CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218643Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	218643
Supporting document/s:	SDN001
Applicant's letter date:	10/16/2024
CDER stamp date:	10/16/2024
Product:	Articaine Sterile Topical Ophthalmic Solution, 8%
Indication:	Ocular surface anesthesia prior to ocular procedures and/or intraocular injections
Applicant:	American Genomics LLC (Hobe Sound, FL)
Review Division:	DPT- ORPURM/OSM, supporting the Division of Ophthalmology Products (DO)
Reviewer:	Erin Ruhland, PhD
Supervisor/Team Leader:	Aling Dong, PhD, DABT
Division Director:	Kimberly Hatfield, PhD
Project Manager:	Nick Connis

Disclaimer

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1 Executive Summary

1.1 Introduction

The Applicant has submitted a 505(b)(2) NDA for Articaine Sterile Topical Ophthalmic Solution, 8% (b) (4) relying on the Listed Drug (LD) Septocaine® (articaine/epinephrine for injection; NDA 020971). The proposed indication is ocular surface anesthesia prior to ocular procedures and/or intraocular injections.

1.2 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 (b) (4) is 4.8 mg/eye/day (9.6 mg/day bilateral dose). The approved injected dose of Septocaine® exceeds the dose of (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 this review).

In patients who received a unilateral topical ocular administration of (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.

1.3 Recommendations

1.3.1 Approvability

- This NDA is approvable from a Pharmacology/Toxicology perspective.

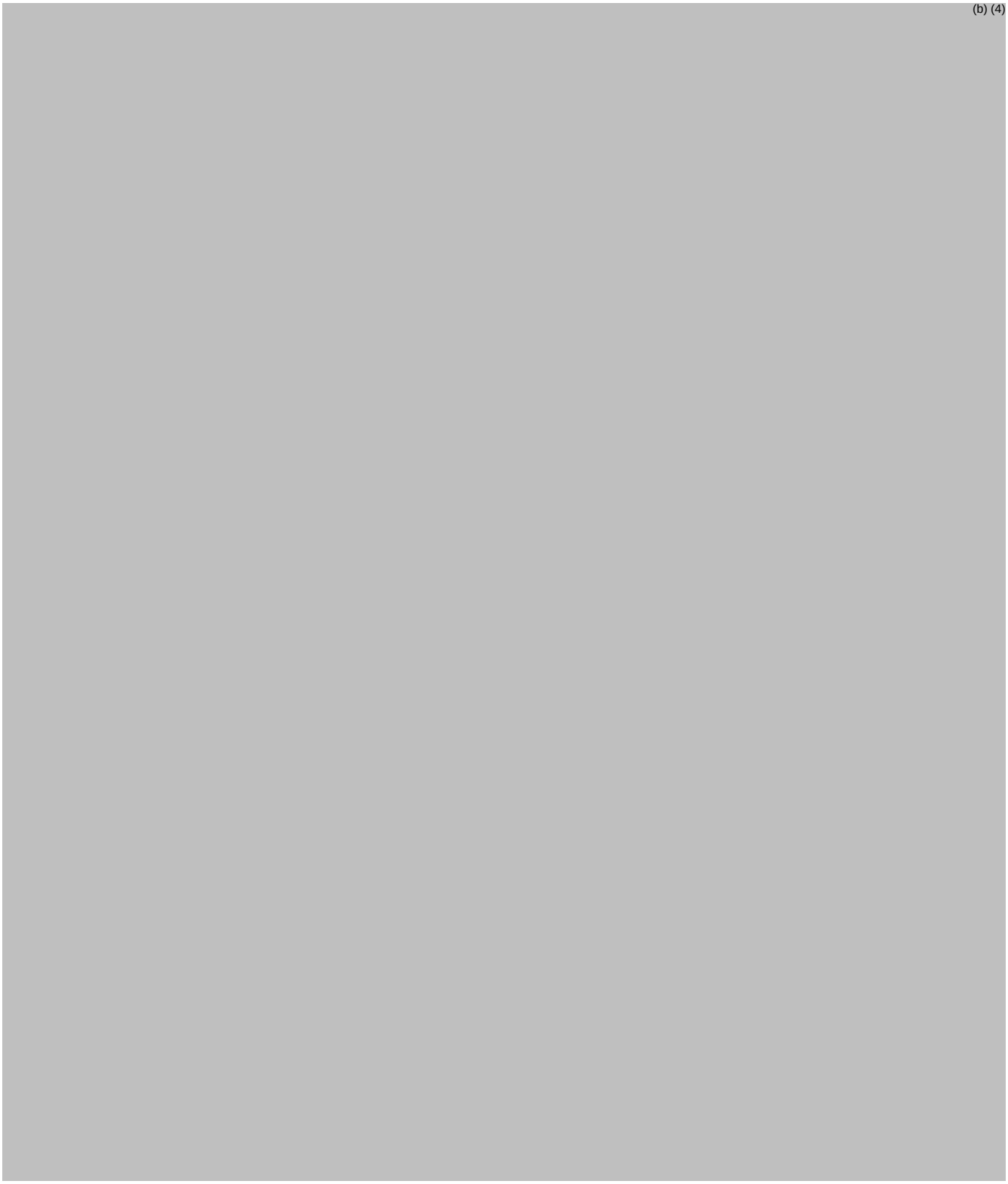
1.3.3 Labeling

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

(b) (4)

