factor of 88- and 44-fold for a unilateral and bilateral dose, respectively.

Following intraoral administration of a 476 mg dose of Septocaine®, mean articaine C_{max} was 2037 and 2145 ng/mL for articaine solution containing epinephrine 1:100,000 and 1:200,000, respectively (Septocaine® package insert; see Appendix A of [the Pharmacology Toxicology review finalized 7/9/25].

In patients who received a unilateral topical ocular administration of [redacted] (b) (4) (2 drops, 30 seconds apart in the study eye; 4.8 mg), a mean C_{max} of 5.4 ng/mL was reported.
The difference in C_{max} between the LD and the Applicant's formulation is approximately 400-fold.
This adequately establishes a bridge to the LD based on clinical exposure.

Recommendations

Approvability

This NDA is approvable from a Pharmacology/Toxicology perspective.

Labeling
Applicant's Proposed PLLR Labeling for [redacted] (b) (4) (Nonclinical sections and relevant Clinical Pharmacology sections)

[redacted] (b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

7. Clinical Pharmacology

From the Clinical Pharmacology review finalized on June 20, 2025:

Articaine is amide local anesthetic. The Applicant (American Genomics, LLC) has submitted the 505 (b) (2) new drug application (NDA) seeking marketing approval for Cyklx (articaine 8% sterile topical ophthalmic solution) for ocular surface anesthesia prior to ocular procedures and/or intraocular injections. The applicant is relying on information from the published literature and publicly available prescribing information, along with the Agency's finding of the safety and effectiveness of Septocaine (NDA 020971, articaine hydrochloride and epinephrine bitartrate, reference listed drug) in conjunction with the completed quality, nonclinical and clinical program to support this 505(b)(2) NDA submission. The proposed dosing regimen of Cyklx is 2 drops applied 30 seconds apart to the ocular surface.

The clinical development program for articaine 8% sterile topical ophthalmic solution included a phase 1, open-label, single-dose study in healthy subjects (study AG-920-CS101) and a phase 3, vehicle- controlled, parallel-group evaluation of the local anesthetic effect of articaine 8% sterile topical ophthalmic solution (studies AG-920-CS301 and AG-920-CS302).

The focus of this review is to evaluate the systemic exposure in the clinical pharmacology study AG-920-CS101.

Recommendations

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 218643 and finds the application acceptable to support approval from a clinical pharmacology perspective.

Key Review Issues and Recommendations

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness of proposed articaine 8% sterile topical ophthalmic solution was based on the pivotal clinical studies AG-920-CS301 and AG-920-CS302 in healthy subjects.
General dosing instructions	The recommended dosing regimen is 2 drops applied 30 seconds apart to the ocular surface prior to ocular procedures and/or intraocular injections.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments recommendations based on any intrinsic or extrinsic factors.
Labeling	The proposed Clinical Pharmacology relevant information in Section 12.3 appears acceptable.
Bridge between the to-be-marketed product and the clinical trial product	Not applicable. There is no difference between the clinical trial formulation and the to be marketed formulation

8. Clinical Efficacy

Clinical studies AG-920-CS301 and AG-920-CS302 were double-masked, randomized, placebo-controlled parallel design studies in healthy subjects in the United States. Clinical data for studies AG-920-CS301, AG-920-CS302, AG-920-CS303, AG-920-CS304 and AG-920-CS101 were also reviewed to support safety and efficacy. Subjects who provided informed consent and 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 identical appearing placebo into one (study) eye (2 drops 30 seconds apart).
To assess efficacy, subjects underwent a conjunctival pinch procedure and the pain associated with the pinch was rated by the subject. Study drug dosing and conjunctival pinch procedure were performed by the study staff. The placebo control, the vehicle without the active ingredient of the drug product, was deemed to be ethically acceptable.

Demographic Characteristics in Phase 3
Baseline characteristics were well balanced among the treatment groups with regard to demographic data.

