CLINICAL REVIEW of NDA 218643

Application Type	NDA
Application Number(s)	218643
Priority or Standard	Standard
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Division/Office	DO/OND/OSM
Reviewer Name(s)	Shilpa Rose, MD
Review Completion Date	See DAARTS stamp date
Established/Proper Name	Articaine sterile topical ophthalmic solution 8%
Code Names	AG-920
Proposed Trade Name	Cyklx
Applicant	American Genomics, LLC
Dosage Form(s)	Topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	The recommended dose is 2 drops applied 30 seconds apart to the ocular surface.
Applicant Proposed Indication(s)/Population(s)	For ocular surface anesthesia prior to ocular procedures and/or intraocular injections.
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult and pediatric patients aged 0 to 17

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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
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
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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

1. Executive Summary

1.1. Product Introduction

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.

Articaine Sterile Topical Ophthalmic Solution Drug Product (DP) 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 30 µL. Each individual vial is embossed with the lot number (b) (4) . Each pouch is inkjet coded with the lot number for identification.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 218643 for CYKLX (articaine sterile ophthalmic solution) 8% is recommended for approval for ocular surface anesthesia prior to ocular procedures and/or intraocular injections. Five trials (AG-920-CS301, AG-920-CS302, AG-920-CS303, AG-920-CS304 and AG-920-CS101) were submitted with this NDA to support the approval. Articaine sterile topical ophthalmic solution is safe and effective in providing ocular surface anesthesia prior to ocular procedures and/or intraocular injections.

In both Phase 3 studies, AG-920-CS301 and AG-920-CS302, CYKLX (articaine sterile 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 4-14 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.

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.

APPEARS THIS WAY ON ORIGINAL

1.3. **Benefit-Ri**sk Asse**ssme**nt

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 CYKLX (articaine 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 CYKLX (articaine ophthalmic solution) 8%. The treatment effect (difference from placebo) was 65% in both studies (P<0.0001). In both studies, subjects treated with CYKLX (articaine ophthalmic solution) 8% 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. CYKLX (articaine ophthalmic solution) 8% was therapeutically equivalent to proparacaine. AG-920-CS101 was a Pharmacokinetic study and AG-920-CS303 was a safety study.

The safety of CYKLX (articaine ophthalmic solution) 8% was assessed in over 330 subjects exposed to the product across 5 trials. The most common adverse event with CYKLX 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 CYKLX (articaine ophthalmic solution) 8% 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 CYKLX was effective in providing ocular surface anesthesia prior to ocular procedures and/or intraocular injections. • One trial, AG-920-CS304 demonstrated that CYKLX 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 CYKLX 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 CYKLX (articaine ophthalmic solution) 8% for providing ocular surface anesthesia prior to ocular procedures and/or intraocular injections favors its use for the intended indication.

1.4. Patient Experience Data

Trials AG-920-CS301, AG-920-CS302, AG-920-CS303
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, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Study endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	See Section 6
		☐	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	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Topical anesthesia is desired to effectively perform ophthalmic examinations and ocular procedures/injections. Ideally, the anesthetic can be easily applied, will provide effective anesthesia throughout the procedure, and has a duration of action that minimizes the risks of patient self-injury after the procedure is complete.

Analysis of Current Treatment Options

Product Name/ Established Name	Relevant Indication	NDA / ANDA Number Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tetracaine Tetracaine hydrochloride ophthalmic solution 0.5%	For procedures requiring rapid and short-acting topical ophthalmic anesthesia	NDA 208-135; 2015	One drop topically in the eye(s) as needed			
Tetracaine Tetracaine ophthalmic solution, 0.5%	For procedures requiring a rapid short-acting topical ophthalmic anesthetic	NDA 210812; 2019	One drop to the eye as needed			
Alcaine Proparacaine ophthalmic solution, 0.5%	For topical anesthesia in ophthalmic practice	ANDA 80-027 ANDA 40-277 ANDA 87-681 ANDA 40-074	ALCAINE®Solution 0.5% 15mL is a topical local anesthetic indicated for corneal anesthesia of short duration, such as during tonometry or gonioscopy, and for the removal of corneal foreign bodies; and for short corneal and conjunctival procedures.		Prolonged use of a topical ocular anesthetic is not recommended. It may produce permanent corneal opacification with accompanying visual loss.	
Akten Lidocaine ophthalmic gel, 3.5%	For local anesthetic indicated for ocular surface anesthesia during ophthalmic procedures	NDA 22-221	Topical eye anesthetic used for ocular surface anesthesia during ophthalmologic procedures.			

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Articaine Sterile Topical Ophthalmic Solution 8% has not been marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical development of Articaine Sterile Topical Ophthalmic Solution 8% was conducted under IND 145052. These clinical studies were conducted consistent with FDA feedback obtained from two Type B meetings: a Pre-IND meeting (27 September 2019) and a Pre-NDA meeting (23 October 2023).

To support the NDA, American Genomics relied on the Agency's previous findings of systemic safety for the approved listed drug (LD), Septocaine® (articaine HCl and epinephrine, NDA 20-971).), in addition to Applicant-conducted studies. The bridge for the use of Septocaine® as the reference listed drug was based on both dose and exposure. The maximum recommended human dose for Septocaine® is 7.9 mg/kg (476 mg in a 60 kg human), while the maximum proposed human dose of AG-920 is 0.08 mg/kg (2x~30 µl drop of 8% AG-920, 4.8 mg in a 60 kg human). This is a 99-fold difference. Human plasma Cmax at a Septocaine® dose level of 7.9 mg/kg is 2037 ng/mL, while human plasma Cmax following AG-920 administration of 0.08 mg/kg is 5.4 ng/mL, which is a 377-fold difference (Table 3). American Genomics proposes that these dose and exposure margins support the bridge to the previously established data for Septocaine®.

3.3. Foreign Regulatory Actions and Marketing History

CYKLX (articaine ophthalmic solution) 8% has not been approved for marketing in any other country. Septocaine®, a dental product, is marketed in the U.S. and elsewhere in the world. In this application, the Sponsor is referencing Septocaine, and the proposed package insert for AG-920 reflects the latest package insert for Septocaine.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

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.

4.2. Product Quality

The CYKLX (articaine ophthalmic solution) 8% drug product (DP) is a non-preserved aqueous solution contained within a 0.5 mL single-dose low-density polyethylene (LDPE) blow-fill-seal (BFS) vial. The fill volume for this product is 0.40 ± (b) (4) mL. The vials are separated into cards of 5 vials each and packaged into an aluminum foil overwrap (b) (4) The LDPE BFS vial and the foil overwrap constitute the primary container closure system.

Drug Product Composition-Final

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 Articaine, as free base (b) (4)

Refer to the Office of Pharmaceutic Quality review for additional details.

4.3. Clinical Microbiology

N/A. The product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

Clinical use is supported by nonclinical pharmacology, pharmacokinetic and toxicology studies – either conducted by the Sponsor, or by relying on the Agency's prior findings for the LD. The GLP toxicology studies conducted with the clinical formulation (identical to the to-be-marketed formulation) includes studies AG-920-TOX-001 and AG-920-TOX-002 with a NOAEL of 11.2 mg/eye, which exceeds the proposed to-be-marketed dose in humans. The scientific bridge to justify reliance on the use of Septocaine is based on both dose and exposure (M2.4.5). As recommended by FDA, the Sponsor provides this table listing the information essential to the approval of the product drug that is provided by reliance on FDA's previous finding of safety and effectiveness for the listed drug and reliance on published literature.