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

(b) (4)



2 Drug Information

2.1 Drug

Articaine Sterile Topical Ophthalmic Solution, 8%

CAS Registry Number: 23964-57-0

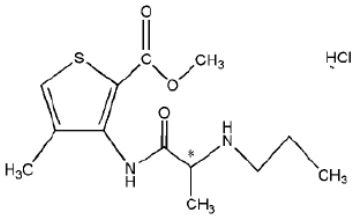
Generic Name: Articaine, Articaine HCl

Code Name: AG-920

Chemical Name: Methyl 4-methyl-3-[[(2RS)-2-(propylamino) propanoyl] amino] thiophene-2-carboxylate hydrochloride

Molecular Formula/Molecular Weight: $C_{13}H_{21}ClN_2O_3S$ / 320.84 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Amide Local Anesthetic

2.2 Relevant INDs, NDAs, BLAs and DMFs

- DMF (b) (4)
- IND 145,052 [Clinical development of (b) (4) (articaine hydrochloride, 8%)]
- NDA 020971: Septocaine® (articaine hydrochloride and epinephrine injection), for intraoral submucosal infiltration use.
    - Approved 4/3/2000
    - Maximum approved human dose (per labeling): 7 mg/kg of articaine HCl (420 mg for a 60 kg adult)
    - Listed Drug (LD) for this 505(b)(2) NDA

2.3 Drug Formulation

Component	Function	Target Concentration (% w/v)	Amount per Vial (0.4 mL)
Articaine Hydrochloride (USP)	Active Ingredient	9.02[1]	(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)

2.4 Comments on Novel Excipients

- All excipients have been previously qualified for topical ophthalmic instillation at concentrations above those proposed in the formulation.

2.5 Comments on Impurities/Degradants of Concern

Impurities

The Applicant proposes a specification for "Impurity B" which exceeds the qualification threshold per ICH Q3b. The Applicant proposes a specification of no more than (b) (4)% in the drug product. Impurity B was identified as articaine acid or articainic acid (4-methyl-3-[[(2RS)-2-(propylamino) propanoyl] amino] thiophene-2-carboxylic acid). Articainic acid is a metabolite of articaine hydrochloride formed through the action of esterase enzymes. Systemic exposure to articainic acid following topical ocular instillation of articaine was demonstrated in the toxicokinetic analysis performed in the nonclinical toxicity studies. As a metabolite of the active compound, no further qualification of the impurity is necessary.

Leachables

Leachable studies were conducted with the drug product stored within the container closure system/packaging. In one leachables study (TTP-AXK-M0055.01), no leachables were detected above 20 ppm under the storage conditions of 25°C/40% RH for 0, 3-months, 6-months and 9-months.

In a separate leachables study (TTP-AXK-M0044.01), the drug product/CCS/packaging were stored at 25ºC/40%RH for 0, 3-months, 6-months,9-months, 12-months, 18-months and 24-months. Two leachables were detected above the 20ppm qualification threshold at the 9- month timepoint; they were undetectable at later timepoints. Additional toxicity assessment was conducted.

Leachable compound identity	CAS Number	Maximum observed concentration (µg/mL; ppm) at 1 to 36-months on stability	Maximum Dose (µg)
(b) (4)			

Two assessments (toxicological consults) submitted by the Applicant concluded that the leachable compounds yielded acceptable margins of safety and negligible potential toxicological risks to the patient. The assessments were made to determine the potential for 1) ocular irritation and toxicity 2) systemic toxicity and 3) genotoxicity.

LD_{50} values for each compound were presented in the reports. The LD_{50} of (b) (4) was cited as (b) (4) mg/kg and the LD_{50} of (b) (4) was reported as (b) (4) mg/kg. These values greatly exceed the amounts of the impurities found in the drug product but provide little other assurance of safety.

No empirical data were provided which can be used to specifically support ocular safety of the leachables. The Applicant makes the argument that the actual dose topically applied to the eye for a compound at (b) (4) ppm is much less since "a majority of the instilled volume (approx. 80-90%) drains into the nasolacrimal duct" and thus the applied dose would constitute less than 20ppm. This argument is not acceptable as the qualification threshold for an ocular product has been set as no-more-than 20ppm regardless of its disposition following administration. A weight of evidence (WoE) approach was used to aid in determining whether a limit of NMT (b) (4) ppm will be acceptable for the two leachables that exceed the 20ppm qualification threshold without the need for further qualification.

Aspects of the WoE were based on:

- the single use of the product for the indication
- the inconsistent nature of the findings (only found in 1 of 2 studies and only at the 9-month timepoint)
- the Applicant's toxicology consult documents
- the classification of the compounds and experimental data for severe eye irritants.