Demographic Profile of Patients in Controlled Efficacy Trials in Adult Subjects

Study	*AG-920-CS301*				*AG-920-CS302*			
Group	*Overall*	*AG-920*	*Placebo*	*p-value*	*Overall*	*AG-920*	*Placebo*	*p-value*
N	120	60	60	60	120	60	60	60
Age (years)				0.4700				0.4424
n	120	60	60		120	60	60	
Mean	31.31	32.60	30.02		35.9	34.9	37.0	
SD	12.57	13.72	11.26		30.5	28.0	33.0	
Median	27.00	27.00	27.00		15.0	15.6	14.4	
Minimum	18.00	18.00	19.00		74.0	74.0	63.0	
Maximum	65.00	64.00	65.00		18.0	18.0	18.0	
≥ 65 years of age, n (%)	1 (0.8)	0 (0.0)	1 (1.7)		4 (3.3)	4 (6.7)	---	
Gender, n (%)				0.8541				0.3580
Female	67 (55.8)	33 (55.0)	34 (56.7)		67 (55.8)	31 (51.7)	36 (60.0)	
Male	53 (44.2)	27 (45.0)	26 (43.3)		53 (44.2)	29 (48.3)	24 (40.0)	
Race, n (%)				0.5724				1.000
American Indian Or Alaska Native	1 (0.8)	1 (1.7)	0 (0.0)		---	---	---	
Asian	20 (16.7)	10 (16.7)	10 (16.7)		2 (1.7)	1 (1.7)	1 (1.7)	
Native Hawaiian Or Other Pacific Islander	1 (0.8)	0 (0.0)	1 (1.7)		---	---	---	
White	98 (81.7)	49 (81.7)	49 (81.7)		116 (96.7)	58 (96.7)	58 (96.7)	
Other					2 (1.7)	1 (1.7)	1 (1.7)	
Ethnicity, n (%)				1.0000				1.0000
Hispanic	26 (21.7)	13 (21.7)	13 (21.7)		118 (98.3)	59 (98.3)	59 (98.3)	
Non-Hispanic	94 (78.3)	47 (78.3)	47 (78.3)		2 (1.7)	1 (1.7)	1 (1.7)	
p-value								
Color of Iris, n (%)				0.8395				0.1919
Blue	26 (21.7)	12 (20.0)	14 (23.3)		---	---	---	
Brown	61 (50.8)	33 (55.0)	28 (46.7)		106 (88.3)	56 (93.3)	50 (83.3)	
Green	9 (7.5)	4 (6.7)	5 (8.3)		2 (1.7)		2 (3.3)	
Hazel	24 (20.0)	11 (18.3)	13 (21.7)		10 (8.3)	4 (6.7)	6 (10.0)	
Black	---	---	---		2 (1.7)	---	2 (3.3)	2 (3.3)
Study Eye, n (%)				0.7150				0.0176

Study	*AG-920-CS301*				*AG-920-CS302*			
Group	*Overall*	*AG-920*	*Placebo*	*p-value*	*Overall*	*AG-920*	*Placebo*	*p-value*
Left	60 (50.0)	31 (51.7)	29 (48.3)		61 (50.8)	24 (40.0)	37 (61.7)	
Right	60 (50.0)	29 (48.3)	31 (51.7)		59 (49.2)	36 (60.0)	23 (38.3)	

Source: Module 2.7.3 Summary of Clinical Efficacy, Table 2

In two similarly designed, confirmatory, phase 3, randomized, placebo-controlled, double-masked, parallel studies in healthy subjects, more than two-thirds of subjects treated with AG-920 were anesthetized at 5 minutes. The treatment effect (difference from placebo) was 65% in both studies (P<0.0001).

The two studies, each at a geographically different site, differed in the placebo response rate: 3.3% in AG-920-CS301 and 18.3% in AG-920-CS302. The applicant provided one published paper using this same methodology at a different site 15 years prior (Busbee, Massachusetts) in which the placebo response rate was 22%. The applicant also noted the placebo response rate in the studies supporting the approval of Iheezo® (chloroprocaine gel) ranged from 12% to 20% (Iheezo® Package Insert).

