510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K232286

B Applicant

Quidel Corporation

C Proprietary and Established Names

Savanna HSV 1+2/VZV Assay, Savanna HSV 1+2/VZV Control Set, Savanna Instrument

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PGI	Class II	21 CFR 866.3309 - Herpes Virus Nucleic Acid-Based Cutaneous And Mucocutaneous Lesion Panel	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:
Clearance of a new device.

B Measurand:
Target DNA sequences from conserved regions of the herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and varicella-zoster virus (VZV) genes.

C Type of Test:
Molecular diagnostic test using real-time PCR (Polymerization Chain Reaction) technology for the qualitative detection and differentiation of HSV-1, HSV-2 and VZV DNA isolated and purified from human cutaneous or mucocutaneous lesion samples.

III Intended Use/Indications for Use:

A Intended Use(s):

The Savanna HSV 1+2/VZV Assay is an automated, rapid multianalyte real-time PCR test for the simultaneous qualitative detection and differentiation of herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus DNA isolated from human cutaneous or mucocutaneous lesion samples obtained from symptomatic patients suspected of active herpes simplex virus 1, herpes simplex virus 2 and/or varicella-zoster infection. This in vitro diagnostic test is intended to aid in the diagnosis of patients with signs or symptoms of herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus infection.

The Savanna HSV 1+2/VZV Assay is intended to aid in the diagnosis of herpes simplex virus 1, herpes simplex virus 2 and varicella-zoster virus active infections. The results of this test should not be used as the sole basis for diagnosis, treatment or other management decisions and must be combined with clinical observations, patient history and/or epidemiological information. Negative results do not preclude herpes simplex virus type 1, herpes simplex virus type 2, or varicella-zoster virus infection that is not detected by a cutaneous or mucocutaneous lesion swab specimen. Positive results do not rule out co-infection with other organisms. Additional laboratory testing (e.g., viral culture, immunoassay, serology) may be necessary for patient evaluation. Savanna HSV 1+2/VZV Assay is for professional use. The Savanna HSV 1+2/VZV Assay is intended for use only with the Savanna instrument.

Warning: The Savanna HSV 1+2/VZV Assay is not intended for use with the cerebrospinal fluid (CSF) or to aid in the diagnosis of HSV or VZV infection of the central nervous system (CNS). The Savanna HSV 1+2/VZV Assay is not intended for use in prenatal screening.

B Indication(s) for Use:

Same as Intended Use

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Savanna instrument.

IV Device/System Characteristics:

A Device Description:

The Savanna HSV 1+2/VZV Assay amplifies and detects HSV-1, HSV-2 and VZV viral DNA isolated from cutaneous or mucocutaneous lesion samples obtained from symptomatic patients suspected of active herpes simplex virus 1, herpes simplex virus 2 and/or varicella-zoster infection.

The assay consists of a single, self-contained assay cartridge (see Table 1) employing real-time PCR technology for use with the Savanna instrument.

Table 1: Savanna HSV 1+2/VZV Assay components

Component	Quantity	Storage
Individually Packaged Test Cartridges	12 cartridges/kit	2°C to 30°C
250 µL transfer Pipettes	12 pipettes/kit	2°C to 30°C
Package Insert	1/kit (or by website)	NA
Quick Reference Instructions	1/kit (or by website)	NA

External controls for HSV-1, HSV-2, or VZV (Savanna HSV 1+2/VZV Assay Control Set which contains positive and negative controls) serve as external processing and extraction controls in verifying the performance of the Savanna HSV 1+2/VZV Assay.

B Principle of Operation:

Patient sample is dispensed into the sample port of the Savanna cartridge and then placed manually in the Savanna instrument. The Savanna instruments automates running of the assay and result reporting.

The Savanna HSV 1+2/VZV Assay consists of a single, self-contained assay cartridge and employs real-time PCR technology for use with the Savanna instrument to detect and differentiate DNA from herpes simplex virus type 1, herpes simplex virus type 2 and varicella-zoster virus.

The Savanna platform extracts, amplifies and detects DNA present in cutaneous or mucocutaneous lesion swab specimens obtained from symptomatic patients. Identification of HSV-1, HSV-2, and VZV occurs by the use of target-specific primers and fluorescent-labeled probes that hybridize to conserved regions in the viral genomes.

There are two types of Quality Control for the Savanna HSV 1+2/VZV Assay Cartridge: Built-in Process Control and External Controls that are sold separately for use.