Data have been presented that compounds known as severe ocular irritants showed no irritancy/toxicity at 100ppm levels following several instillations and that the threshold of 20ppm offered an additional 5x margin of safety for threshold purposes.[1] Of those compound classes classified as the most irritating, the two leachables did not appear to fit into those "most irritating" classifications.

[1] Richardson, ME, 2015, "Investigation of an Ocular Irritation Threshold for Leachables and Impurities in Pharmaceutical Products" presented for Product Quality Research Institute; https://pqri.org/wp-content/uploads/2015/08/pdf/Poster3_Richardson_PQRI%20poster_OI%20Threshold.pdf

Given the single administration of articaine hydrochloride during ophthalmic procedures and injections, the risk for genotoxicity for a one instance intake of (b) (4) g is not concerning given the permissibility threshold of no-more-than (NMT) 1.5 µg/day of concern for genotoxic compounds administered chronically for a lifetime. The WoE analysis has concluded that the specification of NMT (b) (4) ppm is acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

(b) (4) (Articaine Sterile Topical Ophthalmic Solution, 8%) is indicated for ocular surface anesthesia in adult and pediatric patients prior to ocular procedures and/or intraocular injections. The maximum recommended daily human dose is 2 drops applied 30 seconds apart to the ocular surface. The drop size is 0.03 mL/drop.

Given the indication of anesthesia prior to intraocular injections, it is assumed that a bilateral dose may be administered in cases of inpatient bilateral intraocular injections such as though prescribed to treat various retinal and other intraocular diseases.

At a concentration of 8% articaine hydrochloride, the daily dose is 4.8 mg/eye/day or 9.6 mg/day as the total bilateral daily dose.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetics

- Study AG-920-ADME-001: Ocular pharmacokinetics study of a single administration of 8% articaine (AG-920) in Dutch Belted rabbits
- Study 2018-141: Determination of articaine melanin binding

Toxicology

- AG-920-TOX-001: A single dose bilateral surface instillation ocular toxicity and toxicokinetics study followed by a 7-day recovery period in male Dutch Belted rabbits
- AG-920-TOX-002: A single occasion two-dose bilateral surface instillation ocular toxicity and toxicokinetics study followed by a 7-day recovery period in male Dutch Belted rabbits

Published Studies

- Verhoeven, R., *et al*., 2022, “Early Nonclinical and Clinical Development of AG-920, a repurposed topical ocular anesthetic”

3.2 Studies Not Reviewed

Pharmacokinetics

- Study 2018-121: Preclinical dose tolerability and ocular biodistribution study

    - Utilized formulation of AG-920 ("Formulation F") which is not the to-be-marketed formulation
- 19VAG02: Bioanalytical method validation report for the analysis of articaine and articainic acid in rabbit plasma (NaF/KOx)
- Study 20QAG01: Method qualification report for the analysis of articaine and articainic acid in rabbit aqueous humor and vitreous humor
- Study 20QAG02-001: Method qualification report for the analysis of articaine and articainic acid in rabbit sclera and lens
- Study 20QAG02-002: Method qualification report for the analysis of articaine and articainic acid in rabbit retina, RPE-choroid and ICB
- Study 20QAG02-003: Method qualification report for the analysis of articaine and articainic acid in rabbit conjunctiva, cornea, and optic nerve

3.3 Previous Reviews/Documents Referenced

- Labeling for NDA020971: Septocaine® (articaine hydrochloride and epinephrine injection)
    - https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0eba0bd2-ccb6-4f7e-8d0c-e4b4e6cdce03

- Pharmacology Review for NDA020971
    - Not available in DARRTS database
    - Accessed through drugs@fda website
        - https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/020971_SEPTOCAINE_PHARMR.PDF

4 Pharmacology

4.1 Primary Pharmacology

Excepted from current Septocaine® labeling:

Articaine HCl 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.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study AG-920-ADME-001: Ocular pharmacokinetics study of a single administration of 8% articaine (AG-920) in Dutch Belted rabbits (non-GLP)

- Ocular distribution study of the to-be-marketed formulation
- Male Dutch Belted rabbits received a single bilateral administration of AG-920 via topical ocular instillation of two 35 µL drops/eye with a 30 second dosing interval between drops(n=24). Plasma was collected at baseline, 15 and 30 minutes, and 1-, 2-, 4-, 8-, 12-, 24-, 48-, and 72-hours post-dose. Ocular matrices including bulbar conjunctiva, sclera, cornea, aqueous humor, iris/ciliary body, lens, vitreous humor, retina, choroid/retinal pigment epithelium (RPE), and optic nerve were collected following termination at 30 minutes, 1-, 2-, 4-, 8-, 24-, 48-, and 72-hours post-dose. Palpebral conjunctiva was inadvertently not collected. Articaine and its metabolite articainic acid concentration in each tissue was analyzed by validated reversed phase liquid chromatography and tandem mass spectrometry (LC-MS/MS).
- Articaine distributed to all tissues analyzed with a rank order of exposure (AUC): iris/ciliary body > RPE/choroid > cornea > bulbar conjunctiva > sclera > retina ≈ aqueous humor > lens > optic nerve > vitreous humor. Plasma exposure was detected.
- Articainic acid followed a somewhat different distribution pattern of exposure: cornea > aqueous humor > iris/ciliary body > lens > bulbar conjunctiva > RPE/choroid > sclera > vitreous humor ≈ retina ≈ optic nerve. Plasma exposure did not appear to have been measured.