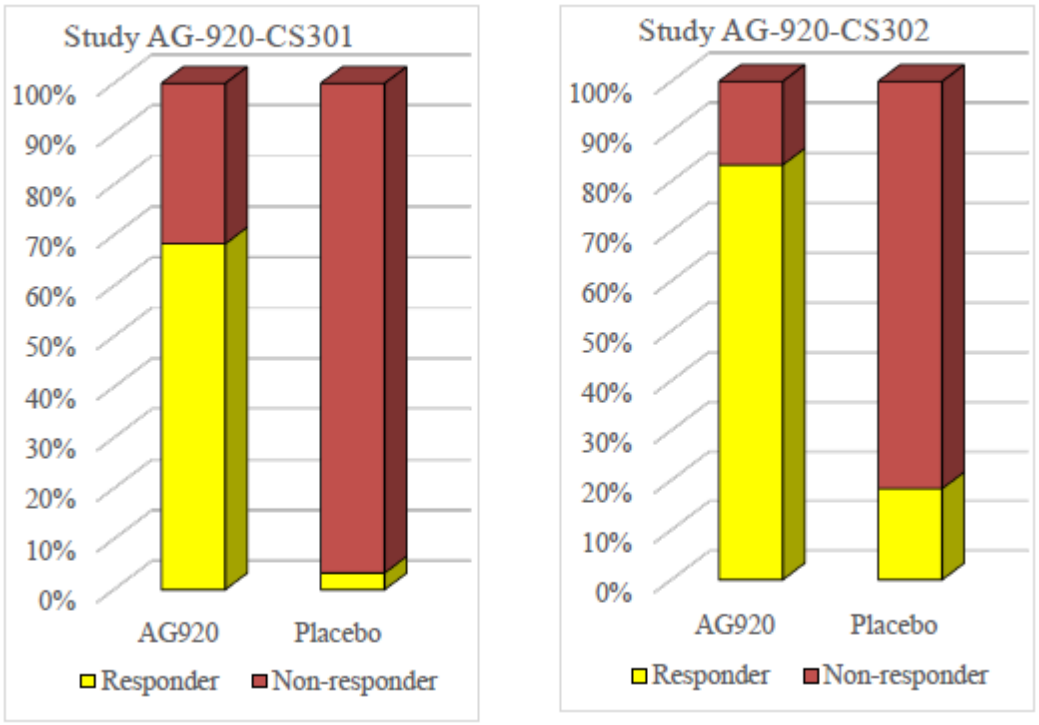
Reviewer's Comment: *Multiple factors may contribute to the difference in placebo response rate between the studies; for example, patients' previous exposure to topical anesthetics, subject and investigators expectations, etc.*

Table 4: Primary endpoint: Summary of Proportion of Subjects with No Pain at 5 Minutes (ITT Population, Adults Subjects)

Study	*AG-920-CS301*			*AG-920-CS302*		
Group	*Overall*	*AG-920*	*Placebo*	*Overall*	*AG-920*	*Placebo*
N	120	60	60	120	60	60
Proportion of Subjects with No Pain at 5 Minutes	43 (35.8)	41 (68.3)	2 (3.3)	61 (50.8)	50 (83.3)	11 (18.3)
Proportion of Subjects with Pain at 5 Minutes	77 (64.2)	19 (31.7)	58 (96.7)	59 (49.2)	10 (16.7)	49 (81.7)
Difference in proportion of responders (%) between treatment groups	65.00%			65.00%		
p-value for between treatment group comparison	<0.0001			<0.0001		
95% Confidence interval (CI) for the difference in proportion of responders between the two treatment groups	52.4% to 77.6%			47.5% to 75.3%		

