DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

QIAGEN
KIMBERLY MAPP, Ph.D.
MANAGER, REGULATORY AFFAIRS
1201 CLOPPER ROAD
GAITHERSBURG MD 20878

December 19, 2014

Re: K142738
Trade/Device Name: *artus*® HSV-1/2 QS-RGQ MDx Kit
Regulation Number: 21 CFR 866.3305
Regulation Name: Herpes simplex virus serological assays
Regulatory Class: II
Product Code: OQO
Dated: September 23, 2014
Received: September 23, 2014

Dear Dr. Mapp:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Uwe Scherf -S for

Sally A. Hojvat, M.Sc., Ph.D.
Director
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K142738

Device Name
artus® HSV-1/2 QS-RGQ MDx Kit

Indications for Use *(Describe)*
The artus HSV-1/2 QS-RGQ MDx Kit is an in vitro real-time PCR DNA amplification assay performed on the QIAsymphony RGQ MDx system for the direct qualitative detection and differentiation of herpes simplex virus (HSV-1 and HSV-2) DNA in genital or oral vesicular lesions from male and female patients suspected of HSV infection.

The assay is intended for use as an aid in diagnosis of HSV infection in symptomatic patients.

Warning: The artus HSV-1/2 QS-RGQ MDx Kit is not FDA-cleared for use with cerebrospinal fluid (CSF) or for prenatal screening.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

510(k) SUMMARY

General Information

Submitted by: QIAGEN
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Date Prepared: November 24, 2014

Device Name: *artus*® HSV-1/2 QS-RGQ MDx Kit

Trade Name: *artus*® HSV-1/2 QS-RGQ MDx Kit
Common Name: Herpes Simplex Virus detection assay

Classification: Class II

Predicate Device

Manufacturer	**Product Name**	**510(k) No.**
Eragen Biosciences	MultiCode®-RTx Herpes Simplex Virus 1 & 2 Kit	K100336

Device Description

The *artus* HSV-1/2 QS-RGQ MDx Kit is an *in vitro* PCR assay for the qualitative detection and differentiation of nucleic acids encoding the Glycoprotein D and UL30 genes isolated from HSV-1 and HSV-2 DNA present in genital or oral lesions from male and female patients. Samples are extracted and prepared for PCR using the QIAsymphony SP/AS instrument with the QIAsymphony DSP Virus/Pathogen Mini Kit. Amplification and detection are carried out using the *artus* HSV-1/2 QS-RGQ MDx Kit with the Rotor-Gene Q MDx (RGQ MDx) and Rotor-Gene AssayManager software. The presence of a HSV-1 or HSV-2 target sequence is indicated by the fluorescent signal generated through the use of fluorescently labeled oligonucleotide probes. The probes do not generate a signal unless they are specifically bound to the amplified product. The

amplification cycle at which fluorescent signal is detected by the RGQ MDx is inversely proportional to the HSV-1 and/or HSV-2 target concentration present in the original specimen. A plasmid construct containing DNA unrelated to HSV-1 and HSV‑2 is introduced into each specimen during sample preparation to serve as an internal control. Run as a separate control, the positive control serves to demonstrate that the HSV-1/2 PCR reagents are functional. In addition, the positive control functions as a process control, to demonstrate that sample preparation has proceeded correctly during the run.

Intended Use

The *artus* HSV-1/2 QS-RGQ MDx Kit is an *in vitro* real-time PCR DNA amplification assay performed on the QIAsymphony RGQ MDx system for the direct qualitative detection and differentiation of herpes simplex virus (HSV-1 and HSV-2) DNA in genital or oral vesicular lesions from male and female patients suspected of HSV infection.

The assay is intended for use as an aid in diagnosis of HSV infection in symptomatic patients.

Warning: The *artus* HSV-1/2 QS-RGQ MDx Kit is not FDA-cleared for use with cerebrospinal fluid (CSF) or for prenatal screening.

Comparison of the *artus*® HSV-1/2 QS-RGQ MDx Kit and the Predicate Device

The *artus* HSV-1/2 QS-RGQ MDx Kit is substantially equivalent to the predicate device:

- K100336: Eragen Biosciences MultiCode®-RTx Herpes Simplex Virus 1 & 2 Kit

Similarities and differences between the *artus* HSV-1/2 QS-RGQ MDx Kit and the predicate device are shown in Table 1.