Articaine Mean Pharmacokinetic Parameters (From Front to Back of Eye)

Matrix	Tmax (h)	Cmax (ng/mL)	T1/2 (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	MRTlast (h)	MRTinf (h)
Bulbar Conjunctiva	1.0	8910	12.9	37200	38300	16.5	18.5
Sclera	0.50	7180	9.01	22100	22300	5.42	6.05
Cornea	0.50	20700	13.5	63000	63700	12.7	13.6
Aqueous Humor	0.50	7090	10.1	9690	9760	10.9	11.4
Iris/Ciliary Body	0.50	55400	11.5	208000	210000	7.27	7.83
Lens	0.50	965	5.41	3840	3890	6.06	6.64
Vitreous Humor	0.50	100	4.57	278	290	3.43	4.56
Retina	0.50	3740	4.72	9700	9860	3.14	3.58
RPE/Choroid	0.50	46000	9.54	150000	150000	5.73	5.93
Optic Nerve	0.50	704	2.05	1140	1190	2.04	2.40
Plasma	0.25	419	3.68	274	281	0.768	1.48

Articainic Acid Ocular Tissue Exposure PK Parameters (1 of 2)

Matrix	Tmax (h)	Cmax (ng/g)	Cmax SE (ng/g)	AUClast (h*ng/g)	AUClast SE (h*ng/g)	AUCinf (h*ng/g)	%Extrap (%)
Bulbar Conjunctiva	0.50	6320	869	11800	1620	12000	1.91
Cornea	0.50	29500	3270	85500	4880	86800	1.53
ICB	0.50	6220	1090	21000	945	21200	0.94
Lens	1.0	667	84.3	17700	912	20300	12.91
Optic Nerve	0.50	235	17.8	269	20.1		*
Retina	0.50	158	24.7	338	21.1	360	6.18
RPE/Choroid	0.50	1440	171	3120	245	3400	8.30
Sclera	0.50	1340	132	1950	95.2	2360	17.50
Aqueous Humor	2.0	5530	361	23500	961	23500	0.15
Vitreous Humor	8.0	9.27	0.787	341	15.4	383	10.84

Study 2018-141: Determination of articaine melanin binding

- Articaine (500 to 50,000 ng/mL) was spiked into phosphate buffered saline (PBS), albino rabbit choroid homogenate (non-melanin control), bovine choroid homogenate or *Sepia officinalis* melanin in PBS. Samples were prepared in triplicate, incubated for 60 minutes, and centrifuged. The supernatants were removed, and an LC/MS/ MS method was utilized for analysis of articaine binding.

Articaine Melanin Binding

Melanin Type	Articaine Concentration	% Recovery relative to PBS	% Bound relative to Albino Choroid
Pigmented Choroid (Melanin)	500 ng/mL	67.7%	0%
	5000 ng/mL	75.4%	7.4%
	50,000 ng/mL	86.6%	2.7%
***sepia officinalis* melanin**	500 ng/mL	22.0%	78.0%
	5000 ng/mL	36.5%	63.5%
	50,000 ng/mL	60.1%	39.9%
Albino Choroid (non-melanin control)	500 ng/mL	63.7%	NA
	5000 ng/mL	81.5%	NA
	50,000 ng/mL	89.1%	NA

NA – not applicable

- Articaine displayed measurable binding to melanin in pigmented choroid and sepia officinalis ink. The binding of articaine to both pigmented choroid and sepia officinalis ink is considered weak as it appears to saturate at low concentrations and would likely not be retained at significant levels from a typical dose in physiological conditions.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: A single dose bilateral surface instillation ocular toxicity and toxicokinetics study followed by a 7-day recovery period in male Dutch Belted rabbits

Study no.:	AG-920-TOX-001
Study report location:	\\CDSESUB1\EVSPROD\nda218643\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\74822b\ag-920-tox-001-final-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/25/2019
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	AG-920 (8% articaine); Lot# 00519A; 97.9% purity

Key Study Findings

- No adverse toxicity, ocular or systemic, was associated with a single bilateral topical ocular administration (2 drops/eye) of AG-920 (8% articaine hydrochloride; 5.6 mg/eye/day; 11.2 mg total daily dose)

Methods

Doses:	Treatment: • Bilateral 8% AG-920 (5.6 mg/eye/day; 11.2 mg total daily dose) Control • Left eye: Saline; Right eye: vehicle
Frequency of dosing:	QD (2 drops); 30 second dosing interval between drops
Route of administration:	Topical ocular instillation
Dose volume:	(b) (4) mL/drop
Formulation/Vehicle:	Clinical formulation / vehicle
Species/Strain:	Rabbit / Dutch Belted
Number/Sex/Group:	Main Study: 6 males/group Recovery: 2 males/group
Age:	Approximately 5 months
Weight:	1.6 – 1.9 kg
Deviation from study protocol:	No deviations affected the conduct or integrity of the study or the interpretability of study results.