Source of information	Information provided
NDA 20-971: Septocaine	Pharmacology
NDA 20-971: Septocaine	Pharmacokinetics (Nonclinical and Clinical Systemic, and Clinical Dental)
NDA 20-971: Septocaine	Toxicology: Genotoxicity, Nonclinical Systemic Toxicity
Allman 2001, Allman 2002, Fahim 2012, Fathi 2002, Gouws 2004, Ozdemir 2004, Raman 2008, Steele 2009.	Clinical safety of intraocular (peribulbar or subtenon) injection of articaine during ocular surgery

From the submission:

> Nonclinical data in rabbits showed that AG-920 induced a local ocular anesthetic effect for at least 20 minutes when administered topically to the rabbit eye, which resolved by 60 minutes post-dose. Articaine does not significantly bind to melanin. Plasma exposure to articaine following ocular surface instillation of AG-920 in the rabbit peaked at 0.25 hours post-dose, articaine rapidly converted to the inactive metabolite articainic acid, and samples were generally not quantifiable after 24 hours post-dose. Ocular concentrations of articaine were highest in iris/ciliary body, RPE/choroid, cornea, bulbar conjunctiva, and sclera, and articaine rapidly metabolized to articainic acid within the globe. These data demonstrate that AG-920 penetrates the globe following ocular surface instillation, delivering articaine to the target tissues that require anesthesia during intravitreal injections. The NOAEL for the second ocular toxicity study was 8%

AG-920 (the maximum feasible dose) administered as four 35 µL drops by ocular surface instillation to Dutch Belted rabbits (11.2 mg/eye, 22.4 mg/animal, or approximately 11.8 mg/kg). No treatment-related adverse effects were noted in any nonclinical study of AG-920. Reproductive and genetic toxicity studies were conducted for the reference listed drug, and carcinogenicity studies are not warranted for AG-920 based on the short duration of dosing and limited systemic exposure. Excipients, impurities, extractables, and leachables were all sufficiently qualified in the ocular toxicity studies of AG-920.

AG-920 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 30 µL each. This will result in a total dose of articaine of 4.8 mg/eye, 4.8 mg/subject, and 0.08 mg/kg for a 60 kg human. When compared to the NOAEL from second GLP rabbit ocular toxicity study, this dose level is supported by a 2.3X local safety margin and a 48X systemic safety margin (Table 2). The NOAEL was generated using the maximum feasible concentration and an exaggerated dosing paradigm using the to-be-marketed formulation. The bridge for the use of Septocaine® as the reference listed drug is based on both dose and exposure. The maximum recommended human dose for Septocaine® is 7.9 mg/kg (476 mg in a 60 kg human), while the maximum proposed human dose of AG-920 is 0.08 mg/kg (2x ~30 µl drop of 8% AG-920, 4.8 mg in a 60 kg human). This is a 99-fold difference. Human plasma Cmax at a Septocaine® dose level of 7.9 mg/kg is 2037 ng/mL, while human plasma Cmax following AG-920 administration of 0.08 mg/kg is 5.4 ng/mL, which is a 377-fold difference (Table 3). These dose and exposure margins support the bridge to the previously established data for Septocaine®.

The nonclinical data presented in this NDA provides adequate safety support for the approval of Articaine sterile topical ophthalmic solution 8% at the intended marketing dosing recommendation of 2 drops applied 30 seconds apart to the ocular surface.

The Pharmacology/Toxicology team recommends approval. Refer to the Pharmacology Toxicology review finalized on 7/9/25 for additional details.

4.5. Clinical Pharmacology

AG-920-CS101 was a Phase 1, open-label, non-comparative study in healthy subjects performed in the US. It was designed to assess systemic exposure to articaine and its metabolite articainic acid after dosing a single topical ocular administration of AG-920 in the randomized study eye. The primary objective of this study was to assess systemic exposure to articaine and its metabolite articainic acid after dosing a single topical ocular administration of AG-920. The secondary objective was to assess the ocular safety of AG-920 in healthy subjects. In general, the PK profile of articaine in plasma was well characterized for both articaine and articainic acid since the mean %AUCextrap was less than 5% and Kel dependent parameters were estimated

in the majority of subjects. Articaine is metabolized by plasma carboxyesterase to its primary metabolite, articainic acid which is inactive.

Pharmacokinetics

Articaine

Mean Cmax of 5.423 ng/mL was reached at a median Tmax of 0.250 hours. The overall exposure was under 7 ng*hr/mL. The mean t½ was approximately 1.5 hours.

Articainic Acid

Mean Cmax of articainic acid of 21.34 ng/mL was reached at a median Tmax of 1.001 hours. The overall exposure was approximately 10 times greater than the parent at approximately 63-67 ng*hr/mL. The mean t½ was approximately 2.3 hours.

Safety

The 8% articaine sterile topical solution (containing 80 mg/mL of articaine HCl) administered as 2 drops 30 seconds apart was safe and well tolerated by the subjects in this study.

Refer to the Clinical Pharmacology review finalized on 6/20/2025 for additional details.

4.6 Devices and Companion Diagnostic Issues

The Form 356h indicated that it is a combination product (item 24 checked). The dispenser of the product is considered a device. The product is regulated as a drug-device combination product. CDRH confirmed that no CDRH consult is necessary for BFS single-dose (b) (4) eyedroppers.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Listing of Clinical Trials Relevant to this NDA

Type of Study	Study dentifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Study Design and Type of Control	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	AG-920-CS101	5.3.3.1	To assess systemic exposure to articaine and its metabolite articainic acid	Open-label, Non-comparative	AG-920 Sterile Ophthalmic Solution 8%; Topical, ocular, one dose	14	Healthy Subjects	1 day	Complete, Clinical Study Report
E/S	AG-920-CS301	5.3.5.1	To evaluate anesthetic efficacy of AG-920.	Double-masked, placebo controlled, parallel	AG-920 Sterile Ophthalmic Solution 8%; Topical, ocular, one dose	120	Healthy Subjects	1 day	Complete, Clinical Study Report
E/S	AG-920-CS302	5.3.5.1	To evaluate anesthetic efficacy of AG-920.	Double-masked, placebo controlled, parallel	AG-920 Sterile Ophthalmic Solution 8%; Topical, ocular, one dose	120	Healthy Subjects	I day	Complete, Clinical Study Report
S	AG-920-CS303	5.3.5.1	To evaluate the ocular safety of a single topical ocular administration of	Double-masked, placebo controlled, parallel	AG-920 Sterile Ophthalmic Solution 8%; Topical, ocular, one dose	249	Healthy Subjects	1 day	Complete, Clinical Study Report

			AG-920						
E/S	AG-920-CS304	5.3.5.1	To evaluate the anesthetic efficacy of AG-920	Single-masked, parallel	AG-920 Sterile Ophthalmic Solution 8%; Topical, ocular, one dose	60	(Pediatric) Healthy Subjects	I day	Complete, Clinical Study Report

5.2. Review Strategy

Clinical data for studies AG-920-CS301, AG-920-CS302, AG-920-CS303, AG-920-CS304 and AG-920-CS101 were reviewed to support safety and efficacy. AG-920-CS301 and AG-920-CS302 were double-masked, randomized, placebo-controlled parallel design studies in healthy subjects in the United States. Articaine sterile topical ophthalmic solution 8% was compared to placebo control (the vehicle without the active ingredient of the drug product) AG-920-CS304 was a pediatric efficacy and safety study. Articaine sterile ophthalmic solution 8% was compared to proparacaine in a single-masked parallel study of healthy pediatric patients ages 10 and younger. AG-920-CS101 was a Pharmacokinetic study and AG-920-CS303 was a safety study.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. AG-920-CS301

6.1.1. Study Design

Overview and Objective

This study is a randomized, placebo-controlled, double-masked, parallel design study in healthy subjects performed in the US. It is designed to evaluate the safety and anesthetic efficacy of one dose of Articaine Sterile Topical Ophthalmic Solution (AG-920). In this study, 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 looking placebo into one (study) eye (2 drops 30 seconds apart). Subjects underwent a conjunctival pinch procedure and the pain associated with the pinch was rated. IMP dosing and conjunctival pinch procedure were performed by the study staff. Healthy subjects were exposed to the stimulus of conjunctival pinching. The placebo control (the vehicle without the active ingredient of the drug product) was deemed to be ethically acceptable.

The primary objective of this study was to evaluate anesthetic efficacy of AG-920.