Interpretation of Results: The Savanna software automatically determines the specimen results for each pathogen target ordered. The result for each target will be displayed as (Positive), (Negative), or (Invalid).

Table 2: Savanna HSV 1+2/VZV Assay Results Interpretation per each individual target analyte:

Display	Result	Interpretation
⊕	Positive	DNA from the respective individual pathogen was detected.
⊖	Negative	DNA from the respective individual pathogen was not detected, and the Internal Control was detected.
⊗	Invalid	The Internal Control was not detected. Re-process another aliquot of the same sample or obtain a new sample and re-test with a new Test Cartridge. Begin with Step 1 of the Liquid Sample Transfer Procedure. Refer to the Re-Test Results Interpretation table for final patient result interpretation.

Table 3: Savanna HSV 1+2/VZV Assay Re-Test Results Interpretation per each individual target analyte after initial Invalid result

Analyte Re-Test Results Interpretation		
Initial Test	**Re-test**	**Final Result**
Invalid	Negative	Negative
Invalid	Positive	Positive
Valid Negative	N/A*	Negative
Valid Positive	N/A*	Positive
Invalid	Invalid	Call QuidelOrtho Technical Support

*N/A: Not Applicable

C Instrument Description Information:

1. Instrument Name:

   Savanna instrument

2. Specimen Identification:

   Specimen identification can be entered either via barcode scanning or by manual entry.

3. Specimen Sampling and Handling:

   Lesion swab specimens, including cutaneous or mucocutaneous, collected in commercially available viral transport meda (Copan UTM, Remel M4RT, Remel M5 or Remel M6) can be used with the Savanna HSV 1+2/VZV Assay on the Savanna system.

4. Calibration:

   Not Applicable

5. Quality Control:
There are two types of Quality Control for the Savanna HSV 1+2/VZV Assay Cartridge: Built-in Process Internal Control and External Controls.

a) Process Internal Control (IC)

The Savanna HSV 1+2/VZV Assay contains a process internal control (IC) for each chamber in the cartridge. Internal control is co-processed, amplified and detected simultaneously with the target DNAs, serving as an internal control to monitor sample processing, PCR inhibition, integrity of assay reagents and the operation of the Savanna instrument proceeded correctly for each sample.

b) External Controls

The Savanna HSV 1+2/VZV Control Set contains a pouched Positive Swab and two buffer tubes. The external Positive Control is intended to be used to monitor substantial reagent and instrument failure. The external Negative Control is used to detect reagent or environmental contamination (or carry-over) by pathogen amplicons.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Solana HSV 1+2/VZV Assay

B Predicate 510(k) Number(s):
K162451

C Comparison with Predicate(s):

Device & Predicate Device(s):	Predicate K162451	New Device K232286
Device Trade Name	Solana HSV 1+2/VZV Assay	Savanna HSV 1+2/VZV Assay
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Solana HSV 1+2/VZV Assay is an *in vitro* diagnostic test, using isothermal amplification technology (helicase dependent amplification, HDA), for the qualitative detection and differentiation of herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus DNA isolated and purified from cutaneous or mucocutaneous	The Savanna HSV 1+2/VZV Assay is an automated, rapid multianalyte real-time PCR test for the simultaneous qualitative detection and differentiation of herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus DNA isolated from human cutaneous or mucocutaneous lesion samples obtained from symptomatic patients suspected

	lesion samples obtained from symptomatic patients suspected of active herpes simplex virus 1, herpes simplex virus 2 and/or varicella-zoster infection. The Solana HSV 1+2/VZV Assay is intended to aid in the diagnosis of herpes simplex virus 1, herpes simplex virus 2 and varicella-zoster virus active cutaneous or mucocutaneous infections. Negative results do not preclude herpes simplex virus 1, herpes simplex virus 2 and varicella-zoster virus infections and should not be used as the sole basis for diagnosis, treatment, or other management decisions. The Solana HSV 1+2/VZV Assay is intended for use only with the Solana instrument. ***Warning***: The Solana HSV 1 + 2/VZV Assay is not intended for use with cerebrospinal fluid or to aid in the diagnosis of HSV or VZV infections of the central nervous system (CNS). The Solana HSV 1 + 2/VZV Assay is not intended for use in prenatal screening.	of active herpes simplex virus 1, herpes simplex virus 2 and/or varicella-zoster infection. This *in vitro* diagnostic test is intended to aid in the diagnosis of patients with signs or symptoms of herpes simplex virus type 1, herpes simplex virus type 2, and varicella-zoster virus infection. The Savanna HSV 1+2/VZV Assay is intended to aid in the diagnosis of herpes simplex virus 1, herpes simplex virus 2 and varicella-zoster virus active infections. The results of this test should not be used as the sole basis for diagnosis, treatment or other management decisions and must be combined with clinical observations, patient history and/or epidemiological information. Negative results do not preclude herpes simplex virus type 1, herpes simplex virus type 2, or varicella-zoster virus infection that is not detected by a cutaneous or mucocutaneous lesion swab specimen. Positive results do not rule out co-infection with other organisms. Additional laboratory testing (e.g., viral culture, immunoassay, serology) may be necessary for patient evaluation. Savanna HSV 1+2/VZV Assay is for professional use. The Savanna HSV 1+2/VZV Assay is intended for use only with the Savanna instrument. **Warning**: The Savanna HSV