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Clinical Signs (daily)

- No changes in clinical signs attributed to the test article.

Body Weights (daily)

- No changes in body weight or body weight gain attributed to the test article.

Feed Consumption (daily)

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy [Pre-dose, Hours 2 and 24 post-dose, and on Days 4 and 7 (recovery); slit lamp biomicroscopy and indirect ophthalmoscopy modified Hackett-McDonald scoring]

- Hyperemia/conjunctival congestion [minimal (1+) – mild (2+)]
  - Observed across all groups and eyes including saline and placebo vehicle eyes.

Slit Lamp Ocular Examination Results

Test Material	Pre-treatment	2-3 hours post-Rx	Day 2 post-Rx	Day 4 post-Rx	Day 7 post-Rx
Saline (OS)	-	+1 conjunctiva congestion: 2/8 **1003A, 1006A**	-	-	-
Vehicle (OD)	+1 conjunctiva congestion: 1/8 **1006A**	+1 conjunctiva congestion: 3/8 **1003A, 1006A, 1008B**	+1 conjunctiva congestion: 2/8 **1004A, 1005A**	+1 conjunctiva congestion: 1/2 **1008B**	-
8% AG-920 (OU)	-	+1 conjunctiva congestion: 1/16 **2002A OS** +2 conjunctiva congestion: 1/16 **2003A OD**	+1 conjunctiva congestion: 2/16 **2001A OD, 2003A OS**	-	-

- Corneal opacity (minimal – moderate)
  - Present at pre-treatment observations and not worsened by treatment in both Control and AG-920-treated groups. In one case in the treated animals, a corneal opacity was observed in an animal at the 2 – 3 hr timepoint that was not reported at baseline; however, by 2 days after treatment, the finding was not reported (Animal 2006A)
  - These findings are not considered vehicle or test article related.

Indirect Ophthalmoscopy Examination Results

Test Material	Pre-treatment	2-3 hours post-Rx	Day 2 post-Rx	Day 4 post-Rx	Day 7 post-Rx
Saline (OS)	+2 LNF: 1/8 **1008B** +1 corneal opacity: 2/8 **1003A, 1006A** +1 corneal surface opacity: 1/8 **1003A** +2 corneal surface opacity: 1/8 **1006A**	+2 LNF: 1/8 **1008B** +1 corneal opacity: 2/8 **1003A, 1006A** +1 corneal surface opacity: 1/8 **1003A** +2 corneal surface opacity: 1/8 **1006A**	+2 LNF: 1/8 **1008B** +1 corneal opacity: 2/8 **1003A, 1006A** +1 corneal surface opacity: 1/8 **1003A** +2 corneal surface opacity: 1/8 **1006A**	+2 LNF: 1/2 **1008B**	+2 LNF: 1/2 **1008B**
Vehicle (OD)	+2 LNF: 1/8 **1008B** +3 RPM: 1/8 **1102A**	+2 LNF: 1/8 **1008B** +3 RPM: 1/8 **1102A**	+2 LNF: 1/8 **1008B** +3 RPM: 1/8 **1102A**	+2 LNF: 1/2 **1008B**	+2 LNF: 1/2 **1008B**
8% AG-920 (OU)	+1 corneal opacity: 1/16 **2003A OS** +1 corneal surface opacity: 1/16 **2003A OS**	+1 corneal opacity: 2/16 **2003A OS, 2006A OD** +1 corneal surface opacity: 2/16 **2003A OS 2006A OD**	+1 corneal opacity: 1/16 **2003A OD** +1 corneal surface opacity: 1/16 **2003A OD**	-	-

LNF= Lens opacity, nucleus, focal; RPM= Retina, pigmentation variation, multifocal

- Fluorescein staining ("faint positive")
  - Observed both pre-treatment and following dosing.
  - In some animals, the finding appeared following treatment but was not present at baseline.
    - Appeared in 2 animals in the vehicle (Animals 1008B and 1005A; 2 – 3 hours post dose) and 2 animals in the test article treated groups (animals 2006A and 2008B; 2 – 3 hours or Day 4, respectively) as "very faint to faint" positive findings
    - The finding was equally distributed between vehicle and test article treated animals and was not increased in incidence or severity compared to pre-dose incidence/severity, so it is not thought to be related to treatment. Finding was not reported by Day 7 post-treatment.

Fluorescein Staining Results

Test Material	Pretreatment	2-3 hours post-Rx	Day 2 post-Rx	Day 4 post-Rx	Day 7 post-Rx
Saline (OS)	Very faint positive: 3/8: **1001A, 1002A, 1003A**	-	-	-	-
Vehicle (OD)	Very faint positive: 1/8 **1002A**	Very faint positive: 1/8 **1008B** Faint positive: 1/8 **1005A**	-	-	-
8% AG-920 (OU)	Very faint positive: 3/16 **2002A OD, 2003A OD, 2004A OD**	Faint positive: 1/16 **2006A OD**	-	Very faint positive: 2/4 **2008B OU**	-

Pachymetry [Pre-dose, Hours 2 and 24 post-dose, and on Days 4 and 7 (recovery)]

- No changes in corneal thickness attributed to the test article.