The secondary objectives are as follows:

- To evaluate how long it takes one dose of AG-920 to anesthetize the eye
- To evaluate how long one dose of AG-920 anesthetizes the eye
- To evaluate the safety and tolerability of AG-920

Trial Design

This study was a randomized, placebo-controlled, double-masked, parallel study. Subjects were randomized in a 1:1 ratio to receive AG-920 Sterile Topical Ophthalmic Solution or placebo. They were randomly assigned to receive the IMP dose into one eye only (study eye). The single dose was administered by the clinic staff as two drops in study eye 30 seconds apart. Subjects were reminded that instillation of study drug, like other topical anesthetic drops, may cause a mild stinging or burning sensation upon instillation. Subjects were to be reminded that the instillation of study medication should not be considered as "pain" when the pinch test is conducted. AG-920 and placebo were provided in blow-fill-seal single unit doses (SUDs) packed into sealed foil pouches which were enclosed in a box. Subjects, the Investigator, and all site personnel responsible for performing study assessments remained masked to treatment assignment.

A total of 120 randomized subjects was planned, with 60 subjects assigned to each dose group of AG-920 Sterile Topical Ophthalmic Solution or its vehicle. The safety, intent-to-treat (ITT), and per-protocol (PP) population included all 120 subjects enrolled.

Inclusion criteria

Individuals must have met the following criteria at Screening:
1. Provided written informed consent prior to any study-related procedures being performed.
2. Was male or a non-pregnant, non-lactating female aged 18 years or older. Female subjects of childbearing potential must have had a negative urine pregnancy test at Screening (Visit 1) in order to be eligible for randomization.
3. Were willing and able to follow instructions and be present for the required study visits and Follow-up Phone Call.
4. 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 were allowed.
5. Had an Intraocular Pressure (IOP) between 7 and 30 mmHg.
6. Were certified as healthy by clinical assessment (detailed medical history) including ocular examination.
7. Had verbal communication skills adequate to participate.
8. Were able to tolerate bilateral instillation of Over-the-Counter (OTC) artificial tear product based on investigator judgement. Schedule of Visits and Examinations

Exclusion criteria

Individuals who met any of the following exclusion criteria were ineligible for this study:
1. Had participated in an investigational study (drug or device) within the past 30 days.
2. Had a contraindication to local anesthetics, Septocaine®, or any component of the IMP.
3. Had known decreased corneal or conjunctival sensitivity (e.g., sequelae of herpetic eye disease, corneal graft) or a diagnosed corneal pathology which might have led to decreased

sensitivity.
4. Had ocular surgery (intraocular, refractive, extraocular muscles, eyelid) or general surgery in either eye within the past 90 days (Note: dental restorative work allowed)
5. Had had an intravitreal injection in either eye within 14 days of randomization.
6. Had ocular surface disease requiring punctual plugs.
7. Had evidence of any current ocular inflammation.
8. Subject who had to wear contact lenses on Study Day 1 (Visit 2).
9. Subjects who were currently using, or used within the past 30 days, a systemic opioid or opiate analgesic or topical Non-steroidal Anti-Inflammatory Drug (NSAID).
10. Subjects who could not withhold their intermittent Over-the-Counter (OTC) artificial tear lubricant products for one hour preceding or following study medication.
11. Any condition, including alcohol or drug dependency, that would have limited the subject's ability to comply with the procedures of the protocol (per Investigator's judgment).

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

Assessment of Efficacy:

• Assessment of pain questionnaire following conjunctival pinch procedure described below.

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:

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

Per the protocol, as soon as the subject experienced 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.

Unfortunately, a protocol deviation occurred, and all subjects were pinched at all timepoints up to 5 minutes. All 120 subjects were pinched and assessed for pain at 20, 40, 60 seconds and 5 minutes. All efficacy assessments were conducted at the timepoints shown on the Schedule of Visits and Examinations.

Schedule of Visits and Procedures

Table 1: Schedule of Visits and Procedures

	Visit 1	Visit 2						Phone Follow-Up
	Screening Day -2 to 0/1 Pre-dose	Dose		*Screening & Baseline* Day 1[1]				Day 2-5
Procedures		0 sec	30 sec	20 s post 2nd drop	40 s post 2nd drop	60 s post 2nd drop	5 m	15-60 m post last pinch	
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.

Study Endpoints
Primary Endpoint
The proportion of patients with no pain at 5 minutes. (ITT population)

The Secondary Endpoints:

- Mean time to no pain score (onset)
- Mean duration of anesthetic effect

Safety Endpoints
Visual acuity, biomicroscopy, adverse events (AEs), treatment-emergent adverse events (TEAEs), serious AEs (SAEs), withdrawals due to TEAEs

Statistical Analysis Plan
Primary Endpoint Analysis
The corresponding null and alternative hypotheses 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 placebo.
> H_A: The proportion of subjects with no pain at 5 minutes is different between subjects treated with AG-920 and placebo.

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 0.05), then superiority of AG-920 over placebo will be claimed.

Secondary Endpoint Analysis
For the proportion of subjects with no pain within 5 minutes, 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. A Pearson chi-square test will be used for the comparison of the proportions from the two treatment groups. In addition, a two-sided 95% CI for the difference in proportions between the two treatment groups will be calculated.

For assessing the time to no pain, a subject needs to report no pain at two or more consecutive time points to have their time counted. This time can be either 20, 40 or 60 seconds or 5 minutes. The following are examples: If a subject reports no pain at 20 and 40 seconds, then their time to no pain will be 20 seconds. If a subject reports no pain at 40 seconds and 5 minutes, then their time to no pain will be 40 seconds. If a subject reports no pain at only one consecutive time point, then the subject will not have reached anesthesia, and their time to no

pain will be considered censored. If a subject experiences pain at 20, 40, and 60 seconds and 5 minutes, then pinching will be concluded and this subject will be considered to not have reached anesthesia. For these cases, their time to no pain will be considered censored.

All times will be converted to minutes so the 20 and 40 second timepoints will be 0.33 and 0.67 minutes, respectively. Estimates of the mean time to no pain will be done using Kaplan-Meier estimates, and comparisons between the two treatment groups will be done using a log-rank test. For the mean duration of anesthetic effect as measured in minutes, subjects who do not reach anesthesia will have a duration of zero minutes. For subjects who do reach anesthesia at 20, 40 or 60 seconds following dose administration and then continue to be tested with the conjunctival pinch test starting at 5 minutes, their anesthetic effect times will be either 1, 5, 10, 15, 20, 25 or 30 minutes. The following are examples:

- If a subject has no pain at 20 seconds but then feels pain at 40 and 60 seconds and at 5 minutes, their duration of anesthetic effect will be 0.33 minutes (20 seconds).
- If a subject has no pain at 20, 40 and 60 seconds but then feels pain at the 5-minute pinch test, their duration of anesthetic effect will be 1 minute.
- If a subject feels pain at 20 seconds, feels no pain at 40 and 60 seconds and 5 minutes, but then feels pain again at the 10-minute pinch test, their duration of anesthetic effect will be 4.33 minutes (5 minutes minus 40 seconds).If a subject never feels pain at any of the pinch tests during the 30 minutes, then their duration of anesthetic effect will be 30 minutes.

Comparisons between the two treatment groups for the mean duration of anesthetic effect will be made using a two-sample t-test. The estimated difference in mean duration will be presented as AG-920 minus placebo, together with its 95% confidence interval and P value.

There are no interim analyses of efficacy planned for this study.

Protocol Amendments

The original protocol of 9 June 2020 was amended on 16 September 2020. The study was ongoing with subjects randomized, treated, and completed, and enrollment continuing. The following substantive changes were made to the original protocol:

In August 2020, the U.S. FDA provided “non-clinical hold” comments on this protocol with respect to the statistical issues. In addition, in reviewing the protocol, minor inconsistencies and typographical issues were found. The following substantive edits were made with Amendment #1.

3. Table 1: Randomization was inadvertently listed as occurring at Visit 1 (Screening). It was moved to Visit 2 (Screening and Baseline).