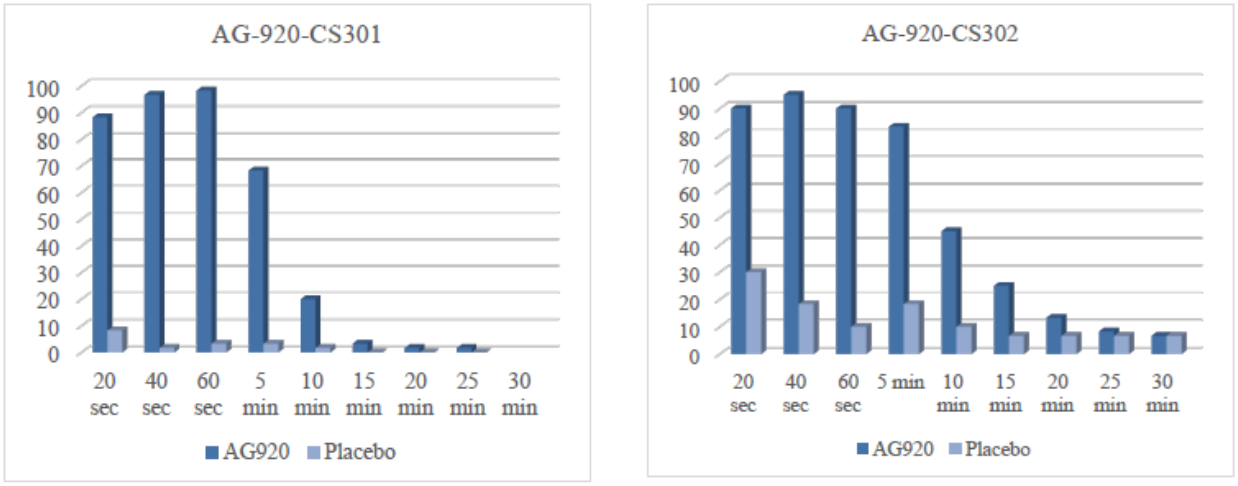
N (% of subjects)
Source: Module 2.7.3 Summary of Clinical Efficacy, Table 4

Figure 1: **Primary endpoint: Summary of Proportion of Subjects with No Pain at 5 Minutes (ITT Population, Adults Subjects)**



Dose/Dose Response, Durability of Response, Persistence of Effect

Figure 2: **Time-Course of Proportion of Subjects with No Pain**



9. Safety

The clinical development program for Articaine Sterile Topical Ophthalmic Solution involved a total of 563 subjects. Of these, 330 were exposed to Articaine Sterile Topical Ophthalmic Solution, all at the 8% strength. All subjects received a single dose (two drops, 30 seconds apart). Of these subjects, a subset of 16 (13 active, 3 placebo) underwent specular microscopy pre-study and 3 months subsequently. Consistent with the indication, all subjects were healthy volunteers. Study AG-920-CS304 was conducted in pediatric subjects. All other studies were conducted in adult.

Table 2: Exposure to Articaine Sterile Topical Ophthalmic Solution

		Treatment			
Study Number	***Type***	***AG-920***	***Placebo***	***Proparacaine***	**Total**
AG-920-CS101	Phase 1	14	0	0	**14**
AG-920-CS301	Phase 3	60	60	0	**120**
AG-920-CS302	Phase 3	60	60	0	**120**
AG-920-CS303	Safety	166	83	0	**249**
AG-920-CS304	Pediatric	30	0	30	**60**
Total		330	203	30	**563**

Source: Module 2.7.4 Summary of Clinical Safety, Section 2.7.4.1.2

Reviewer's Comments:
The overall exposure to articaine ophthalmic solution was adequate to assess its safety when administered topically for the intended indication.

Subject Disposition
Among the 563 subjects in five clinical studies, there were only two subjects who did not complete the study.

Both of these were in Study AG-920-CS303. Subject (b) (6) (AG-920 group) had a protocol deviation and was inadvertently enrolled although they did not meet inclusion criteria 7. Subject (b) (6) (placebo group) was lost to follow-up. Both were in the specular microscopy subset.