Tonometry [Pre-dose, Hours 2 and 24 post-dose, and on Days 4 and 7 (recovery)]

- No changes in intraocular pressure attributed to the test article.

Gross Pathology

- No changes in macroscopic observations attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Yes; standard battery

Peer Review: No

Histological Findings: No changes in microscopic observations attributed to the test article.

Toxicokinetics (Pre-dose and 0.25, 1, 2, 4, 8 and 24 hours pos-dose; Recovery animals also sampled at 48, 72 and 144 hours post-dose)

Day 1 Toxicokinetics following topical ocular administration of articaine ophthalmic solution, 8%

Analyte	Dose	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)	AUC_{0-24} (ng hr/mL)	AUC_{0-inf} (ng hr/mL)
Articaine	11.2mg*	886	0.25	6.49	598	601
Articainic acid		2010	0.25	6.62	1600	1620

*bilateral ocular dose of 5.6 mg/eye (administered as 2 drops/eye)

Dosing Solution Analysis

- The Applicant provided the following statement: Active Batch 00519A was manufactured on June 24, 2019. Based on available stability data, the current retest period is (b) (4) .
- No other information provided. For a single dose study conducted within the specified shelf-life of the product, this is sufficient.

Conclusion

- No adverse findings were associated with the bilateral instillation of AG-920 as two drops separated by 30-seconds. The NOAEL is 5.6 mg/eye/day; 11.2 mg total daily dose.
    - *Reviewer's note: While the NOAEL is 2 drops/eye, the time between drops was 30 seconds which may not allow adequate time between drops for complete absorption of the first drop before the second is applied. This matches the clinical dosing regimen.*

Study title: A single occasion two-dose bilateral surface instillation ocular toxicity and toxicokinetics study followed by a 7-day recovery period in male Dutch Belted rabbits

Study no.:	AG-920-TOX-002
Study report location:	\\CDSESUB1\EVSPROD\nda218643\0001\m4\42-stud-rep\423-tox\4231-single-dose-tox\700672b\700672b.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7/26/2021
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	AG-920, Lot#01219B, Purity: 99.95%

Key Study Findings

- No adverse toxicity, ocular or systemic, was associated with two bilateral topical ocular doses (10 minutes apart, 2 drops/eye/dose) of AG-920 (8% articaine hydrochloride; 11.2 mg/eye/day; 22.4 mg/animal total daily dose).

Methods

Doses:	Treatment: • Bilateral 8% AG-920 (11.2 mg/eye/day; 22.4 mg total daily dose) Control • Left eye: Saline; Right eye: vehicle
Frequency of dosing:	2 drops/eye followed 10 minutes later by a second dose for a total of 4 drops/eye/day.
Route of administration:	Topical ocular instillation
Dose volume:	(b) (4) mL/drop (2.8 mg/drop)
Formulation/Vehicle:	Clinical formulation / vehicle
Species/Strain:	Rabbit / Dutch Belted
Number/Sex/Group:	Main Study: 6 males/group Recovery (7-days): 2 males/group
Age:	5 – 6 months
Weight:	1.8 – 1.9 kg
Deviation from study protocol:	No deviations affected the conduct or integrity of the study or the interpretability of study results.

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Feed Consumption

- No changes in feed consumption attributed to the test article.

Ophthalmoscopy

- Conjunctival hyperemia (minimal – moderate)
  - Observed in all groups; increased incidence at 2-3 hours post dosing test in AG-920 treated animals
  - Mostly resolved by 24 hours post-dose; completely resolved by Day 7.

Slit Lamp Ocular Examination Results

Test Material	Pre-treatment	2-3 hours post-Rx	24 hours post-Rx	Day 4 post-Rx	Day 7 post-Rx
Saline (OS)	-	+1 conjunctiva congestion: 1/8 **1105A**	+3 conjunctiva congestion: 1/8 **1105A**	-	-
Control/Vehicle (OD)	-	-	-	-	-
AG-920 (OU)	+1 conjunctiva congestion: 2/8 **2102A OU, 2007B OD**	+1 conjunctiva congestion: 3/8 **2001A OD, 2007B OD, 2008B OD** +2 conjunctiva congestion: 2/8 **2001A OS 2008B OS**	+1 conjunctiva congestion: 1/16 **2008B OS**	+1 conjunctiva congestion: 1/4 **2007B OD**	-

Fluorescein Staining

- Faint fluorescein staining was observed across all groups including saline and vehicle control pre-test and following treatment. No change in fluorescein staining was attributed to the test article.

