Office of Clinical Pharmacology Review

NDA Number	218643
Link to EDR	\\CDSESUB1\evsprod\NDA218643\0001
Submission Date	10/16/2024
Submission Type	NDA 505(b)(2); Standard
Brand Name	Cyklx
Generic Name	Articaine sterile topical ophthalmic solution 8%
Dosage Form and Regimen	The recommended dose of articaine sterile topical ophthalmic solution is 2 drops applied 30 seconds apart to the ocular surface.
Route of Administration	Ocular
Proposed Indication	For ocular surface anesthesia prior to ocular procedures and/or intraocular injections
Applicant	American Genomics , LLC
Associated IND	145052
OCP Review Team	Youssef Mousa, Ph.D.; Ping Ji, Ph.D.

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1 Executive Summary

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

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

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

1.1. Recommendations

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

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

1.2. Post Marketing Requirement

None

2 Summary of Clinical Pharmacology Assessment

The clinical pharmacology assessment includes the review of the systemic PK data obtained from study AG-920-CS101 and review of bioanalytical method associated with this study.

2.1. Pharmacology and Clinical Pharmacokinetics

Articaine is an amide local anesthetic. The Applicant conducted an open-label, non-comparative study (AG-920-CS101) to evaluate the systemic exposure to articaine and its inactive metabolite articainic acid after a single topical ocular dose of articaine 8% sterile topical ophthalmic solution (AG 920) administered as 2 drops 30 seconds apart in healthy adult subjects. The mean peak plasma concentration (C_{max}) was 5.423 ng/mL achieved at 0.25-hour post-dose. The overall exposure to articaine was less than 7 ng*hr/mL. The mean elimination half-life (t½) for articaine was approximately 1.5 hours. The C_{max} for articainic acid was 21.34 ng/mL achieved at 1 hour post-dose. The overall exposure to articainic acid was approximately 10 times greater than the parent at approximately 63-67 ng*hr/mL. The mean t½ for articainic acid was approximately 2.3 hours.

2.1.1. General Dosing and Therapeutic Individualization

2.1.1.1. General Dosing

The recommended dosing regimen is 2 drops applied 30 seconds apart to the ocular surface prior to ocular procedures and/or intraocular injections.

2.1.1.2. Therapeutic Individualization

Therapeutic individualization is not applicable for proposed drug product.

2.1.1.3. Outstanding issues

None.

2.1.1.4. Summary of Labeling Recommendations

None.

3 Comprehensive Clinical Pharmacology Review

3.1. Overview of the Product and Regulatory Background

Articaine 8% sterile topical ophthalmic solution (80 mg/mL) was developed as an amide local anesthetic indicated for ocular surface anesthesia prior to ocular procedures and/or intraocular injections. The product was evaluated under IND 145052. A summary of key clinical pharmacology-related regulatory interactions with the Applicant are listed in below Table 1.

Table 1. Key Clinical Pharmacology-Related Regulatory Interactions with the Applicant

PIND 145052 (09/20/2019)	– The Agency recommended to assess systemic exposure to articaine and its metabolites. – The Agency recommended a dose ranging trials and clarified that such trials are not required.
PIND 145052 (10/23/2019)	– The FDA agreed that a masked, randomized vehicle-controlled study of pain following conjunctival pinching is acceptable to demonstrate efficacy of ocular anesthesia. – The FDA stated that two adequate and well-controlled studies would be required to demonstrate efficacy in an NDA submission. – The FDA clarified that a study of systemic exposure may include eight to 12 individuals (patients or healthy volunteers).
IND 145052 08/13/2020	For first-in-human protocol, FDA recommended the evaluation of systemic PK exposure to articaine following topical ocular administration during the clinical development program. This evaluation can be performed using sparse PK sampling in a subset of 8 to 10 evaluable patients in one of the planned clinical trials or as a separate PK, safety, tolerability study in the same number of healthy subjects following ocular administration of the to-be-marketed product.

Source: Reviewer's summary based on meeting minutes (DARRTS; IND 145052)

3.2. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology data obtained from study AG-920-CS101 are summarized below in the Table 2.