Table 4: Summary of Demographic Characteristics (Safety Population: All Studies)

Characteristic	AG-920 n (%)	Placebo n (%)	Proparacaine n (%)	All Subjects n (%)
Age (years)				
N	330	203	30	563
Mean (SD)	34.2 (17.65)	36.2 (14.71)	6.3 (2.53)	33.4 (17.40)
Median	29.0	31.0	6.8	29.0
Minimum, Maximum	0.6, 79.0	18.0, 72.0	1.7, 9.8	0.6, 79.0
Age Group (years), n (%)				
<18	30 (9.1%)	0 (0.0%)	30 (100.0%)	60 (10.7%)
18-29	136 (41.2%)	94 (46.3%)	0 (0.0%)	230 (40.9%)
30-39	53 (16.1%)	35 (17.2%)	0 (0.0%)	88 (15.6%)
40-49	31 (9.4%)	25 (12.3%)	0 (0.0%)	56 (9.9%)
50-64	58 (17.6%)	39 (19.2%)	0 (0.0%)	97 (17.2%)
65+	22 (6.7%)	10 (4.9%)	0 (0.0%)	32 (5.7%)
Sex, n (%)				
Female	195 (59.1%)	118 (58.1%)	16 (53.3%)	329 (58.4%)
Male	135 (40.9%)	85 (41.9%)	14 (46.7%)	234 (41.6%)
Race, n (%)				
American Indian or Alaska Native	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Asian	24 (7.3%)	16 (7.9%)	0 (0.0%)	40 (7.1%)
Black or African American	2 (0.6%)	2 (1.0%)	1 (3.3%)	5 (0.9%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
White	302 (91.5%)	182 (89.7%)	29 (96.7%)	513 (91.1%)
Other	1 (0.3%)	1 (0.5%)	0 (0.0%)	2 (0.4%)
Ethnicity, n (%)				
Hispanic or Latino	221 (67.0%)	128 (63.1%)	29 (96.7%)	378 (67.1%)
Not Hispanic or Latino	109 (33.0%)	75 (36.9%)	1 (3.3%)	185 (32.9%)

Characteristic	AG-920 n (%)	Placebo n (%)	Proparacaine n (%)	All Subjects n (%)
Iris Color, n (%)				
Black	0 (0.0%)	2 (1.0%)	0 (0.0%)	2 (0.4%)
Blue	23 (7.0%)	21 (10.3%)	0 (0.0%)	44 (7.8%)
Brown	247 (74.8%)	144 (70.9%)	28 (93.3%)	419 (74.4%)
Green	17 (5.2%)	10 (4.9%)	2 (6.7%)	29 (5.2%)
Hazel	29 (8.8%)	26 (12.8%)	0 (0.0%)	55 (9.8%)
Unknown	14 (4.2%)	0 (0.0%)	0 (0.0%)	14 (2.5%)

SD = standard deviation.

This table includes all five studies: AG-920-CS101, AG-920-CS301, AG-920-CS302, AG-920-CS303 and AG-920-CS304.

The safety population includes randomized subjects who received at least one drop of the study medication. Percentages are based on the total number of subjects in each group (N). Iris color was not collected in study AG-920-CS101.

Source: ISS Table 2.1

Deaths and Serious Adverse Events

No deaths or serious adverse events occurred during any of the clinical studies.

Treatment-Emergent Adverse Events by Preferred Terminology (Safety Population)