Fluorescein Staining Results

Test Material	Pretreatment	2-3 hours post-Rx	24 hours post-Rx	Day 4 post-Rx	Day 7 post-Rx
Saline (OS)	Faint positive: 5/8: **1001A, 1002A, 1003A, 1004A, 1105A**	Faint positive: 3/8: **1002A, 1004A, 1006A**	Faint positive: 1/8: **1006A**	Faint positive: 1/4: **1008B**	Faint positive: 1/4: **1008B**
Control/Vehicle (OD)	Faint positive: 3/8: **1002A, 1003A, 1105A**	Faint positive: 2/8: **1001A, 1006A**	Faint positive: 2/8: **1004A, 1007B**	-	-
AG-920 (OU)	Faint positive: 1/16 **2003A OS**	Faint positive: 5/16 **2102A OS, 2007B OS 2001A OD, 2004A OD, 2007B OD** Positive: 1/16 **2006A OD**	Faint positive: 1/16 **2003A OD**	Faint positive: 1/4 **2008B OS**	-

Pachymetry [Pre-dose, Hours 2 and 24 post-dose, and on Days 4 and 7 (recovery)]

- No changes in corneal thickness attributed to the test article.

Tonometry [Pre-dose, Hours 2 and 24 post-dose, and on Days 4 and 7 (recovery)]

- No changes in intraocular pressure attributed to the test article.

Gross Pathology

- No changes in macroscopic observations attributed to the test article.

Organ Weights

- No changes in organ weights attributed to the test article.

Histopathology

Adequate Battery: Yes; standard

Peer Review: No.

Histological Findings: No changes in microscopic observations attributed to the test article.

Toxicokinetics (Pre-dose and 0.25, 1, 2, 4, 8 and 24 hours pos-dose; Recovery animals also sampled at 48, 72 and 144 hours post-dose)

Analyte	Dose	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)	AUC_{0-24} (ng hr/mL)	AUC_{0-inf} (ng hr/mL)
Articaine	44.8mg*	1030	0.25	0.618	777	764
Articainic acid		2290	0.25	0680	2180	2240

Dosing Solution Analysis

- The Applicant provided the following statement: Active Batch 01219B was manufactured on November 18, 2019. Based on available stability data, the current retest period is (b) (4) .
- No other information provided. For a single day study conducted within the specified shelf-life of the product, this is sufficient.

Publications:

- Leuschner, J., and D. Leblanc, 1999, "Studies on the toxicological profile of the local anaesthetic articaine", *Arzneimittelforschung*, 49(2): 126 – 132.

  - This published article reported the results of four-week repeat dose toxicology studies in Sprague Dawley rats and beagle dogs following daily subcutaneous administration of articaine. Genotoxicity and reproductive toxicity studies were also performed but will not be reviewed since the results are similar to those already submitted and reviewed for Septocaine® (see below).
    - <u>Rats</u>
      - Male and female rats, 10 per sex per dose group, received daily subcutaneously Water for Injection, 25, 50 or 100 mg articaine/kg/day for a total of 4 weeks. Clinical assessment and laboratory tests including histopathology were conducted.
        - The 50 and 100 mg/kg/day doses of articaine were in the lethal range. A dose-related decrease in hemoglobin, and dose related increases in leukocytes, platelets and reticulocytes were noted.
        - A dose-related increase in blood urea was noted at the 50 mg/kg/day dose level and increases in total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noted at the 100 mg/kg/day dose level.
        - Histopathology revealed at all dose levels an increase in the incidence and/or severity of skin ulcerations, epidermal/dermal and subcutaneous necrosis at the injection site, and inflammatory cell infiltration reflective of an irritant effect of the articaine formulation. The No Observed Adverse Effect Level (NOAEL) in the rats was 25 mg/kg/day of articaine.
    - <u>Dogs</u>
      - Male and female beagle dogs, 3 per sex per dose group, received daily subcutaneously Water for Injection, 20, 40 or 80 mg articaine/kg/day for a total of 4 weeks. Clinical

assessment and laboratory tests including histopathology were conducted.

- Behavioral changes including vomiting, increased salivation, ataxia, sedation, defecation, clonic or tonoclonic convulsions, and abnormal positioning were noted at the high dose level of 80 mg/kg/day doses of articaine. None of the animals died prematurely.
- Increases in ALT and AST were noted at the 80 mg/kg/day dose level. Histopathology revealed no pathological or systemic changes.
- The NOAEL in the dogs was 40 mg/kg/day of articaine.

7 Genetic Toxicology

Excepted from current Septocaine® labeling:

Five standard mutagenicity tests, including three in vitro tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test, and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleus tests (one with articaine and epinephrine 1:100,000 and one with articaine HCl alone) showed no mutagenic effects.

8 Carcinogenicity

Excepted from current Septocaine® labeling:

Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted.

9 Reproductive and Developmental Toxicology

Excepted from current Septocaine® labeling:

In embryo-fetal toxicity studies in rabbits, 80 mg/kg, subcutaneously (approximately 4 times the MRHD based on body surface area) caused fetal death and increased fetal skeletal variations, but these effects may be attributable to severe maternal toxicity, including seizures, observed at this dose. In contrast, no embryo-fetal toxicities were observed when articaine and epinephrine (1:100,000) was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the MRHD based on body surface area).