6. Statistics (Section 9):

a. There was an error in numbering of sub-headings which was corrected.

b. Per FDA comments, this section was changed in several places to reflect that the primary population for efficacy was changed FROM Per-protocol TO Intent-to- Treat.
c. Additional changes were a clarification of the definition of population, an expansion on the description for accounting for missing, unused, or spurious data (Sections 9.2, 9.3, 9.4.3, 9.4.6, 9.4.8, and 9.5).
7. Typographical corrections including: "Two-tailed" was changed to "Two-sided" (several sections)

As noted in Section 9.5.1.1, a protocol deviation occurred, and all subjects were pinched at all timepoints up to 5 minutes. All 120 subjects were pinched and assessed for pain at 20, 40, 60 seconds and 5 minutes.

The initial SAP (dated, 07 December 2020, Version 1.0), was amended (17 June 2021, Version 2.0) to reflect minor changes and additions in the draft Tables and Listings.

6.1.2. Study Results

Compliance with Good Clinical Practices
This study was conducted per the principles of Good Clinical Practices (GCP).

Patient Disposition

One hundred and twenty (120) subjects were screened, randomized and treated, all of whom completed the study (Table 2). No subjects failed to meet inclusion/exclusion criteria, including ability to tolerate an Over-the-Counter artificial tear.

Subject Disposition (All Screened Subjects)

Table 2: Subject Disposition by Site: (All Screened Subjects)

	Statistic	*Treatment Arm*		*Overall (N = 120)*
		Treatment A (N = 60)	*Treatment B (N = 60)*	
Subjects Screened	n			120
Subjects Randomized	n (%)	60 (100)	60 (100)	120 (100)
Subjects Dosed	n (%)	60 (100)	60 (100)	120 (100)
Subjects Completed	n (%)	60 (100)	60 (100)	120 (100)

N: The number of subjects randomized for each Treatment Arm and Overall;

n: The number of subjects in the specific category; %: Calculated using the number of subjects randomized for each Treatment Arm and Overall, as denominator (n/N)*100.

Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920)
Treatment B: Placebo

Source: Table 14.1.3, Listing 16.2.1.1

Data Sets Analyzed

The safety, ITT and PP populations included 120 subjects (Table 4).

Table 4: Study Populations: (All Randomized Subjects)

		Treatment Arm		
	Statistics	*Treatment A*	*Treatment B*	*Overall*
Randomized Population	N (%)	60 (100)	60 (100)	120 (100)
Intention-to-Treat (ITT) Population	N (%)	60 (100)	60 (100)	120 (100)
Per Protocol (PP) Population	N (%)	60 (100)	60 (100)	120 (100)
Safety Population	N (%)	60 (100)	60 (100)	120 (100)

N: The number of subjects in respective population for each Treatment Arm and Overall; %: Calculated using the number of subjects in the Randomized population for each treatment arm and Overall;
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920)
Treatment B: Placebo
Source: Table 14.1.1

Protocol Violations/Deviations

Protocol deviations were reported for 64 subjects (53%).
All of these protocol deviations except one had to do with subjects having the pinch assessment done at all time points (20, 40, 60 seconds and 5 minutes regardless of pain response). The site tested all subjects at each time point, irrespective of whether they were anesthetized. This was contrary to the protocol, in which subjects who were anesthetized at 20 seconds were NOT to be tested at 40 seconds, and those anesthetized at 40 seconds were NOT to be tested at 60 seconds. At a technical review meeting held prior to unmasking the treatment, it was decided that this protocol deviation would NOT preclude any subjects from analysis.

Reviewer's Comment: *Agree with the Applicant's decision not to remove these subjects with protocol deviations from the analysis.*

The only other protocol deviation was a single subject (Subject (b) (6), Placebo) who was inadvertently dosed a second drop of study medication out of a different vial (although the

same product). The deviation was also considered not major, and the subject was analyzed as randomized (Appendix 16.1.9). No subject treatment was unmasked during the course of the study.

Table of Demographic Characteristics

The demographic and baseline characteristics were similar between the treatment groups. There were more females (67/120, 56%) than males (53/120 (44%), the mean age was 31.3 (± 12.6) years (range 18-65 years), and the majority of subjects were white (98/120, 82%). The most frequent eye color was brown (61/120, 51%) followed by blue (26/120, 22%) and hazel (24/120, 20%, Table 5).

Table 5: Subject Demographics (Randomized Population)

Characteristics	*Treatment A (N=60)*	*Treatment B (N=60)*	*Overall (N=120)*
Age (years)			
n	60	60	120
Mean	32.60	30.02	31.31
SD	13.72	11.26	12.57
Median	27.00	27.00	27.00
Minimum	18.00	19.00	18.00
Maximum	64.00	65.00	65.00
@p-value			0.4700
≥ 65 years of age, n (%)	0 (0.0)	1 (1.7)	1 (0.8)
Gender, n (%)			
Female	33 (55.0)	34 (56.7)	67 (55.8)
Male	27 (45.0)	26 (43.3)	53 (44.2)
p-value			0.8541
Race, n (%)			
American Indian Or Alaska Native	1 (1.7)	0 (0.0)	1 (0.8)
Asian	10 (16.7)	10 (16.7)	20 (16.7)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	1 (1.7)	1 (0.8)
White	49 (81.7)	49 (81.7)	98 (81.7)
p-value			0.5724
Ethnicity, n (%)			
Hispanic	13 (21.7)	13 (21.7)	26 (21.7)
Non-Hispanic	47 (78.3)	47 (78.3)	94 (78.3)
p-value			1.0000
Color of Iris, n (%)			
Blue	12 (20.0)	14 (23.3)	26 (21.7)
Brown	33 (55.0)	28 (46.7)	61 (50.8)
Green	4 (6.7)	5 (8.3)	9 (7.5)
Hazel	11 (18.3)	13 (21.7)	24 (20.0)
p-value			0.8395
Subject of Child-bearing Potential, n (%)			
N/A	27 (45.0)	26 (43.3)	53 (44.2)
NO	7 (11.7)	4 (6.7)	11 (9.2)
YES	26 (43.3)	30 (50.0)	56 (46.7)
p-value			0.5704
Reason Not of Child-bearing Potential, n (%)			
Hysterectomy	2 (3.3)	0 (0.0)	2 (1.7)
Postmenopausal (At Least 1 Year Since The Last Menstrual Period)	3 (5.0)	3 (5.0)	6 (5.0)
Tubal Ligation	2 (3.3)	1 (1.7)	3 (2.5)

Characteristics	*Treatment A (N=60)*	*Treatment B (N=60)*	*Overall (N=120)*
p-value			0.4411
Study Eye, n (%)			
Left	31 (51.7)	29 (48.3)	60 (50.0)
Right	29 (48.3)	31 (51.7)	60 (50.0)
p-value			0.7150

N: The number of subjects in the Randomized Population for each Treatment and Overall, n: The number of subjects in the specific category.
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920)
Treatment B: Placebo
@p-value calculated by using Wilcoxon test p-value calculated using Chi-square test Source: Table 14.1.2

Most subjects had a medical history (66/120, 55%), the most frequent of which were eye disorders (28/120, 23%), most of which were dry eye (15/120, 13%), immune system disorders (19/120, 16%), most of which were drug hypersensitivity (15/120, 13%), psychiatric disorders (15/120, 13%), most of which were anxiety (11/120, 9%), and nervous system disorders (12/120, 10%), most of which were headaches (8/120, 7%); Table 14.1.4.

Most subjects had prior or concomitant medications (75/120, 63%), the most frequent of which were multivitamins (20/120, 17%), and oral contraceptives (15/120, 13%), and Vitamin D (12/120, 10%), Table 14.1.5.

There was no analysis of efficacy or safety measures by demographic characteristics.