System Organ Class Preferred Term	AG-920 (N=286) n (%)	Placebo (N=203) n (%)	All Subjects (N=489) n (%)
Overall	72 (25.2%)	24 (11.8%)	96 (19.6%)
Instillation site pain	70 (24.5%)	14 (6.9%)	84 (17.2%)
Dysgeusia	4 (2.4%)	0 (0.0%)	4 (0.8%)
Conjunctival hyperemia	4 (1.4%)	9 (4.4%)	13 (2.7%)
Eye pain	0 (0.0%)	2 (1.0%)	2 (0.4%)
Ocular hyperemia	1 (0.3%)	0 (0.0%)	1 (0.2%)
Pharyngeal hypoesthesia	1 (0.3%)	0 (0.0%)	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class. This table includes the three Phase 3 studies in adults: AG-920-CS301, AG-920-CS302 and AG-920-CS303.
The safety population includes randomized subjects who received at least one drop of the study medication. n is the number of subjects with at least one treatment-emergent adverse event within the SOC or PT; percentages are based on the total number of subjects enrolled in each group (N). Subjects are counted only once under each SOC or PT for which they have at least one treatment-emergent adverse event. SOCs and PTs are ordered by decreasing frequency based on all subjects. Adverse events were coded using MedDRA version 26.1. Source: ISS Table 3.6

Reviewer's Comment: *There was a higher incidence of adverse events in the AG-920 (25.2%) versus placebo (11.8%). The most frequently reported adverse events occurring in greater than 1% of subjects were instillation site pain (24.5%), dysgeusia (2.4%) and conjunctival hyperemia (1.4%). These adverse events should be included in product labeling.*

Corneal Endothelial Cell Assessment

In study AG-920-CS303, a subset of 18 subjects underwent bilateral specular microscopy at screening and 90 days after dosing. Of the 16 subjects completing, 13 were in the AG-920 group and 3 were in the placebo group. At baseline, mean endothelial cell density was 2,500 to 2,900 cells/mm^2 in each group. When evaluated 90 days after dosing, mean endothelial cell density in the study eye decreased by 24 cells/mm^2 in the AG-920 group, and 44 cells/mm2 in the placebo group. In the fellow untreated eye, mean endothelial cell density decreased by 33 cells/mm^2 in the AG-920 group, and 85 cells/mm^2 in the placebo group. For neither study nor fellow eyes was this difference between treatments statistically significant (p >=0.1261). While trained and certified, for some of the subjects, the technicians at baseline and 3 months were different, which may have contributed to the variability. There was little change of note in average area, coefficient of variance, and percent hexagonal cells in the study or fellow eyes.

Vital signs, clinical laboratory evaluations and electrocardiograms were not assessed.

Integrated Assessment of Safety

The data from AG-920-CS301, AG-920-CS302, and AG-920-CS304 demonstrate the safety of Articaine Sterile Topical Ophthalmic Solution (AG-920) 8% for adults and pediatric patients aged 0-17.

Overall, there was a higher incidence of adverse events in the AG-920 (25.2%) versus placebo (11.8%). The most frequently reported adverse events occurring in greater than 1% of subjects were instillation site pain (24.5%), dysgeusia (2.4%) and conjunctival hyperemia (1.4%). These adverse events should be included in product labeling.

Post marketing Requirements and Commitments

A subset of 16 (13 active, 3 placebo) underwent specular microscopy pre-study and 3 months subsequently.

It is recommended that a post marketing commitment to evaluate the effect of the product on the corneal endothelium in at least 100 patients at 12 months be requested. See Section 16 of this review.

10. Advisory Committee Meeting

There were no issues that were thought to benefit from a discussion at an Advisory Committee Meeting. No Advisory Committee Meeting was held for this application.

11. Pediatrics

This application triggers PREA as a new active ingredient. To assess PREA, the Applicant requested a pediatric assessment for pediatric patients age 0-17 years. At the PeRC meeting on July 19, 2025, the committee agreed that this pediatric population had been adequately assessed in Study AG-920-CS304.

Study AG-920-CS304

Study AG-920-CS304 was a Phase 3, randomized, 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). 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.

Inclusion Criteria:

- 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 was willing to sign and date an informed consent form (ICF) and, where appropriate, the subject was willing to sign a consent 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.

Exclusion Criteria:

- Had participated in an investigational study (drug or device) within the past 30 days.