In pre- and postnatal developmental studies subcutaneous administration of articaine hydrochloride to pregnant rats throughout gestation and lactation, at a dose of 80 mg/kg (approximately 2 times the MRHD based on body surface area)

increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe maternal toxicity in some animals. A dose of 40 mg/kg (approximately equal to the MRHD on a mg/m2 basis) did not produce these effects. A similar study using articaine and epinephrine (1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.

No effects on male or female fertility were observed in rats for articaine and epinephrine 1:100,000 administered subcutaneously in doses up to 80 mg/kg/day (approximately 2 times the MRHD based on body surface area).

10 Integrated Summary and Safety Evaluation

Ocular and Systemic Safety Margins over NOAEL

Topical Instillation (Ocular Toxicity)			
Toxicity	Species	NOAEL (mg/eye)	Safety Margin over NOAEL Based on Applied Dose*
No adverse ocular toxicity following doubling of clinical dosing regimen (see Study AG-920-TOX-002)	Rabbit	11.2 mg/eye	2.3-fold
Subcutaneous Administration (Systemic Toxicity)			
Toxicity	Species	NOAEL (mg/kg/day)	Safety Margin over NOAEL Based on Body Surface Area Conversion of Bilateral Dose†
• Lethality • Decreased hemoglobin • Increased leukocytes, platelets and reticulocytes • Increased blood urea • Increased total bilirubin, ALT and AST • Skin irritation	Rat	25	25-fold
• Behavioral changes including convulsions • Increased ALT and AST	Dog	40	135-fold
Subcutaneous Administration (Reproductive Toxicity)			
No adverse effect on fertility / fetal development	Rat	80	81-fold
Increased stillbirths and adversely affected passive avoidance	Rat	40	41-fold
Maternal toxicity, increased fetal death and fetal skeletal variations	Rabbit	40	81-fold

*** ocular margins are based on a unilateral human dose of 2 drops (4.8 mg)**

† systemic margins are based on a bilateral human dose of 2 drops/eye (9.6 mg)

APPENDIX A for current approved labeling (nonclinical and other relevant sections only) for SEPTOCAINE®

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects - Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women with SEPTOCAINE. Articaine hydrochloride and epinephrine (1:100,000) has been shown to increase fetal deaths and skeletal variations in rabbits when given in doses approximately 4 times the maximum recommended human dose (MRHD). SEPTOCAINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo-fetal toxicity studies in rabbits, 80 mg/kg, subcutaneously (approximately 4 times the MRHD based on body surface area) caused fetal death and increased fetal skeletal variations, but these effects may be attributable to severe maternal toxicity, including seizures, observed at this dose. In contrast, no embryo-fetal toxicities were observed when articaine and epinephrine (1:100,000) was administered subcutaneously throughout organogenesis at doses up to 40 mg/kg in rabbits and 80 mg/kg in rats (approximately 2 times the MRHD based on body surface area).

In pre- and postnatal developmental studies subcutaneous administration of articaine hydrochloride to pregnant rats throughout gestation and lactation, at a dose of 80 mg/kg (approximately 2 times the MRHD based on body surface area) increased the number of stillbirths and adversely affected passive avoidance, a measure of learning, in pups. This dose also produced severe maternal toxicity in some animals. A dose of 40 mg/kg (approximately equal to the MRHD on a mg/m2 basis) did not produce these effects. A similar study using articaine and epinephrine (1:100,000) rather than articaine hydrochloride alone produced maternal toxicity, but no effects on offspring.

8.3 Nursing Mothers
It is not known whether SEPTOCAINE is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SEPTOCAINE is administered to a nursing woman. When using SEPTOCAINE, nursing mothers may choose to pump and discard breast milk for approximately 4 hours (based on plasma half life) following an injection of SEPTOCAINE (to minimize infant ingestion) and then resume breastfeeding.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Articaine HCl 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. Epinephrine is a vasoconstrictor added to articaine HCl to slow absorption into the general circulation and thus prolong maintenance of an active tissue concentration.

12.3 Pharmacokinetics

Absorption

Following dental injection by the submucosal route of an articaine solution containing epinephrine 1:200,000, articaine reaches peak blood concentration about 25 minutes after a single dose injection and 48 minutes after three doses. Peak plasma levels of articaine achieved after 68 and 204 mg doses are 385 and 900 ng/mL, respectively. Following intraoral administration of a near maximum dose of 476 mg, articaine reaches peak blood concentrations of 2037 and 2145 ng/mL for articaine solution containing epinephrine 1:100,000 and 1:200,000, respectively, approximately 22 minutes post-dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to evaluate the carcinogenic potential of articaine HCl in animals have not been conducted. Five standard mutagenicity tests, including three in vitro tests (the nonmammalian Ames test, the mammalian Chinese hamster ovary chromosomal aberration test, and a mammalian gene mutation test with articaine HCl) and two in vivo mouse micronucleus tests (one with articaine and epinephrine 1:100,000 and one with articaine HCl alone) showed no mutagenic effects.

No effects on male or female fertility were observed in rats for articaine and epinephrine 1:100,000 administered subcutaneously in doses up to 80 mg/kg/day (approximately 2 times the MRHD based on body surface area)

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/s/

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