Table 1: Comparison of the *artus* HSV-1/2 QS-RGQ MDx Kit with the predicate device

Characteristic	Device	Predicate
Name	*artus*® HSV-1/2 QS-RGQ MDx Kit	Eragen Biosciences MultiCode®-RTx Herpes Simplex Virus 1 & 2 Kit
Similarities		
Intended Use	The *artus* HSV-1/2 QS-RGQ MDx Kit is an *in vitro* real-time PCR DNA amplification assay performed on the QIAsymphony RGQ MDx system for the direct qualitative detection and differentiation of herpes simplex virus (HSV-1 and HSV-2) DNA in genital or oral vesicular lesions from male and female patients suspected of HSV infection. The assay is intended for use as an aid in diagnosis of HSV infection in symptomatic patients. Warning: The *artus* HSV-1/2 QS-RGQ MDx Kit is not FDA-cleared for use with cerebrospinal fluid (CSF) or for prenatal screening.	The MultiCode®-RTx Herpes Simplex Virus 1 & 2 Kit is a polymerase chain reaction (PCR)-based qualitative *in vitro* diagnostic test for the detection and typing of herpes simplex virus (HSV1&2) DNA in vaginal lesions. It is indicated for use in the detection and typing of HSV-1 or HSV-2 in vaginal lesion swab specimens from symptomatic female patients as an aid in the diagnosis of genital herpes infection. ***Warning:*** The device is not FDA cleared for the use with cerebral spinal fluid (CSF) or any lesions other than vaginal. The assay is not intended to be used for male penile specimens, for prenatal screening, or females under the age of 18 years.
Assay Targets	HSV-1 HSV-2	HSV-1 HSV-2
Amplification and Detection Technology	Real-time PCR DNA amplification	Real-time PCR DNA amplification
Assay Controls	Positive Control, Negative Control and Internal Control included in the kit.	Positive Control, Negative Control and Internal Control included in the kit.
Differences		
Specimen Type	Male and female genital or oral herpetic lesions	Female vaginal lesions

Performance Characteristics – Non-Clinical Studies

Analytical Sensitivity (Limit of Detection)

The limit of detection (LoD) was assessed for the *artus* HSV-1/2 QS-RGQ MDx Kit using 2 strains of HSV-1 (MacIntyre and Isolate #15 from Zeptometrix™ Corporation. (ZMC)) and two strains of HSV-2 (MS and Isolate #2 from Zeptometrix™ Corporation). The LoD is defined as the HSV titer ($TCID_{50}$/mL) detected with a probability of 95% or greater and was determined by probit analysis. The results, representative of the analytical sensitivity of the *artus* HSV-1/2 QS-RGQ MDx Kit, are summarized in Table 2.

Table 2: Limit of Detection

Strain	LoD (95 % CI) $TCID_{50}$/mL
HSV-1 Macintyre	4.42×10^{0} (2.81×10^{0} - 9.14×10^{0})
HSV-1 Isolate 15	1.82×10^{1} (0.96×10^{1} - 5.47×10^{1})
HSV-2 MS	9.78×10^{-1} (6.6×10^{-1} - 2.01×10^{0})
HSV-2 Isolate 2	1.91×10^{2} (1.26×10^{2} - 3.55×10^{2})

Analytical Reactivity

The analytical reactivity of the *artus* HSV-1/2 QS-RGQ MDx Kit was assessed to determine whether the kit could detect a broad range of HSV-1 and HSV-2 strains. Strains were obtained from ZMC. A total of 39 strains (20 HSV-1 and 19 HSV-2) were diluted in M4RT viral transport medium to 2–3X LoD and tested with the *artus* HSV-1/2 QS-RGQ MDx Kit (Table 3). The intended HSV-1 or HSV-2 was detected in all strains tested.

Table 3: Strains Tested in Analytical Reactivity

Organism	Part No.	Organism	Part No.
HSV-1, Isolate #2	0810183CF	HSV-2, Isolate #3	0810204CF
HSV-1, Isolate #3	0810184CF	HSV-2, Isolate #4	0810205CF
HSV-1, Isolate #4	0810185CF	HSV-2, Isolate #5	0810206CF
HSV-1, Isolate #5	0810186CF	HSV-2, Isolate #6	0810207CF
HSV-1, Isolate #6	0810187CF	HSV-2, Isolate #7	0810208CF
HSV-1, Isolate #7	0810188CF	HSV-2, Isolate #8	0810209CF
HSV-1, Isolate #8	0810189CF	HSV-2, Isolate #9	0810210CF
HSV-1, Isolate #9	0810190CF	HSV-2, Isolate #10	0810211CF
HSV-1, Isolate #10	0810191CF	HSV-2, Isolate #11	0810212CF
HSV-1, Isolate #11	0810192CF	HSV-2, Isolate #12	0810213CF
HSV-1, Isolate #12	0810193CF	HSV-2, Isolate #13	0810214CF