Table 2. Clinical Pharmacology Data Obtained From Study AG-920-CS101 and Septocaine

Clinical Pharmacology	Study AG-920-CS101 in NDA 218643	Septocaine
Active ingredients	Articaine 8%	articaine HCl 4% + epinephrine bitartrate 0.009 mg/mL or 0.018 mg/mL
Mechanism of action Indication	Articaine HCl is an amide local anesthetic for ocular surface anesthesia prior to ocular procedures and/or intraocular injections	Articaine HCl, an amide local anesthetic, and epinephrine, a vasoconstrictor, indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures in adults and pediatric patients 4 years of age or older.
Absorption	Following the application of a single dose (i.e., 2 drops applied 30 seconds apart) to ocular service, C_{max} of articaine was 5.423 ng/mL achieved at 0.25 hour (the first	Following maxillary infiltration of two doses of 1.7 mL and 5.1 mL of Septocaine (4% articaine + epinephrine 0.018 mg/mL) in

	collection time post-dosing). The area under the plasma concentration-time profile over 24 hours (AUC_{0-t}) and to infinity (AUC_{0-inf}) of articaine were 5.1 and 6.68 ng*hr/mL, respectively. The C_{max} of metabolite articainic acid was 21.34 ng/mL achieved at 1 hour (the first collection time post-dosing). The AUC_{0-24} and AUC_{0-inf} of articainic acid were 62.92 and 66.61 ng*hr/mL, respectively.	healthy subjects, mean Cmax of articaine and its metabolite following the 68 mg dose was 385 ng/mL and 1429 ng/mL, respectively, and that following the 204 mg dose was 899 ng/mL and 3793 ng/mL, respectively. Mean AUC_{0-inf} of articaine and its metabolite following the 68 mg dose was 631 ng.hr/mL and 3751 ng.hr/mL, respectively, and that following the 204 mg dose was 1542 ng.hr/mL and 11543 ng.hr/mL, respectively. Following intraoral administration of a near maximum dose of 476 mg, articaine C_{max} was 2037 and 2145 ng/mL for articaine solution containing epinephrine 0.009 and 0.018 mg/mL, respectively, approximately 22 minutes post-dose.
Elimination	The terminal elimination half-life (t½) of articaine was 1.5 hour.	At the dose of 476 mg of articaine, the elimination half-life was 43.8 minutes and 44.4 minutes for articaine solution containing epinephrine 0.009 and 0.018 mg/mL, respectively.
Metabolism	Plasma concentrations of articainic acid metabolite were measured.	Articaine HCl is metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is inactive.
Excretion	Not studied	Articaine is excreted primarily through urine with 53-57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. Articaine constitutes only 2% of the total dose excreted in urine.

Source: Reviewer's generated table based on the PK data from study AG-920-CS101 in NDA 218643 and from Septocaine label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020971s042lbl.pdf) and clinical pharmacology and biopharmaceutics review (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/020971_SEPTOCAINE_BIOPHARMR.PDF).

3.3. Clinical Pharmacology Questions

To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology information on systemic exposure does not provide pivotal or supportive evidence of effectiveness of articaine 8% sterile topical ophthalmic solution. Since articaine is administered as eye drop and the site of action is local (the eye), the systematic exposure is not

expected to affect treatment effect by mechanism. The effectiveness was established based on the vehicle- controlled, parallel-group evaluation of the local anesthetic effect of articaine sterile topical ophthalmic solution in pivotal studies AG-920-CS301 and AG-920-CS302.