		1+2/VZV Assay is not intended for use with the cerebrospinal fluid (CSF) or to aid in the diagnosis of HSV or VZV infections of the central nervous system (CNS). The Savanna HSV 1+2/VZV Assay is not intended for use in prenatal screening.
Qualitative	Yes	Same
Analyte	Viral DNA from HSV 1, HSV 2 and VZV	Same
Specimen Type	Cutaneous or mucocutaneous lesion swabs in transport medium	Same
Automated Analysis	Yes	Same
General Device Characteristic Differences		
Instrument	Solana	Savanna
Test Principle	Isothermal Helicase-Dependent Amplification (HDA)	PCR
Development Time	50 min	Within 24 min
Kit Storage	2ºC to 8ºC	2ºC to 30ºC
External Controls	Positive and Negative Controls (Available as a separate kit)	Positive and Negative Controls (Available as a separate kit)
Quality Control Features	Competitive Process Control (PRC)	Process Internal Control (IC)

VI Standards/Guidance Documents Referenced:

Not Applicable.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:
   Within-Laboratory Precision: A 20-day within-laboratory precision study was performed using 3 Savanna HSV 1+2/VZV Assay cartridge lots. The viral materials used to generate the positive panel members were contrived in Negative Buccal Matrix and included HSV1

Isolate 2, HSV2 G, and VZV Ellen. Precision test panel samples contained negative samples (no analyte)), low positive samples (1x LoD) for HSV-1, HSV-2 and VZV, and moderate positive samples (4x LoD) for HSV-1, HSV-2 and VZV. The percent of negative or positive sample detection is presented below in **Table 4** by target analyte along with the within-laboratory precision results.

Table 4: Savanna HSV 1+2/VZV Assay Within-Laboratory Precision

Analyte	Sample	Agreement with Expected Results	Detected Mean Ct	Repeatability		Between Runs		Between Days		Between Lot		Total	
				SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
	Negative	239/240 (99.6%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HSV-1	Low Positive	237/239 (99.2%	36.4	1.50	4.1	0.07	0.2	0.19	0.5	0.50	1.4	1.60	4.4
	Moderate Positive	239/240 (99.6%)	34.3	1.06	3.1	0.70	2.0	0.00	0.0	0.41	1.2	1.33	3.9
	Negative	239/240 (99.6%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HSV-2	Low Positive	239/239 (100%)	33.9	0.95	2.8	0.49	1.5	0.05	0.2	0.42	1.3	1.16	3.4
	Moderate Positive	240/240 (100%)	31.9	0.98	3.1	0.46	1.5	0.00	0.0	0.00	0.0	1.09	3.4
	Negative	242/242 (100%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VZV	Low Positive	238/239 (99.6%)	35.7	0.77	2.2	0.11	0.3	0.20	0.6	0.19	0.5	0.83	2.3
	Moderate Positive	240/241 (99.6%)	34.1	0.54	1.6	0.00	0.0	0.11	0.3	0.18	0.5	0.58	1.7

Reproducibility Study (multi-site precision): The reproducibility of the Savanna HSV 1+2/VZV Assay was evaluated at 3 sites (two external and one internal) over 5-days using the same samples panel used in the within-labopratory precision study. Each site used 3 device lots, wherein each day, 1 panel was tested by operators in 2 replicates ((5 days x 3 device lots x 3 sites x 2 operators x 2 replicates = 180). Mean Ct values with variance components (SD and %CV) are shown in **Table 5**.