Organism	Part No.	Organism	Part No.
HSV-1, Isolate #13	0810194CF	HSV-2, Isolate #14	0810215CF
HSV-1, Isolate #14	0810195CF	HSV-2, Isolate #15	0810216CF
HSV-1, Isolate #15	0810196CF	HSV-2, Isolate #16	0810217CF
HSV-1, Isolate #16	0810197CF	HSV-2, Isolate #17	0810218CF
HSV-1, Isolate #17	0810198CF	HSV-2, Isolate #18	0810219CF
HSV-1, Isolate #18	0810199CF	HSV-2, Isolate #19	0810220CF
HSV-1, Isolate #19	0810200CF	HSV-2, Isolate #20	0810221CF
HSV-1, Isolate #20	0810201CF	HSV-2, Isolate #21	0810222CF
HSV-1, Isolate #21	0810202CF		

Cross-Reactivity and Microbial Interference

A panel of microorganisms that may be present in patient specimens was tested to determine whether these microorganisms interfered with the detection of HSV-1 or HSV-2 or were cross-reactive with the *artus* HSV-1/2 QS-RGQ MDx Kit (Table 4). Organisms were tested at a target concentration of approximately 1 x 10^6 CFU/ml for bacteria (with the exception of *Neisseria gonorrhea*, which was tested at 3.5 x 10^5 CFU/mL due to the low titer of the stock culture) and fungi or ≥1 x 10^5 $TCID_{50}$/ml for viruses separately in the presence of 2–3X LoD of each of three HSV strains: HSV-1 MacIntyre, HSV-1 Isolate #15, or HSV-2 MS. None of the potential interfering organisms cross-reacted or interfered with the detection of any of the HSV strains by the *artus* HSV-1/2 QS-RGQ MDx Kit.

Table 4: Organisms Tested in Cross Reactivity and Microbial Interference

Organism	Source ID
Acinetobacter calcaceticus	ATCC 51432
Acinetobacter lwoffi	ATCC 17925
Adenovirus type 2	ZMC 0810110CF
Bacteroides fragilis	ZMC 0601533
Candida albicans	ATCC 10231
Candida glabrata	ZMC Z007
Candida guilliermondii	ZMC Z008
Candida krusei	ZMC Z009
Candida lustaniae	ATCC 42720
Candida parapsilosis	ZMC Z011
Candida tropicalis	ZMC Z012
Chlamydia trachomatis	ATCC VR-885
Cytomegalovirus	ZMC 0810003CF
Enterobacter cloacae	ATCC 13047

Organism	Source ID
Enterovirus	ZMC 0810047CF
Epstein-Barr Virus	ZMC 0810008CF
Escherichia coli	ATCC 23571
Fusobacterium nucleatum	ATCC 25586
Gardnerella vaginalis	ATCC 14019
Haemophilus ducreyi	ATCC 700724D-5
Human Genomic DNA	Promega G3041
Human Herpes Virus 6	ZMC 0810003CF
Human Herpes Virus 7	ZMC 0810071CF
Human papilloma virus 16	ATCC 45113
Human papilloma virus 18	ATCC 45152
Herpes Simplex Virus 1 (HSV-1), isolate 20	0810201CF
Herpes Simplex Virus 2 (HSV-2), isolate 20	0810221CF
Klebsiella pneumoniae	ATCC 13883
Lactobacillus acidophilus	ATCC 4356
Mobiluncus curtsii	ATCC 43063
Mobiluncus mulieris	ATCC 35240
Moraxella catarrhalis	ATCC 8176
Mycoplasma hominis	ATCC 23114D
Neisseria gonorrhea	ATCC 9793
Neisseria meningitides	ATCC 13077
Prevotella melaninogenica	ATCC 25845
Rubella Virus	ZMC 0810048CF
Simian Virus type 40 (SV40)	VRMC-2
Staphylococcus aureus (MRSA)	ATCC 43300
*Staphylococcus aureus (*MSSA)	ATCC 29213
Staphylococcus epidermidis (MRSE)	ATCC 51625
Staphylococcus saprophyticus	ATCC 15305
Streptococcus mitis	ZMC Clinical isolate
Streptococcus mutans	ZMC Z072
Streptococcus pneumoniae	ZMC 19F-Z022
Streptococcus pyogenes	ATCC 8669
Streptococcus salivarius	ATCC 13419
Toxoplasma gondii	ZMC 0810007CF
Treponema pallidum	ATCC 632912
Trichomonas vaginalis	ATCC PRA-98D
Varicella-Zoster Virus (VZV)	ZMC 0810171CF