Efficacy Results – Primary Endpoint

Table 6: Summary of Proportion of Subjects with No Pain at 5 Minutes (ITT Population)

Description	*Statistics*	*Treatment A (N = 60)*	*Treatment B (N = 60)*	*Overall (N = 120)*
Proportion of Subjects with No Pain at 5 Minutes	n (%)	41 (68.3)	2 (3.3)	43 (35.8)
Proportion of Subjects with Pain at 5 Minutes	n (%)	19 (31.7)	58 (96.7)	77 (64.2)
Difference in proportion of responders (%) between treatment groups				65.00%
p-value for between treatment group comparison				<0.0001
95% Confidence interval (CI) for the difference in proportion of responders between the two treatment groups				52.38% - 77.62%

N: The number of subjects in the respective population; n: The number of subjects in the specific category;
%: Calculated using the number of subjects in the respective population as the denominator (n/N)*100
A Responder is defined as a subject with no pain at 5 minutes
p-value and 95% CI calculated using Pearson chi-square for between treatment group comparison
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920)
Treatment B: Placebo
Source: Table 14.2.1.1

Reviewer's Comment: *The study met its primary efficacy endpoint. The proportion of patients to achieve the primary endpoint of "no pain at 5 minutes" was 68.3% in the treatment group versus 3.3% in the vehicle group. This difference of 65% (95% confidence interval, 52.4 to 77.6%) was statistically significant (p <0.0001).*

Efficacy Results – Secondary Endpoints

Summary of Time to No Pain Within 5 Minutes During Pinch Test

Table 7: Summary of Proportion of Subjects with No Pain within 5 Minutes (ITT Population)

Description	*Statistics*	*Treatment A (N = 60)*	*Treatment B (N = 60)*	*Overall N = 120)*
Proportion of Subjects with No Pain within 5 Minutes	n (%)	59 (98.3)	2 (3.3)	61 (50.8)
Proportion of Subjects with Pain within 5 Minutes	n (%)	1 (1.7)	58 (96.7)	59 (49.2)
Difference in proportion of responders (%) between treatment groups				95.00%
p-value for between treatment group comparison				<0.0001
95% Confidence interval (CI) for the difference in proportion of responders between the two treatment groups				89.42% - 100.00%

N: The number of subjects in the respective population; n: The number of subjects in the specific category; %: Calculated using the number of subjects in the respective population as the denominator (n/N)*100
A Responder is defined as a subject with No Pain within 5 Minutes if they have two consecutive time points where they report No Pain. p-value and 95% CI calculated using Pearson chi-square for between treatment group comparison
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920)
Treatment B: Placebo
Source: Table 14.2.1.2

Reviewer's Comment: *The secondary endpoint, no pain within 5 minutes, achieved statistical significance with 98.3% (59/60) of the subjects in the AG-920 treatment group compared to 3.3% (2/60) in the vehicle group meeting the endpoint. This difference of 95% (95% confidence interval, 89.4 to 100.0%) was statistically significant (p < 0.0001, Table 7).*

Onset of anesthesia

Table 9: Onset of anesthesia (minutes)

Statistics	Treatment A (N = 60)	Treatment B (N = 60)
n	60	5
Mean	0.442	0.330
SD	0.6072	0.0000
Median	0.330	0.330
Min	0.33	0.33

Statistics	Treatment A (N = 60)	Treatment B (N = 60)
Max	5.00	0.33
p-value	<0.0001	

N: The number of subjects in the ITT population; n: The number of subjects evaluated.
p-value is calculated using Wilcoxon Rank Sum Test.
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920) Treatment
B: Placebo
Source: Table 14.2.5.1

Reviewer's Comment: *The secondary efficacy endpoint, mean onset of anesthesia, was statistically significant in favor of the AG-920 treatment group. However, due to the rapid onset of anesthesia in nearly all subjects in the AG-920 treatment group and only rare anesthesia in the vehicle treatment group, this analysis is not meaningful was 0.44 ± 0.6 (mean ± SD) minutes. A Kaplan-Meier analysis was also conducted on time to no pain (onset) which was not meaningful (Table 14.2.1.3).*

Duration of Anesthesia

Table 10: Duration of anesthesia (minutes)

Statistics	Treatment A (N = 60)	Treatment B (N = 60)
n	60	60
Mean	4.833	0.267
SD	3.8158	1.4325
Median	5.000	0.000
Min	0.33	0.00
Max	20.00	10.00
p-value	<0.0001	

N: The number of subjects in the ITT population; n: The number of subjects evaluated. p-value is calculated using Wilcoxon Rank Sum Test.
Treatment A: Articaine Sterile Topical Ophthalmic Solution (AG-920) Treatment B: Placebo
N: The number of subjects in the ITT population; n: The number of subjects evaluated. p-value is calculated using Two Sample T-test.
Source: Table 14.2.4.1

Reviewer's Comments: *The mean duration of anesthesia in the AG-920 treatment group was 4.8 ± 3.8 (mean ± SD) minutes, compared to the vehicle treatment group which was 0.27 ± 1.4 minutes (p < 0.0001, Table 10). The duration of anesthesia ranged from less than 1 minute to 20 minutes in the AG-920 treatment group.*

Data Quality and Integrity
This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Dose/Dose Response
Dose response was evaluated in the non-clinical development program.

Durability of Response

Of the subjects in the AG-920 treatment group, 68.3% (41/60) achieved the primary efficacy endpoint of "no pain at 5 minutes", compared to 3.3% (2/60) in the vehicle group. This difference of 65% (95% confidence interval, 52.4 to 77.6%) was statistically significant ($p < 0.0001$).

Of the subjects in the AG-920 treatment group, 98.3% (59/60) achieved a secondary efficacy endpoint of "no pain within 5 minutes", compared to 3.3% (2/60) in the vehicle group. This difference of 95% (95% confidence interval, 89.4 to 100.0%) was statistically significant ($p <0.01$).

At each time point from 20 seconds (0.33 minutes) through 25 minutes, a substantially greater proportion of subjects in the AG-920 treatment group responded (no pain) than in the vehicle group. The mean onset of anesthesia in the AG-920 treatment group was 0.44 ± 0.6 (mean ± SD) minutes. Five subjects in the vehicle group also experienced anesthesia ($p < 0.0001$). The mean duration of anesthesia in the AG-920 treatment group was 4.8 ± 3.8 (mean ± SD) minutes, compared to the vehicle treatment group which was 0.27 ± 1.4 minutes ($p < 0.0001$).

6.2. AG-920-CS302

6.2.1. Study Design

Overview and Objective

The primary objective of this study was to evaluate anesthetic efficacy of AG-920.

The secondary objectives are as follows:

- To evaluate how long it takes one dose of AG-920 to anesthetize the eye
- To evaluate how long one dose of AG-920 anesthetizes the eye
- To evaluate the safety and tolerability of AG-920

Trial Design

The design of this study as a randomized, placebo-controlled, double-masked, parallel study. 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 IMP in the study eye either AG-920 or Placebo. The single dose was administered by the clinic staff as two drops in study eye 30 seconds apart. Subjects were reminded that instillation of study drug, like other topical anesthetic drops, may cause a mild stinging or burning sensation upon instillation and that this should not be considered as "pain" when the pinch test is conducted. The IMP was provided in blow-fill-seal single unit doses (SUDs) packed into sealed foil pouches which were enclosed in a box. Subjects, the Investigator, and all site personnel responsible for performing study assessments remained masked to treatment assignment.

Assessment of efficacy was as follows:

• 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:

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

Per the protocol, as soon as the subject experienced 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.

Inclusion Criteria

Individuals must have met the following criteria at Screening:

1. Provided written informed consent prior to any study-related procedures being performed.
2. Was male or a non-pregnant, non-lactating female aged 18 years or older. Female subjects of childbearing potential must have had a negative urine pregnancy test at Screening (Visit 1) in order to be eligible for randomization.
3. Were willing and able to follow instructions and be present for the required study visits and Follow-up Phone Call.
4. 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 were allowed.

Exclusion Criteria

Individuals who met any of the following exclusion criteria were ineligible for this study:

1. Had participated in an investigational study (drug or device) within the past 30 days.
2. Had a contraindication to local anesthetics, Septocaine®, or any component of the IMP.
3. Had known decreased corneal or conjunctival sensitivity (e.g., sequelae of herpetic eye disease, corneal graft) or a diagnosed corneal pathology which might have led to decreased sensitivity.