Refer to the clinical and statistical reviews for more information on efficacy and safety assessments.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of articaine 8% sterile topical ophthalmic solution is appropriate based on effectiveness and safety demonstrated in two randomized and controlled clinical trials in which a single dose (2 drops applied 30 seconds apart to the ocular surface) of articaine solution was applied to ocular surface.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Therapeutic individualization for articaine 8% sterile topical ophthalmic solution based on intrinsic and extrinsic factors is not considered necessary because treatment is to be restricted to the eye.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

4 APPENDICES

4.1. Clinical Pharmacology Studies

4.1.1. Study AG-920-CS101

The Applicant has conducted a phase 1, open-label, non-comparative study (AG-920-CS101) to evaluate the systemic exposure to articaine and its metabolite articainic acid after a single topical ocular dose of articaine 8% sterile topical ophthalmic solution (AG 920), administered as 2 drops 30 seconds apart, in the randomized study eye in healthy adult subjects.

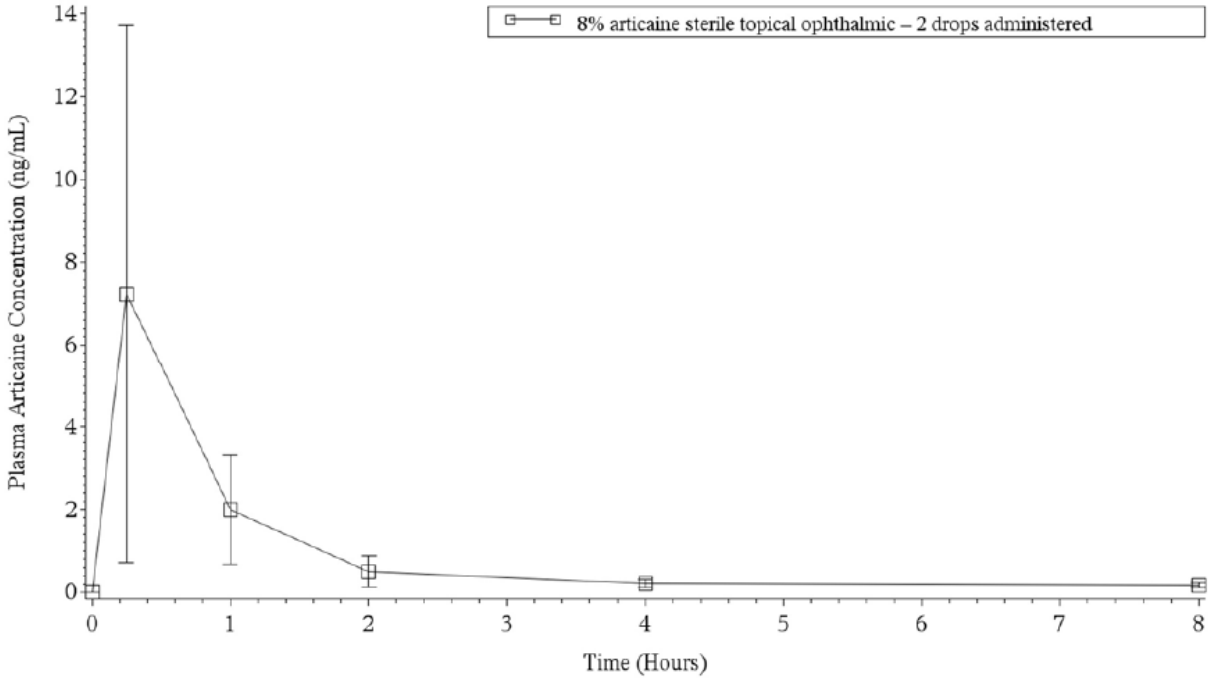
Blood samples to evaluate the pharmacokinetic (PK) of articaine and articainic acid were taken at pre-dose and 0.25, 1, 2, 4, and 24 hours post-dose. The analytical range for articaine was 0.1 – 80 ng/mL, and for articainic acid was 0.2 – 160 ng/mL.

4.1.1.1. Pharmacokinetic Results for Articaine

Mean plasma articaine concentration-time profile following the administration of articaine 8% sterile topical ophthalmic solution administered as 2 drops 30 seconds apart is depicted in Figure 1. Articaine plasma concentrations were measurable in all subjects by 0.25 hours post-dose, in most subjects at 4 hours post-dose and in 2 subjects at 8 hours post-dose. By the end of sampling time (24 hours) all concentrations were below limit of quantification (BLQ).