Precision

The precision of the *artus* HSV-1/2 QS-RGQ MDx Kit was assessed using a seven-member precision panel consisting of 2 strains of HSV: HSV-1 MacIntyre and HSV-2 MS, diluted in M4RT viral transport medium. Panel members were formulated with a single HSV strain present (HSV-1 or HSV-2) at three concentrations; Positive (~2-3X LoD), Low Positive (1X LoD), and High Negative (<1X LoD, targeting a 20-80% positivity rate). A seventh panel member (Negative) was prepared using M4RT viral transport medium only. The data obtained were used to determine the mean C_T, standard deviation (ST DEV) and the coefficient of variation (%CV) for each target and the internal control.

For the within laboratory repeatability study, the seven-member panel was tested in replicates of three, once a day for a total of twelve days. The testing was conducted by two alternating operators using one QIAsymphony RGQ MDx (QS-RGQ MDx) instrument platform and one reagent kit lot (Table 5).

Table 5: Within-Laboratory Repeatability Study Results

Sample	HSV-1			HSV-2			IC			Detected/ Total
	Mean C_T	ST DEV	%CV	Mean C_T	ST DEV	%CV	Mean C_T	ST DEV	%CV	
HSV-1 Positive	32.56	0.32	0.97%	N/A	N/A	N/A	31.79	0.64	2.00%	35/35*
HSV-1 Low Positive	33.89	0.35	1.03%	N/A	N/A	N/A	31.85	0.66	2.07%	36/36
HSV-1 High Negative	37.52	0.63	1.69%	N/A	N/A	N/A	31.73	0.59	1.87%	23/36
HSV-2 Positive	N/A	N/A	N/A	33.73	0.41	1.22%	31.72	0.63	1.98%	36/36
HSV-2 Low Positive	N/A	N/A	N/A	36.73	1.05	2.86%	31.69	0.63	2.00%	36/36
HSV-2 High Negative	N/A	N/A	N/A	38.35	1.01	2.64%	31.82	0.57	1.80%	9/36
HSV Negative	N/A	N/A	N/A	N/A	N/A	N/A	31.88	0.52	1.64%	0/36

* Total number of samples is less than 36 due to exclusion of 1 invalid sample

To measure site-to-site reproducibility, the 7-member panel was run by 2 users at each of 3 external sites. Each of the 2 users performed 5 runs on alternating testing days for a total of 90 test results per panel member. Panel members were tested in replicates of 3 that were randomized and blinded to the user. A single QIAsymphony RGQ MDx instrument platform and one lot of the *artus* HSV-1/2 QS-RGQ MDx Kit were used at each site to conduct the study (Table 6).