• Had a known contraindication to local anesthetics, Septocaine®, any component of the Investigational Medical Product (IMP) or proparacaine HCl Ophthalmic Solution.
• Children with known autism spectrum disorders or known to have heightened sensitivity.
• 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.).
• Had 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.
• Manifest nystagmus
• Had had ocular surgery (intraocular, refractive, extraocular muscles, eyelid) or general surgery in either eye within the past 45 days (Note: dental restorative work allowed).
• Had had an intravitreal injection in either eye within 14 days of randomization.
• Had ocular surface disease requiring punctal plugs, or evidence of current ocular inflammation.
• Subject who must wear contact lenses on Study Day 1 (Visit 2).
• Was currently using, or used within the past 7 days, a systemic or topical Non-steroidal Anti-Inflammatory Drug (NSAID).
• Was currently using, or used within the past 30 days, a systemic opioid or opiate analgesic.
• The subject's parent(s) or legal guardian(s) was a study team member (i.e., had direct involvement in this study or other studies under the direction of the Investigator or the study center) or was a family member of either the Investigator or other team members.

Table 3: Demographic Profile of Patients in the Pediatric Study

Characteristics	Parameter	All Subjects	Treatment Group		P value (ANOVA/Chi-square)
			AG-920	Proparacaine	
-- No of Subjects --	N	60	30	30	.
Age (year)	N	60	30	30	.
	Mean	5.8	5.2	6.3	0.1515
	Median	6.2	5.3	6.8	
	SD	2.9	3.1	2.5	
	Maximum	10.8	10.8	9.8	
	Minimum	0.6	0.6	1.7	
Age Group [n (%)]	01 month to <02 years (Infants)	9 (15.0)	7 (23.3)	2 (6.7)	0.0706
	02 years to <12 years (Children)	51 (85.0)	23 (76.7)	28 (93.3)	
Sex [n (%)]	Female	33 (55.0)	17 (56.7)	16 (53.3)	0.7952
	Male	27 (45.0)	13 (43.3)	14 (46.7)	

Ethnicity [n (%)]	Hispanic/Latino	59 (98.3)	30 (100.0)	29 (96.7)	0.3132
	Non-Hispanic/Latino	1 (1.7)	0	1 (3.3)	
Race [n (%)]	Black/African American	1 (1.7)	0	1 (3.3)	0.3132
	White/Caucasian	59 (98.3)	30 (100.0)	29 (96.7)	

% is based on number of subjects in each group
Source: Module 2.7.3, Table 3

In Study AG-920-CS304 in pediatric subjects, the primary efficacy endpoint was whether the investigator was able to perform the eye examination. In all subjects in each treatment group, the investigator was able to perform the eye examination without additional local anesthetic (Table 8). The examinations performed included slit lamp examination, dilated ophthalmoscopy, and scleral depression.

Table 8: Study AG-920-CS304: Physician Performed Eye Exam

		Treatment Group	
Characteristics	*Parameter*	*AG-920*	*Proparacaine*
-- No of Subjects --	N	30	30
Physician Performed Eye Exam [n (%)]	Yes	30 (100.0)	30 (100.0)

Source: Module 2.7.3 Summary of Clinical Efficacy, Table 8

Reviewer's Comment: *AG-920 was therapeutically equivalent to marketed proparacaine with respect to subjects achieving adequate local anesthesia to conduct an ophthalmic examination. There were no clinically significant safety or tolerability findings when AG-920 was administered to pediatric subjects.*

12. Biostatistics

From the Statistical Review finalized on 7/21/2025:

EXECUTIVE SUMMARY

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.

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.

13.Financial Disclosure

Covered Clinical Study (AG-920-CS301, AG-920-CS302, and AG-920-CS304)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.Study Integrity

The clinical investigators, Drs. Wirta and Gonzalez were inspected in support of this NDA. Based on the results of these inspections, the data generated by these clinical sites and submitted by the sponsor and the sponsor's oversight of these studies appear to be acceptable.

15.DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized their review of the package insert, foil pouch, container and carton on 3/24/2025. DMEPA provided their identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Ophthalmology (DO) and for the applicant, American Genomics, LLC.