The mean maximum plasma concentration (C_{max}) of articaine of 5.423 ng/mL was reached at a median time (T_{max}) of 0.250 hours (the first collection time post-dosing). The area under the plasma concentration-time profile over 24 hours (AUC_{0-t}) and to infinity (AUC_{0-inf}) of articaine were 5.1 and 6.68 ng*hr/mL, respectively. The mean elimination half-life (t½) was approximately 1.5 hours (Table 4).

Figure 1. Mean Plasma Articaine Concentration-Time Profiles Following the Administration of 8% Articaine Sterile Topical Ophthalmic Solution Administered as 2 Drops 30 Seconds Apart (mITT Population)



Source: Study AG-920-CS101 CSR, Figure 14.2.2.1

Table 3. Summary of Plasma Articaine Pharmacokinetics Following the Administration of 8% Articaine Sterile Topical Ophthalmic Solution Administered as 2 Drops 30 Seconds Apart (mITT Population)

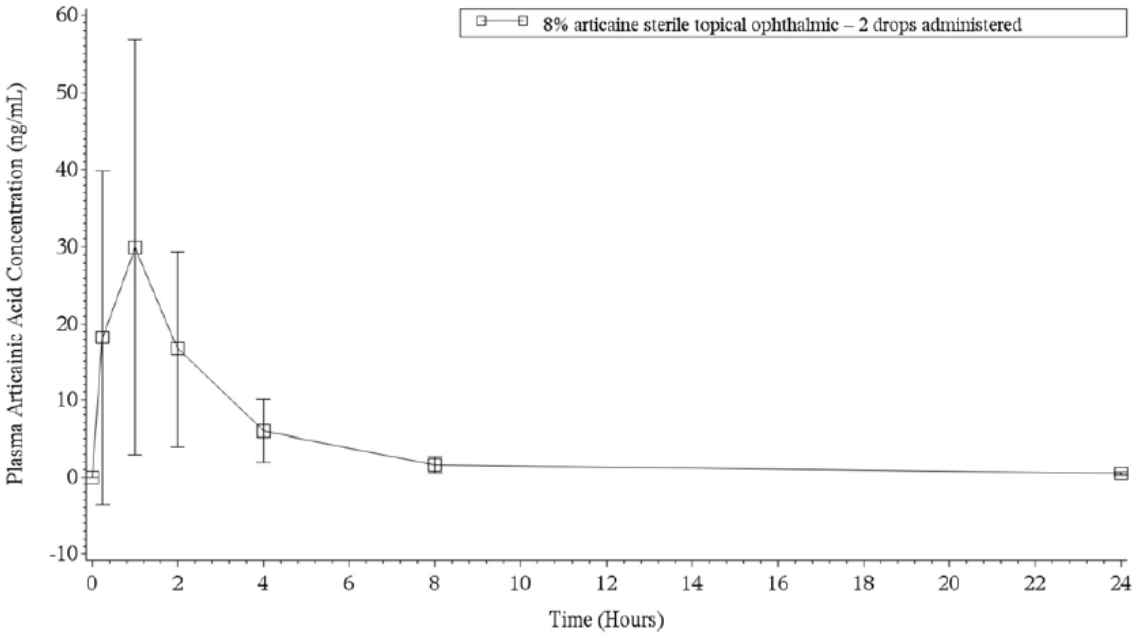
Pharmacokinetic Parameters	8% Articaine Sterile Topical Ophthalmic – 2 drops administered
AUC0-t (ng*hr/mL)	5.106 (76.7) [n=14]
AUC0-inf (ng*hr/mL)	6.683 (79.3) [n=8]
AUC%extrap (%)	4.468 (74.2) [n=8]
Cmax (ng/mL)	5.423 (86.1) [n=14]
Tmax (hr)	0.250 (0.25, 1.03) [n=14]
Kel (1/hr)	0.5959 ± 0.27179 [n=8]
t½ (hr)	1.493 ± 0.9172 [n=8]
CL/F (L/hr)	872.5 ± 533.59 [n=8]