Table 6: Site-to-Site Reproducibility Study Results

Panel member	Site	HSV-1/HSV-2			IC			Detected/ Total
		Mean C_T	ST DEV	%CV	Mean C_T	ST DEV	%CV	
HSV-1 Positive	Site 1	31.40	1.04	3.30%	30.87	0.35	1.12%	27/27
	Site 2	31.44	0.35	1.10%	30.80	0.37	1.19%	29/29
	Site 3	31.20	0.32	1.03%	30.45	0.30	0.98%	26/26
	Overall	31.35	0.66	2.09%	30.71	0.38	1.24%	82/82*
HSV-1 Low Positive	Site 1	33.01	0.40	1.20%	30.91	0.34	1.11%	30/30
	Site 2	32.78	0.44	1.34%	30.76	0.38	1.24%	30/30
	Site 3	32.37	0.89	2.74%	30.47	0.35	1.13%	30/30
	Overall	32.72	0.66	2.03%	30.71	0.40	1.29%	90/90
HSV-1 High Negative	Site 1	36.34	0.88	2.41%	30.85	0.29	0.93%	19/30
	Site 2	36.27	0.74	2.05%	30.67	0.40	1.29%	15/30
	Site 3	36.77	1.06	2.88%	30.44	0.30	1.00%	17/30
	Overall	36.46	0.92	2.51%	30.66	0.37	1.20%	51/90
HSV-2 Positive	Site 1	33.19	0.36	1.08%	30.89	0.30	0.99%	30/30
	Site 2	32.85	0.35	1.05%	30.75	0.35	1.15%	30/30
	Site 3	32.46	0.33	1.03%	30.47	0.29	0.95%	30/30
	Overall	32.83	0.45	1.38%	30.70	0.36	1.17%	90/90
HSV-2 Low Positive	Site 1	36.12	0.96	2.65%	30.84	0.29	0.95%	30/30
	Site 2	35.53	0.66	1.85%	30.73	0.32	1.04%	30/30
	Site 3	35.81	0.92	2.58%	30.49	0.30	0.97%	30/30
	Overall	35.82	0.88	2.46%	30.69	0.33	1.08%	90/90
HSV-2 High Negative	Site 1	38.09	0.55	1.44%	30.91	0.31	0.99%	5/30
	Site 2	37.69	2.30	6.09%	30.71	0.37	1.20%	5/30
	Site 3	37.27	N/A	N/A	30.50	0.32	1.04%	1/30
	Overall	37.83	1.52	4.01%	30.71	0.37	1.20%	11/90
HSV Negative	Site 1	N/A	N/A	N/A	30.88	0.30	0.96%	0/30
	Site 2	N/A	N/A	N/A	30.72	0.36	1.16%	0/30
	Site 3	N/A	N/A	N/A	30.53	0.32	1.04%	0/30
	Overall	N/A	N/A	N/A	30.71	0.35	1.14%	0/90

* Total number of samples is less than 90 due to exclusion of invalid samples

Target Carryover Study

Absence of carryover between samples for the entire workflow was demonstrated by performing 5 runs with alternating high positive ($\geq 1.0 \times 10^5$ $TCID_{50}$/mL) and negative samples. All samples were detected correctly, generating a carryover rate of 0.0%.

Interfering Substances

A panel of 24 substances that may be present in oral/genital patient specimens was tested to determine whether these substances interfered with the performance of the *artus* HSV-1/2 QS-RGQ MDx Kit (Table 7). Two strains of HSV: HSV-1 MacIntyre and HSV-2 MS, were diluted to approximately 2–3X LOD in M4RT viral transport medium and spiked with each potentially inhibitory substance. None of the substances showed an inhibitory effect on the detection of HSV-1 or HSV-2 by the *artus* HSV-1/2 QS-RGQ MDx Kit.

Table 7: Potentially Interfering Substances Tested

Substance	Potential Interferent/Active Ingredient	Concentration Of Substance Added To Reaction	Concentration Of Active Ingredient Added To Reaction
Whole blood with EDTA	Hemoglobin, lactoferin	100%	5% v/v
Buffy coat	White blood cells	100%	5% v/v
Acyclovir	Acycloguanosine	5 mg/ml	5 mg/ml
Albumin	Albumin	5 mg/ml	5 mg/ml
Casein	Casein	5 mg/ml	5 mg/ml
Female urine*	Urea	100%	Not listed
Male urine*	Urea	100%	Not listed
K-Y® Brand jelly	Glycerin, hydroxyethyl cellulose, chlorhexidine, gluconate, gluconolactone, methylparaben, sodium hydroxide	100%	Not listed
Douche*	Octoxynol-9, citric acid, sodium benzoate, disodium EDTA	100%	Not listed
Spermicide*	Nonoxynol-9	100%	7%
Yeast·Gard®*	*Candida albicans* ×27 HPUS†, *Candida parapsilosis* ×27 HPUS, *Pulsatilla* ×27 HPUS	100%	Not listed
Monistat® 1*	Miconazole nitrate	100%	2% v/v
Vagisil® Cream*	Benzocaine, resorcinol	100%	Benzocaine 20% Resorcinol 3%
Monistat 3*	Miconazole nitrate	100%	2% v/v
Triconazole 1*	Triconazole	100%	6.5% v/v