DMEPA's concerns were incorporated into the draft labeling and conveyed to the applicant as appropriate.

In response to the Agency's information request dated July 24, 2025, the Applicant submitted the revised package insert, carton and container labeling on August 5, 2025. Review of that submission led to the following comments relayed to the applicant:

4 RECOMMENDATIONS FOR AMERICAN GENOMICS, LLC

A. Container Label

1. The established name is missing on the label. Per 21 CFR 201.10(i), the label must include at a minimum the proprietary name, established name, identifying lot and name of manufacturer. Additionally, per USP General Chapter <7>, the label of an official drug product shall bear the expiration date. To comply with 21 CFR 201.10(i) and USP General Chapter <7>, add the established name on the label. Additionally, from a medication safety perspective, we recommend including the strength to further facilitate product identification of the product. To comply, you may choose to emboss the requested identifying product information. Please note, text that is raised or recessed (i.e., embossed) without color, on clear, transparent, or translucent containers (e.g., low-density polyethylene (LDPE) vials) is generally illegible. Alternative strategies include affixing a paper label to each tail of the blow-fill seal vial or individually wrapping each unit, among other possible strategies, so that all critical identifying product information is available throughout the entire medication use process.
2. We note that 21 CFR 201.25(b)(1)(i)(F) lists as exempt "Low-density polyethylene form fill and seal containers that are not packaged with an overwrap." However, the proposed LDPE vials are contained within an overwrap, thus the barcode requirements apply. However, the regulation also allows for exemptions, including when the barcode requirement would not be technologically feasible. In order to obtain a waiver from the linear barcode requirements under 21 CFR 201.25(b)(1)(i)(ii), we recommend that you contact the Office of Compliance at CDERBarcodeQuestions@fda.hhs.gov.

B. Foil pouch and Carton Labeling

1. As currently presented, the eye graphic located in the lower half of the principal display panel competes in prominence with the critical product information on the PDP. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements (if any) should be the most prominent information on the PDP. Decrease the prominence of your eye graphic relative to the prominence of the critical information on the PDP. For example, this may be accomplished through increasing the prominence of the critical information and/or minimizing the size of the eye graphic itself or relocating it to another panel.

2. The route of administration is not present on the principal display panel. Failure to include the route of administration on the principal display panel may lead to wrong route errors. Add the route of administration "For Topical Application in the Eye" in accordance with 21 CFR 201.100(b)(3).

3. As currently presented, the product's indication is prominently displayed on the PDP. Additionally, we note the indication statement includes reference to (b) (4) which could be misinterpreted as the product's intended route of administration. The proprietary name, established name along with the product's strength, route of administration, and warning or cautionary statement (if any) should be the most prominent information on the PDP. Remove the indication statement.

4.Ensure the national drug code (NDC) is updated on the labeling when the final NDC is determined.

Applicant revised the labeling and submitted final agreed upon labeling on August 13, 2025, based on a teleconference held on August 12, 2025. See Section 17 of this review.

16.Post-marking Risk Management

On July 16, 2025, the Agency communicated an anticipated postmarketing requirement to American Genomics which reads as follows:

> Conduct a randomized, controlled trial to evaluate the corneal endothelial health of eyes treated with articaine ophthalmic solution, 8% by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and at 3 months in at least 100 patients receiving articaine ophthalmic solution, 8%.
>
> Proposed Schedule Milestones
> o Draft Protocol Submission: 1 month after approval
> o Final Protocol Submission:2 3 months after approval
> o Trial Completion: 3 years after approval
> o Final Report Submission: 3 years, 3 months after approval

American Genomics acknowledged receipt of the anticipated PMR in a communication to the Agency dated August 14, 2025.

17.Labeling

The final agreed upon labeling submitted on August 13, 2025, follows here.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
08/15/2025 10:46:17 AM
Signed for Rhea Lloyd, MD CDTL and self signed