AUCs and Cmax are presented as geometric mean (geometric CV%); Tmax is presented as median (minimum, maximum). AUC0-inf, t½, and Kel could not be estimated for 6 subjects for articaine in plasma since they did not exhibit a terminal log-linear phase in the concentration-versus-time profile.
Source: Study AG-920-CS101 CSR, Table 11-2

4.1.1.2. Pharmacokinetic Results for Articainic Acid

Mean plasma articainic acid concentration-time profile following the administration of 8% articaine sterile topical ophthalmic solution is presented in Figure 2. Articainic acid was quantifiable in all subjects up to 8 hours post-dose, and in only 2 subjects at 24 hours post-dose. The C_{max} of articainic acid was 21.34 ng/mL reached at a median T_{max} of 1.001 hours (the first collection time post-dosing). The AUC_{0-24} and AUC_{0-inf} of articainic acid were 62.92 and 66.61 ng*hr/mL, respectively. The mean t½ of articainic acid was 2.292 hours (Table 4).

Figure 2. Mean Plasma Articainic Acid Concentration-Time Profiles Following the Administration of 8% Articaine Sterile Topical Ophthalmic Solution Administered as 2 Drops 30 Seconds Apart (mITT Population)



Source: Study AG-920-CS101 CSR, Figure 14.2.4.1

Table 4. Summary of Plasma Articainic Acid Pharmacokinetics Following the Administration of Articaine Sterile Topical Ophthalmic Solution, 8% Administered as 2 Drops 30 Seconds Apart (mITT Population)

Pharmacokinetic Parameters	8% Articaine Sterile Topical Ophthalmic – 2 drops administered
AUC0-t (ng*hr/mL)	62.92 (98.9) [n=14]
AUC0-inf (ng*hr/mL)	66.61 (95.0) [n=14]
AUC%extrap (%)	4.517 (83.4) [n=14]
Cmax (ng/mL)	21.34 (107.6) [n=14]
Tmax (hr)	1.001 (0.25, 1.04) [n=14]
Kel (1/hr)	0.3404 ± 0.099912 [n=14]
t½ (hr)	2.292 ± 1.0072 [n=14]

AUCs and Cmax are presented as geometric mean (geometric CV%); Tmax is presented as median (minimum, maximum). Source: Study AG-920-CS101 CSR, Table 11-3

4.1.1.3. Safety Results

All 14 subjects enrolled in the study received the study treatment were included in the safety analysis. There were no deaths, SAEs, or subject discontinuations due to AEs in this study. Overall, one mild AE of eye irritation was experienced by 1 subject (7%) in this study.

4.1.1.4. Bioanalytical Method Validation and Performance

The bioanalytical methods developed and validated for quantification of articaine and articainic acid in human plasma appear acceptable (Table 5).

Table 5. Summary of Bioanalytical Method Validation for Articaine and Articainic Acid

Parameter	Results	
Assay laboratory	(b) (4)	
Methodology	LC-MS/MS	
Method validation report	20VAG01	
Species/matrix/anticoagulant	Human/plasma/NaF, KOx	
Analyte of interest	**Articaine**	**Articainic Acid**
Internal standard	Articaine-d7	Articainic Acid-d7
Calibration range	8 calibration points 0.1 to 80 ng/mL	8 calibration points 0.2 to 160 ng/mL
Inter-run accuracy (%bias)	LLOQQC (0.100 ng/mL): 1.12% Low QC (0.300 ng/mL): -0.711% Medium QC (30 ng/mL): -0.756% High QC (60 ng/mL): -5.2%	LLOQQC (0.2 ng/mL): -2.4% Low QC (0.6 ng/mL): -1.86% Medium QC (60 ng/mL): -1.16% High QC (120 ng/mL): -4.06%
Inter-run precision (%CV)	LLOQQC (0.100 ng/mL): 14.3% Low QC (0.300 ng/mL): 5.97% Medium QC (30 ng/mL): 3.14% High QC (60 ng/mL): 2.54%	LLOQQC (0.2 ng/mL): 4.91% Low QC (0.6 ng/mL): 3% Medium QC (60 ng/mL): 2.69% High QC (120 ng/mL): 1.91%
20 x QC dilution Inter-run accuracy	400 ng/mL: -1.9%	800 mg/mL: -2.97%
20 x QC dilution Inter-run precision	400 ng/mL: 2.99%	800 mg/mL: 1.81%
Regression Model	Linear, $1/x^2$	Linear, $1/x^2$
Recovery (analyte)	Low QC (0.3 ng/mL): 74% Medium QC (30 ng/mL): 83.8% High QC (60 ng/mL): 81.1%	Low QC (0.6 ng/mL): 83.1% Medium QC (60 ng/mL): 83.4% High QC (120 ng/mL): 80.7%
Recovery (IS)	In plasma: 82%	In plasma: 80.7%
Selectivity (individual blank matrix lots)	≤20% LLOQ for analyte No interference for IS	≤20% LLOQ for analyte No interference for IS
Sensitivity	Precision (%CV): 14.3% Accuracy (%bias): 1.12%	Precision (%CV): 4.91% Accuracy (%bias): -2.4%