4. Had ocular surgery (intraocular, refractive, extraocular muscles, eyelid) or general surgery in either eye within the past 90 days (Note: dental restorative work allowed)
5. Had had an intravitreal injection in either eye within 14 days of randomization.
6. Had ocular surface disease requiring punctual plugs.
7. Had evidence of any current ocular inflammation.
8. Subject who had to wear contact lenses on Study Day 1 (Visit 2).
9. Subjects who were currently using, or used within the past 30 days, a systemic opioid
or opiate analgesic or topical Non-steroidal Anti-Inflammatory Drug (NSAID).
10. Subjects who could not withhold their intermittent Over-the-Counter (OTC) artificial tear lubricant products for one hour preceding or following study medication.
11. Any condition, including alcohol or drug dependency, that would have limited the subject's ability to comply with the procedures of the protocol (per Investigator's judgment).
12. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved in the conduct of the study.

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

Schedule of Procedures

Table 1: Schedule of Visits and Procedures

	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.

Statistical Analysis Plan

Primary Endpoint

The proportion of subjects with no pain at 5 minutes. This '5 minute' timepoint refers to the conjunctival pinch that is given 5 minutes after dose administration of study drug.

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 placebo.

H_A: The proportion of subjects with no pain at 5 minutes is different between subjects treated with AG-920 and placebo.

A Pearson chi-square test will be 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 will be 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< 0.05), then superiority of AG-920 over placebo will be claimed.

Secondary Endpoints

- the proportion of subjects with no pain within 5 minutes
- the mean time to no pain score (onset of anesthesia effect in minutes), and
- the duration of anesthetic effect.

For the proportion of subjects with no pain within 5 minutes, 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. A Pearson chi-square test will be used for the comparison of the proportions from the two treatment groups. In addition, a two-sided 95% CI for the difference in proportions between the two treatment groups will be calculated.

For assessing the time to no pain, a subject needs to report no pain at two or more consecutive time points to have their time counted. This time can be either 20, 40 or 60 seconds or 5 minutes. The following are examples: If a subject reports no pain at 20 and 40 seconds, then their time to no pain will be 20 seconds. If a subject reports no pain at 40 seconds and 5 minutes, then their time to no pain will be 40 seconds. If a subject reports no pain at only one consecutive time point, then the subject will not have reached anesthesia, and their time to no pain will be considered censored. If a subject experiences pain at 20, 40, and 60 seconds and 5 minutes, then pinching will be concluded and this subject will be considered to not have reached anesthesia. For these cases, their time to no pain will be considered censored.

All times will be converted to minutes so the 20 and 40 second timepoints will be 0.33 and 0.67 minutes, respectively. Estimates of the mean time to no pain will be done using Kaplan-Meier estimates, and comparisons between the two treatment groups will be done using a log-rank test. For the mean duration of anesthetic effect as measured in minutes, subjects who do not reach anesthesia will have a duration of zero minutes. For subjects who do reach anesthesia at 20, 40 or 60 seconds following dose administration and then continue to be tested with the conjunctival pinch test starting at 5 minutes, their anesthetic effect times will be either 1, 5, 10, 15, 20, 25 or 30 minutes.

The following are examples:

- If a subject has no pain at 20 seconds but then feels pain at 40 and 60 seconds and at 5 minutes, their duration of anesthetic effect will be 0.33 minutes (20 seconds).
- If a subject has no pain at 20, 40 and 60 seconds but then feels pain at the 5-minute pinch test, their duration of anesthetic effect will be 1 minute.

- If a subject feels pain at 20 seconds, feels no pain at 40 and 60 seconds and 5 minutes, but then feels pain again at the 10-minute pinch test, their duration of anesthetic effect will be 4.33 minutes (5 minutes minus 40 seconds).
- If a subject never feels pain at any of the pinch tests during the 30 minutes, then their duration of anesthetic effect will be 30 minutes.

Comparisons between the two treatment groups for the mean duration of anesthetic effect will be made using a two-sample t-test. The estimated difference in mean duration will be presented as AG-920 minus placebo, together with its 95% confidence interval and P value.

There are no interim analyses of efficacy planned for this study.

Protocol Amendments
The original protocol of 18 September 2020 was amended on 21 January 2021. The study was not yet started. Based upon an unmasked evaluation of Study AG-920-CS301, the following modifications were made to the protocol.

1. Corneal "pinch" test added at 40 seconds and 60 seconds irrespective of response at earlier timepoints.
2. Miscellaneous administrative clarifications to improve clarity of protocol and avoid confusion.
3. Changed reference to Investigators Brochure FROM 2020 TO 2021 with new clinical data.

Added underlined text to improve clarity of protocol and avoid confusion: All subjects who discontinue IMP due to a report of an AE must be followed-up and provided appropriate medical care until their signs and symptoms have remitted, stabilized, determined to be chronic, or until abnormal laboratory findings have returned to acceptable or pre-study limits if performed as part of the AE assessment.

Reviewer's comment: *The protocol amendments did not adversely affect the overall study conduct.*

6.2.2. Study Results

Compliance with Good Clinical Practices
This study was conducted per the principles of Good Clinical Practices (GCP).

Subject Disposition
One hundred and twenty-one (121) subjects were screened, of which 120 were randomized and treated, all of whom completed the study. All of the 120 subjects were included in the

safety, ITT, and PP populations in this study.

Table 2: Subject Disposition: (Safety\ITT\PP Population)

Characteristics	*Parameter*	*All Subjects*	*Treatment Group* *AG-920*	*Placebo*
No. of Subjects -	N (%)	120 (100.0)	60 (100.0)	60 (100.0)
Status of Completion [n (%)]	Completed	120 (100.0)	60 (100.0)	60 (100.0)
Primary reason for discontinuation [n (%)]	Completed	120 (100.0)	60 (100.0)	60 (100.0)

Source: Table 14.1.3.1, Listing 16.2.1.2

Data Sets Analyzed
The safety, ITT and PP populations included 120 subjects (Table 5). These analysis populations, which are defined in Section 9.7.1.1, were analyzed as described in Section 9.7.1

Table 3: Study Populations: (All Randomized Subjects)

			Treatment Group	
	Statistics	*Overall*	*AG-920 (N = 60)*	*Placebo (N = 60)*
Randomized Population	N (%)	120 (100)	60 (100)	60 (100)
Intention-to-Treat (ITT) Population	N (%)	120 (100)	60 (100)	60 (100)
Per Protocol (PP) Population	N (%)	120 (100)	60 (100)	60 (100)
Safety Population	N (%)	120 (100)	60 (100)	60 (100)

N: The number of subjects in respective population for each Treatment Arm and Overall; %: Calculated using the number of subjects in the Randomized population for each treatment arm and Overall;

Source: Table 14.1.1.1, 14.1.1.2, 14.1.1.3, 14.1.1.4, 14.1.1.5

Protocol Violations/Deviations

Protocol deviations are summarized in Table 4 and listed in Listing 16.2.2.1 within the protocol. All subjects were included in all analysis populations. Protocol deviations were reported for 4 subjects (3%). These were scheduling variations and inadvertent dosing of left eye (OS) rather than right eye (OD). It was agreed during the meeting that none of the four protocol deviations were considered important enough to have meaningful impact on study conduct or on the primary efficacy or key safety outcomes for an individual subject (Appendix 16.1.9). No subject treatment was unmasked during the study.