Substance	Potential Interferent/Active Ingredient	Concentration Of Substance Added To Reaction	Concentration Of Active Ingredient Added To Reaction
Rite Aid Feminine Wash, Sensitive Skin*	Ammonium laureth sulfate, ammonium lauryl sulfate, decyl glucoside,cocamidopropyl betaine	100%	Not listed
Clotrimazole-7 vaginal cream*	Clotrimazole	100%	1% v/v
Anti-itch cream*	Benzocaine	100%	5% v/v
Listerine® antiseptic mouthwash*	Eucalyptol, menthol, methyl salicylate, thymol	100%	Eucalyptol 0.920% Menthol 0.042% Methyl salicylate 0.060% Thymol 0.064%
Abreva®*	Docosanol	100%	10% v/v
Carmex® lip balm*	Menthol, camphor, phenol	100%	Menthol 0.7% Camphor 1.7% Phenol 0.4%
Releev® cold sore treatment*	Benzalkonium chloride	100%	0.13% v/v
Lip Clear® lysine+*	Zinc oxide	100%	1.2% v/v
Toothpaste*	Stannous fluoride	100%	0.454% v/v

*: Applied directly to sample by swab.
†: HPUS: Homeopathic Pharmacopeia of the United States.

Expected Values

Prevalence: The observed expected values for HSV-1 and HSV-2 during a multi-center clinical trial were calculated for the artus HSV-1/2 QS-RGQ MDx kit. The expected values for the patients ages 18 and older are shown for Genital lesion samples and for all ages for the oral samples. The observed prevalence rates for HSV-1 were estimated as 18.6% (91/489) for genital samples and 42.1% (64/152) for oral samples. The prevalence rates for HSV-2 were estimated as 26.2% (128/489) for genital samples and 0% (0/152) for oral samples. Gender and age distribution is provided in Table 8 and Table 9.

Table 8: Age Distribution for Genital Specimens

Age (Years)	Total # of specimens	HSV-1 Positive	HSV-2 Positive	Negative
18-20	48	11	13	24
21-30	167	32	40	95
31-40	111	18	31	62
41-50	69	12	15	42
51-60	48	10	15	23
61-70	31	4	12	15
71-80	11	4	2	5
81-90	3	0	0	3
91-97	1	0	0	1
Total	489	91/489	128/489	270/489

Table 9: Age Distribution for Oral Specimens

Age (Years)	Total # of specimens	HSV-1 Positive	HSV-2 Positive	Negative
< 1	1	1	0	1
1-10	21	15	0	6
11-20	20	6	0	14
21-30	25	8	0	17
31-40	23	9	0	14
41-50	16	3	0	13
51-60	14	5	0	9
61-70	15	6	0	9
71-80	11	6	0	5
81-90	2	2	0	0
91-97	4	3	0	1
Total	152	64/152	0/152	88/152

Positive and Negative Predictive Value: Hypothetical positive and negative predictive values (PPV & NPV) for the *artus* HSV-1/2 QS-RGQ MDx kit are shown in Table 10. These calculations are based on hypothetical prevalence and overall sensitivity and specificity per specimen type as determined in the clinical study.

For HSV-1, these calculations are based upon an overall sensitivity and specificity of 96% and 94%, respectively, for genital swabs and 94% and 82%, respectively, for oral swabs.

For HSV-2, these calculations are based upon an overall sensitivity and specificity of 97% and 91%, respectively, for genital swabs and 0.0% and 100%, respectively, for oral swabs.

PPV was calculated using: (Sensitivity x Prevalence) / (Sensitivity x Prevalence + [1 - Specificity] x [1 - Prevalence]).

NPV was calculated using: (Specificity x [1 - Prevalence]) / ([1 - Sensitivity] x Prevalence + Specificity x [1 - Prevalence]).

Table10: Positive and Negative Predictive Values (PPV & NPV) for the *artus* assay based on sample type

Prevalence (%)	Genital Swabs				Oral Swabs			
	HSV-1		HSV-2		HSV-1		HSV-2	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)	PPV (%)	NPV (%)
2	24.6%	99.9%	18.0%	99.9%	9.6%	99.9%	N/A	98.0%
5	45.7%	99.8%	36.2%	99.8%	21.6%	99.6%	N/A	95.0%
10	64.0%	99.5%	54.5%	99.6%	36.7%	99.2%	N/A	90.0%
20	80.0%	98.9%	72.9%	99.2%	56.6%	98.2%	N/A	80.0%
30	87.3%	98.2%	82.2%	98.6%	69.1%	97.0%	N/A	70.0%
40	91.4%	97.2%	87.8%	97.8%	77.7%	95.3%	N/A	60.0%
50	94.1%	95.9%	91.5%	96.8%	83.9%	93.2%	N/A	50.0%

N/A = Not Applicable

Mucocutaneous Lesions: A subset of samples from the clinical study was identified as mucocutaneous. Those classified as mucocutaneous included: oral, cervical, vaginal, rectal. Table 11 lists the specific locations for the mucocutaneous lesions that were reported as such in the study along with the total number of samples from each specific location and number of positives.