Matrix effect (LQC, HQC)	6 individual lots (%CV): 6.43, 2.09 Hemolyzed lot (%bias): -9.09, 0 Lipemic lot (%bias): 2.73, 5.88	6 individual lots (%CV): 2.49, 1.31 Hemolyzed Lot (%Dev): 0, 0 Lipemic Lot (%Dev): 0, 0
Carryover	Carryover was >20% of the LLOQ mean peak response in 3 of 3 core runs for Articaine. Three samples impacted by carryover for Articaine were rejected and re-analyzed; reportable data was obtained for two of the three re-analyzed samples.	Carryover was >20% of the LLOQ mean peak response in 1 of 3 core runs for Articainic Acid. No quantifiable samples were impacted by carryover for Articainic Acid.
Benchtop matrix stability in human plasma	4 hours at room temperature	
Freeze/thaw matric stability in human plasma	3 cycles at -80 and 3 cycles at -20, thawed at room temperature.	
Processed sample stability in human plasma	52 hours and 195 hours at room temperature	
Long-term storage stability at -20 °C	35 and 92 days	
Long-term storage stability at -80 °C	35 and 92 days	
Solution Stability (analyte)	Stock (150 µg/mL): 189 days, -20°C and 17 hours, room temperature Spiking (15 µg/mL): 33 days, -20°C and 17 hours, room temperature	Stock (150 µg/mL): 198 days, -20°C and 17 hours, room temperature Spiking (30 µg/mL): 33 days, -20°C and 17 hours, room temperature
Solution Stability (IS)	Stock (100 µg/mL): 225 days, -20°C Spiking (150 µg/mL): 50 days, -20°C	Stock: 198 days, -20°C Spiking (150 µg/mL): 50 days, -20°C
Non-A&P Run Acceptance	The analytical QCs met the acceptance criteria in 2 of 2 non-A&P runs for both analytes	
Re-injection Integrity	Re-injection integrity was established when quantitated against the re-injected curve for 109 hours (room temperature) and against the original injected curve for 110 hours (room temperature)	
Process Conversion	Articainic Acid was detected at levels just above the LLOQ, ranging from 0.253 to 0.265 ng/mL. The results indicate that Articainic Acid may be detected at quantifiable, albeit low, levels in high Articaine concentration study samples due to conversion during sample processing.	
Incurred Sample Re-analysis (ISR)	22/24 samples (91.7%) were within ±20% of reported concentrations	24/24 samples (100%) were within ±20% of reported concentrations

Source: Reviewer's generated table from NDA 218643, SDN 004, Module 5.3.1.4, Bioanalytical Method Validation Report for the Analysis of Articaine and Articainic Acid in Human Plasma (NaF/KOx); and SDN 0001, Module 5.3.3.1 (Study AG-920-CS101), 16.2.5 (Compliance and/or Drug-Concentration Data, Bioanalytical Report, Tables 7 and 8.

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