Reviewer's comment: *The protocol deviations did not adversely affect the overall study conduct.*

Demographic Characteristics

Reviewer's comment: *There were more females (67/120, 56%) than males (53/120, 44%), the mean age was 35.9 (± 15.0) years (range 18-74 years), and the majority of subjects were white (116/120, 97%). The most frequent eye color was brown (106/120, 88%) followed by hazel (10/120, 8%). Mean IOP was 14 mm Hg, and mean visual acuity was logMAR 0.0 (20/20 Snellen). For the most part, there were no statistically significant between-group differences, with two exceptions : 1) there were more subjects ≥ 65 years of age in the AG-920 treatment group than the placebo group (4/60, 3% vs. 0, p = 0.0419), and 2) there were more right study eyes in the AG-920 treatment group than the placebo treatment group (36/60, 60% vs. 23/60, 38%, p = 0.0176; Table 6, Table 7). As planned, the side of study eye (OD vs. OS) was adjusted in the statistical models of the analyses for the efficacy endpoints.*

Table 6: Subject Demographics (Enrolled\Safety\ITT\PP Population)

Characteristics	*Parameter*	*ALL Subjects*	*Treatment Group*		*P value (ANOVA/Chi-square)*
			AG-920	*Placebo*	
-- No of Subjects --	N	120 (100.0)	60 (100.0)	60 (100.0)	.
Age (year)	N	120	60	60	.
	Mean	35.9	34.9	37.0	0.4424
	Median	30.5	28.0	33.0	
	SD	15.0	15.6	14.4	
	Maximum	74.0	74.0	63.0	
	Minimum	18.0	18.0	18.0	
Age Group [n (%)]	18-29 yrs	57 (47.5)	32 (53.3)	25 (41.7)	0.1193
	30-39 yrs	15 (12.5)	6 (10.0)	9 (15.0)	
	40-49 yrs	17 (14.2)	8 (13.3)	9 (15.0)	
	50-64 yrs	27 (22.5)	10 (16.7)	17 (28.3)	

Characteristics	*Parameter*	*ALL Subjects*	*Treatment Group*		*P value (ANOVA/Chi-square)*
			AG-920	*Placebo*	
	65+ yrs	4 (3.3)	4 (6.7)		
Age Group/elderly [n (%)]	<65 yrs	116 (96.7)	56 (93.3)	60 (100.0)	0.0419
	>=65 yrs	4 (3.3)	4 (6.7)		
Sex [n (%)]	Female	67 (55.8)	31 (51.7)	36 (60.0)	0.3580
	Male	53 (44.2)	29 (48.3)	24 (40.0)	
Ethnicity [n (%)]	Hispanic/ Latino	118 (98.3)	59 (98.3)	59 (98.3)	1.0000
	Non-Hispanic/ Latino	2 (1.7)	1 (1.7)	1 (1.7)	
Race [n (%)]	Asian	2 (1.7)	1 (1.7)	1 (1.7)	1.0000
	White/ Caucasian	116 (96.7)	58 (96.7)	58 (96.7)	
	other	2 (1.7)	1 (1.7)	1 (1.7)	

% is based on number of subjects in each group Source: Table 14.1.2.1.1

Reviewer's comment: *The study population was predominantly white (97%) and female (56%) with a mean age of 36 years and the largest age group being age 18 – 29. The treatment groups were balanced.*

PRIMARY ENDPOINT

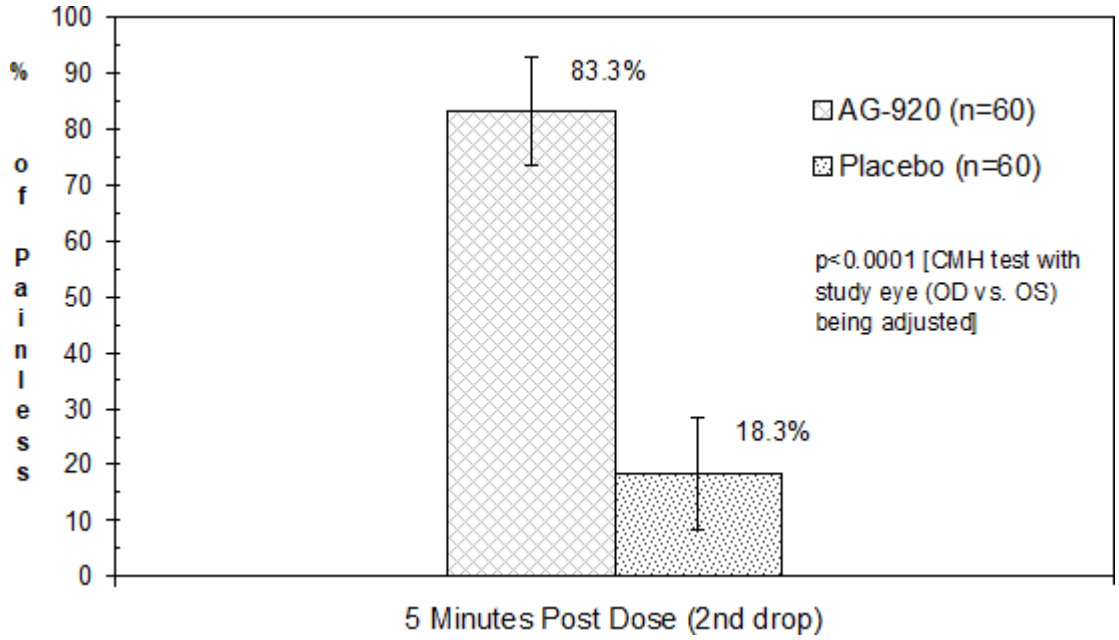
Table 12: Summary and Analysis of Proportion of Subjects with Anesthetic Response at 5 Minutes Post Dose

Category	*Parameters*	*All Subjects*	*Treatment Group*	
			AG-920	*Placebo*
No Anesthetic Response (pain)	N (%)	59 (49.2)	10 (16.7)	49 (81.7)
Anesthetic Response (painless)	N (%)	61 (50.8)	50 (83.3)	11 (18.3)
Number of subjects	N	120	60	60
Difference in % painless (vs. Placebo)	%			65.0
	p value [1]			<0.0001

[1] P value was based on the general association CMH statistics with Study Eye (OD vs. OS) being adjusted

Soutce:Table 14.2.1.1

Figure 2: Proportion of Subjects with Anesthetic Response at 5 Minutes Post dose (95% confidence interval)



Reviewer's Comments
The study met its primary efficacy endpoint with a statistically significant treatment difference (p<0.0001) in favor of AG-920.

6.3. AG-920-CS304

6.3.1. Study Design-

6.3.2 Study Results

Study AG-920-CS304 was a Randomized, Single-Masked, Active-Controlled, Parallel-Group Evaluation of Safety and the Local Anesthetic Effect of Articaine Sterile Topical Ophthalmic Solution (AG-920) in a Pediatric Population.

The findings from this study and full discussion are in 8.6.3 Section of this review.

7. Integrated Review of Effectiveness

The two studies, AG-920-CS301 and AG-920-CS302, demonstrated a statistically significant treatment difference in the primary endpoint, the proportion of subjects with no pain at 5 minutes. The endpoint was assessed using a conjunctival pinch with a forceps given 5 minutes after dose administration of the study drug. The treatment effect (difference from placebo) was 65% in both studies (P<0.0001).

Study AG-920-CS304 was conducted in pediatric patients aged 4-14 years. AG-920 was therapeutically equivalent to marketed proparacaine with respect to subjects achieving adequate local anesthesia enabling a healthcare provider to conduct an ophthalmic examination.

8. Review of Safety

8.1. Safety Review Approach

A total of 5 trials were included in this NDA to support the safety of articaine sterile topical ophthalmic solution 8%. Three studies, AG-920-CS301, AG-920-CS302 and AG-920-CS304 were completed in healthy pediatric and adult subjects. Study AG-920- CS303 was a double-masked, placebo-controlled safety study with 166 subjects exposed to the to-be-marketed dose.

8.2. Review of the Safety Database

APPEARS THIS WAY ON ORIGINAL

8.2.1. Overall Exposure

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 subjects (Table 2). Among the 563 subjects in five clinical studies, there were only two subjects who did not complete the study (ISS Table 1.1). Both of these were in Study AG-920-CS303. One ((b) (6), AG-920 group) had a protocol deviation and was inadvertently enrolled although they did not meet inclusion criteria 7, and the other ((b) (6), placebo group) was lost to follow-up.