Table 11: Mucocutaneous Lesion Sites

Breakdown of Mucocutaneous Samples		HSV-1 Culture Positive	HSV-1 *artus* Positive	HSV-1 Concordant Positive	HSV-2 Culture Positive	HSV-2 *artus* Positive	HSV-2 Concordant Positive
Location	Total						
Bottom Lip	1						
Cervical	21	3	3	2	1	2	1
Clitoral	2						
Corners Of Lips	1						
Penis foreskin	1						
Genital	8	2	3	2		1	
Groin Vesicles	1						
In-Mouth	1	1	1	1			
Vaginal Introitus	1						
L Nares	1						
Labia	47	3	5	3	9	12	9

Breakdown of Mucocutaneous Samples		**HSV-1 Culture Positive**	**HSV-1 *artus* Positive**	**HSV-1 Concordant Positive**	**HSV-2 Culture Positive**	**HSV-2 *artus* Positive**	**HSV-2 Concordant Positive**
Location	**Total**						
Labia Major	1				1	1	1
Left Labia	5				1	1	1
Left Outer Labia	1						
Left Upper Palate	1						
Left Vulvar	1						
Lip	31	17	20	17			
Mons Pubic, Clitoris	1					1	
Mouth	35	10	14	10			
Oral Blister	3		2				
Palate	2	1					
Penile Lesion	2					1	
Rectal	3				1	1	1
Right Labia Papule	2				1	1	1
Right Side Of Mouth	1	1	1	1			
Throat	7	2	1	1			
Tongue	6	2	3	2			
Tooth	1	1	1	1			
Ulcer In Mouth	1	1	1	1			
Upper Hard Palate	1		1				
Upper Lip	4	2	3	2			
Urethral	8		1		2	2	2
Urogenital	4	1	1	1			
Vagina	65	11	11	10	17	20	15
Vaginal Rectal	9	1	2	1		1	
Vesicle	6		2			1	
Vulva	34	7	9	7	6	8	6
Total	**320**	**66**	**85**	**62**	**39**	**53**	**37**

Performance Characteristics – Clinical Studies

Prospective Study: The performance of the *artus* HSV-1/2 QS-RGQ MDx Kit was evaluated at 3 testing sites in 2013-2014, using samples from 5 geographically diverse locations within the United States. A total of 662 male and female genital or oral lesion swabs (510 genital and 152 oral) prospectively collected from symptomatic patients were evaluated. Results from the *artus* HSV-1/2 QS-RGQ MDx Kit were compared to results obtained from the ELVIS® (Enzyme Linked Virus Inducible System) HSV ID and D3 Typing Test System (Diagnostic Hybrids, Athens, OH).

Ninety-six (96) prospective specimens identified as HSV-2 positive by ELVIS viral culture were removed from the initial 510 genital specimens for the calculation of the HSV-1 clinical performance. As a result, there were 566 samples (414 genital and 152 oral) used to determine clinical performance for HSV-1 (see Table 12 thru Table 15). The clinical performance for HSV-1 and HSV-2 mucocutaneous lesions was also assessed (Table 16 and Table 17). Prospectively collected samples that were classified as mucocutaneous included oral, cervical, vaginal, rectal, and any sample taken from a vesicle or lesion.

Table 12: HSV-1 Results for Genital Samples (N=414)

HSV-1		**ELVIS**		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	69	21*	90†
	NEG	3**	321	324
	TOTAL	72	342	414
		95% CI		
Sensitivity – 95.8% (69/72)		88.5% – 98.6%		
Specificity – 93.9% (321/342)		90.8% – 96.0%		
Positive Predictive Value – 76.7%		67.0% – 84.2%		
Negative Predictive Value – 99.1%		97.3% – 99.7%		
Prevalence – 17.0%		14.0% – 21.0%		

*21 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Positive, ELVIS Negative) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that 15 out of 21 were positive for HSV-1, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result.
**3 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Negative, ELVIS Positive) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that all were negative for HSV-1, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result.
† 5 samples were undetermined for ELVIS out of a total of 95 HSV-1 *artus* positive genital samples. Therefore only the 90 samples that were both ELVIS and *artus* positive are listed.

Table 13: HSV-2 Results for Genital Samples (N=510)

HSV-2		ELVIS		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	93	37*	130
	NEG	3**	377	380
	TOTAL	96	414	510
		95% CI		
Sensitivity – 96.9% (93/96)		91.2% – 98.9%		
Specificity – 91.1% (377/414)		87.9% – 93.5%		
Positive Predictive Value – 71.5%		63.3% – 78.6%		
Negative Predictive Value – 99.2%		97.7% – 99.7%		
Prevalence – 19.0%		16.0% – 22.0%		

*32 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Positive, ELVIS Negative) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that 27 out of 32 were positive for HSV-2, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result. The remaining 5 samples were not available for discordant analysis.
**3 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Negative, ELVIS Positive) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that all were negative for HSV-2, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result.

Table 14: HSV-1 Results for Oral Samples (N=152)

HSV-1		ELVIS		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	45	19*	64
	NEG	3**	85	88
	TOTAL	48	104	152
		95% CI		
Sensitivity – 93.8% (45/48)		83.2% – 97.9%		
Specificity – 81.7% (85/104)		73.2% – 88.0%		
Positive Predictive Value – 70.3%		58.2% – 80.1%		
Negative Predictive Value – 96.6%		90.5% – 98.8%		
Prevalence – 32.0%		25.0% – 39.0%		

*19 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Positive, ELVIS Negative) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that 13 out of 19 were positive for HSV-1, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result.
**2 discordant specimens (*artus* HSV-1/2 QS-RGQ MDx Negative, ELVIS Positive) reported were analyzed by alternative PCR followed by bi-directional sequencing and the result was that 2 out of 2 were negative for HSV-1, agreeing with the *artus* HSV-1/2 QS-RGQ MDx result. The remaining 1 specimen was unavailable for discordant analysis testing.

Table 15: HSV-2 Results for Oral Samples (N=152)

HSV-2		ELVIS		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	0	0	0
	NEG	0	152	152
	TOTAL	0	152	152
			95% CI	
Sensitivity – N/A			N/A	
Specificity – 100.0% (152/152)			97.5% – 100.0%	
Positive Predictive Value – N/A			N/A	
Negative Predictive Value – 100.0%			97.5% – 100.0%	
Prevalence – 0.0%			0.0% – 2.0%	

Table 16: HSV-1 Mucocutaneous Samples (N=281)

HSV-1		ELVIS		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	62	23	85
	NEG	4	192	196
	TOTAL	66	215	281
			95% CI	
Sensitivity – 93.9% (62/66)			85.4% – 97.6%	
Specificity – 89.3% (192/215)			84.5% – 92.8%	
Positive Predictive Value – 72.9%			62.7% –81.2%	
Negative Predictive Value – 98.0%			94.9% – 99.2%	
Prevalence – 23.0%			19.0% – 29.0%	

Table 17: HSV-2 Mucocutaneous Samples (N=320)

HSV-2		ELVIS		
		POS	**NEG**	**Total**
***artus* HSV-1/2 QS-RGQ MDx Kit**	**POS**	37	16	53
	NEG	2	265	267
	TOTAL	39	281	320
			95% CI	
Sensitivity – 94.9% (37/39)			83.1% – 98.6%	
Specificity – 94.3% (265/281)			91.0% – 96.5%	
Positive Predictive Value – 69.8%			56.5% – 80.5%	
Negative Predictive Value – 99.3%			97.3% – 99.8%	
Prevalence – 12.0%			9.0% – 16.0%	

HSV-2 Oral Retrospective Sample Study and Contrived Sample Study:
A retrospective study was conducted using oral samples for HSV2 detection. A total of 38 oral retrospective specimens were tested with the *artus* HSV-1/2 QS-RGQ MDx assay and ELVIS HSV ID and D^3 Typing Test System. There were no HSV-2 positive specimens detected in 38 oral specimens.

A contrived specimen study was performed to provide additional performance data for detection of HSV-2 in oral samples. A panel of seventy (70) individual samples consisting of 15 HSV-1/2 negative oral samples, 10 HSV-1 positive oral samples and 45 HSV-1/2 negative oral samples spiked with HSV-2 at a concentration from 3X LoD to 1000X LoD and tested with the *artus* HSV-1/2 QS-RGQ MDx Kit. The HSV-1 positive oral samples and HSV-1/2 negative oral samples obtained from the method comparison study were used to make the panel. All samples were randomized and blinded to the operator prior to testing. HSV-2 was detected in all 45 contrived samples at all concentrations tested, supporting the claim for detection of HSV-2 in oral samples by the *artus* HSV-1/2 QS-RGQ MDx Kit.