Overall 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**

Demographic Profile of Patients (Integrated Safety Population)

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%)

Characteristic	AG-920 n (%)	Placebo n (%)	Proparacaine n (%)	All Subjects n (%)
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%)
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

8.2.2. Adequacy of the safety database

The overall exposure to the Articaine Sterile Topical Ophthalmic Solution (AG-920) 8% during development was adequate to assess the safety profile of this drug product.

8.3. Adequacy of Applicant's Clinical Safety Assessments Issues Regarding Data Integrity and Submission Quality

No issues with data integrity were identified. The application was of sufficient quality to allow a substantive review.

8.3.1. Categorization of Adverse Events

Adverse events for all studies were coded according to the MedDRA dictionary. A treatment emergent adverse event (TEAE) was defined as any AE that was new or worsened in severity after the first dose of study drug. Treatment-emergent AEs were categorized by system organ class (SOC) and preferred term (PT), seriousness, severity, and relationship to study drug.

8.3.2. Routine Clinical Tests

The routine clinical testing to evaluate the safety concerns associated with the treatment of ophthalmic conditions were adequately addressed in the design and conduct of the trials.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in any of the submitted clinical studies.

8.4.2. Serious Adverse Events

No SAEs occurred in any of the submitted clinical studies.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations during the submitted studies.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Ocular and Non-ocular TEAEs (Integrated Safety Population)

There were no AEs in the pediatric study, AG-920-CS304. There was one adverse event in the Phase 1 pharmacokinetic study in normal subjects, AG-920-CS101.

Thus, this summary reports only on the 489 adult subjects in these three studies: AG-920-CS101, AG-920-CS301, AG-920-CS302 and AG-920-CS303.

Most of the events (108/126, 86% in 96/286 subjects, 19.6%) were judged related to study medication. All of the events were judged mild in severity. There were no serious TEAEs, and there were no TEAEs that led to discontinuation of study.

Incidence of Study-Drug-Related 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%)
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%)
Dysgeusia	4 (1.4%)	0 (0.0%)	4 (0.8%)
Dysgeusia	3 (1.0%)	0 (0.0%)	3 (0.6%)
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 Comments: *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.*

Laboratory Findings
No clinical laboratory evaluations were performed during the Applicant-conducted clinical studies.

8.4.5. Vital Signs
Not applicable.

8.4.6. Electrocardiograms (ECGs)
Electrocardiograms were not assessed during this development program.

8.5. Safety Analyses by Demographic Subgroups

Summary of Treatment Emergent Adverse Events by Demographic and Other Characteristics

	Treatment					
	AG-920		Placebo		All subjects	
Subgroup:	*n (%)*	*At risk*	*n (%)*	*At risk*	*n (%)*	*At risk*
Overall	84 (29.4%)	286	30 (14.8%)	203	114 (23.3%)	489
Sex:						
Female	46 (27.1%)	170	17 (14.4%)	118	63 (21.9%)	288
Male	38 (32.8%)	116	13 (15.3%)	85	51 (25.4%)	201
Age:						
<= 30 years	51 (37.8%)	135	18 (18.2%)	99	69 (29.5%)	234
>30 years	33 (21.9%)	151	12 (11.5%)	104	45 (17.6%)	255
Race:						
White	72 (27.7%)	260	27 (14.8%)	182	99 (22.4%)	442
Non-white	12 (46.2%)	26	3 (14.3%)	21	15 (31.9%)	47
Iris color:						
Dark	46 (21.2%)	217	14 (9.6%)	146	60 (16.5%)	363
Light	38 (55.1%)	69	16 (28.1%)	57	54 (42.9%)	126

Source: ISS Tables 3.2, 3.8.1 to 3.8.4

Reviewer's Comment: *The incidence of treatment emergent adverse events was similar across the evaluated demographic groups and similar to the overall study population.*

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

No carcinogenicity studies were conducted with articaine sterile topical ophthalmic solution 8% for this NDA.

8.6.2. Human Reproduction and Pregnancy

There are no adequate and well-controlled studies in pregnant or lactating women with Articaine Sterile Topical Ophthalmic Solution to inform a drug associated risk.

8.6.3. Pediatrics and Assessment of Effects on Growth

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.

The primary endpoint was the proportion of subjects in which an eye exam was able to be performed. The secondary endpoints were the Incidence of AEs, TEAEs, SAEs, withdrawals due to TEAEs. The sample size was as directed by the U.S. FDA for a Pediatric Study Plan. Sixty-one (61) subjects were screened, of which 60 were randomized and treated, all of whom completed the study. 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 (59/60, 98%). The most frequent eye color was brown (58/60, 97%). 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. There were no adverse events reported in this study. In both the study eye and fellow eye, there were no changes of note after dosing, and both treatment groups were similar. All external eye exams in all subjects in both treatment groups were normal. In this pediatric population aged 7 months to <11 years, AG-920 was therapeutically equivalent to marketed proparacaine with respect to subjects achieving adequate local anesthesia to conduct an ophthalmic examination. Further, AG-920 was well tolerated, and there were no clinically significant safety findings. The primary objective of this study was to evaluate the anesthetic efficacy of AG-920 in a pediatric population. This was judged by the proportion of subjects in which an eye examination was able to be performed. This criterion was met in 100% (30/30) subjects treated with AG-920, the same as for subjects treated with the marketed product, proparacaine. The secondary objective of this study was to evaluate the safety and tolerability of AG-920, measured as the incidence of AEs, TEAEs, SAEs, and withdrawals due to TEAEs. There were no adverse events, and no changes observed in biomicroscopy in either the AG-920 or proparacaine treatment effect.
As noted in methods, the investigator and sub-investigators conducted a subjunctive measure – prior to actually conducting the examination, did they think that there was adequate local anesthesia. Ideally, this should have been conjunctival touch, or a similar assessment. Of note, as the Sponsor found out only after study completion, some clinicians also used photophobia in their judgement of local anesthesia. Note also that many or all of these subjects were pharmacologically dilated. As local anesthesia does not affect photophobia, this was an inappropriate criterion. As identified in the protocol, the actual conductance of an examination, rather than the subjunctive assessment measure was considered the primary efficacy measure. In this pediatric population aged 7 months to <11 years, AG-920 was therapeutically equivalent to marketed proparacaine with respect to subjects achieving adequate local anesthesia to conduct an ophthalmic examination. Further, AG-920 was well tolerated, and there were no clinically significant safety findings.

8.6.4. **Overdose**, Drug Abuse Pot**enti**al, Wi**thdra**wal, and Rebou**n**d

Articaine does not have any abuse potential.

8.7. Safety in the Postmarket Setting

There have been no previous approvals for this topical product.

8.8. 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 evaluate the effect of the product on the corneal endothelium in at least 100 patients at 12 months be requested. See CDTL summary memo dated 8/15/2025.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not held for the NDA. There were no issues that were felt to benefit from discussion at an Advisory Committee Meeting.

10. Risk Evaluation and Mitigation Strategies (REMS)

There are no recommended Risk Evaluation or Mitigation strategies for this NDA.

11. Appendices

11.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

11.2. 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)

11.3. List of Investigators

AG-920-CS301

List and Description of Investigators and Participants in the Study

Site Number	Principal Investigator	Site Address		No. of Randomized Subjects
01	David L. Wirta, M.D.	Eye Research Foundation 520 Superior Avenue Suite 235 Newport Beach, CA 92663		120

AG-920-CS302

List and Description of Investigators and Participants in the Study

Site Number	Principal Investigator	Site Address		No. of Randomized Subjects
02	Victor H. Gonzalez, MD	Valley Retina Institute, PA 1309 E. Ridge Road McAllen, TX 78503		120

AG-920-CS304

List and Description of Investigators and Participants in the Study

Site Number	Principal Investigator	Site Address		No. of Randomized Subjects
02	Victor H. Gonzalez, MD	Valley Retina Institute, PA 1309 E. Ridge Road McAllen, TX 78503		61

11.4 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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/s/

SHILPA D ROSE
08/15/2025 09:11:10 AM

WILLIAM M BOYD
08/15/2025 10:22:01 AM