Table 5: Savanna HSV 1+2/VZV Assay Reproducibility

Analyte	Sample	Agreement with Expected Result	Detected Mean Ct	Repeatability		Between Day		Between Site		Between Lot		Between Operator		Reproducibility	
				SD	% CV	SD	% CV	SD	%CV	SD	% CV	SD	% CV	SD	% CV
	Negative	179/179 (100%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HSV-1	Low Positive	179/180 (99.4%)	36.22	1.31	3.6	0.35	1.0	0.06	1.36	1.36	0.4	0.00	0.0	1.36	3.8
	Moderate Positive	179/180 (99.4%)	34.38	1.05	3.1	0.00	0.0	0.27	1.23	1.23	1.6	0.14	0.4	1.23	3.6
	Negative	179/179 (100%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Analyte	Sample	Agreement with Expected Result	Detected Mean Ct	Repeatability		Between Day		Between Site		Between Lot		Between Operator		Reproducibility	
				SD	% CV	SD	% CV	SD	%CV	SD	% CV	SD	% CV	SD	% CV
HSV-2	Low Positive	180/180 (100%)	33.73	1.19	3.5	0.25	0.7	0.00	1.23	1.23	0.0	0.00	0.0	1.23	3.6
	Moderate Positive	180/180 (100%)	31.86	0.96	3.0	0.00	0.0	0.19	1.10	1.10	0.5	0.14	0.4	1.10	3.5
	Negative	179/179 (100%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
VZV	Low Positive	180/180 (100%)	35.79	1.29	3.6	0.00	0.0	0.34	1.34	1.34	0.5	0.00	0.0	1.34	3.7
	Moderate Positive	179/180 (99.4%)	33.99	0.52	1.5	0.00	0.0	0.25	0.64	0.64	0.6	0.17	0.5	0.64	1.9

2. Linearity:
   Not applicable.

3. Analytical Specificity/Interference:

   a. Potential Cross-Reactivity: A study was performed to evaluate the performance of the Savanna HSV 1+2/VZV Assay in samples negative for HSV1, HSV2 and VZV containing 60 microorganisms (virus, bacteria and fungus) that could be found in lesion specimens. The microorganism were tested at clinically relevant levels of viruses and bacteria: $\geq 10^6$ CFU/mL or IFU/mL; viruses: $\geq 10^5$ copies (cp), viral particles (vp) or $TCID_{50}$/mL in negative buccal matrix or NBM. There was no cross-reactivity observed with the 60 microorganisms tested with the Savanna HSV 1+2/VZV Assay at the concentrations indicated in the Table **6** below.

Table 6: Savanna HSV 1+2/VZV Assay Potential Cross-reactivity

Condition Description	Virus/Bacteria/Fungus Concentration	Condition Description	Virus/Bacteria/Fungus Concentration
Acholeplasma laidlawi	1.00E+06 CFU/mL	*Haemophilus influenzae Type B*	1.00E+06 CFU/mL
Acinetobacter calcoaceticus	1.00E+06 CFU/mL	*Hepatitis A virus*	2.70E+05 cp/mL
Acinetobacter lwoffii	1.01E+06 CFU/mL	*Hepatitis B virus*	2.45E+05 cp/mL
Adenovirus 7	1.04E+05 TCID50/mL	*Hepatitis C virus*	4.15E+05 cp/mL
Bacteroides fragilis	1.00E+06 CFU/mL	*HIV-1 Type 1*	1.95E+05 cp/mL
Bordetella bronchiseptica	1.06E+06 CFU/mL	*Human Herpes virus HHV6*	≥ 1.01E+05 TCID50/mL
Bordetella pertussis	1.01E+06 CFU/mL	*Human Herpes virus HHV7*	2.34E+04 TCID50/mL
Candida albicans	1.00E+06 CFU/mL	*Human Herpes virus HHV8*	1.01E+05 TCID50/mL
Candida glabrata	1.03E+06 CFU/mL	*Human Metapneumovirus A1*	1.90E+05 TCID50/mL

Candida krusei	1.14E+06 CFU/mL	*Human papillomavirus HPV-16*	2.85E+05 cp/mL
Candida parapsilosis	1.20E+06 CFU/mL	*Human papillomavirus HPV-18*	2.60E+05 cp/mL
Candida tropicalis	1.04E+06 CFU/mL	*Klebsiella pneumoniae*	1.00E+06 CFU/mL
Chlamydia trachomatis	1.06E+06 CFU/mL	*Lactobacillus acidophilus*	1.04E+06 CFU/mL
Chlamydophila pneumoniae	1.13E+06 CFU/mL	*Measles virus*	1.04E+05 TCID50/mL
Clostridium perfringens	1.00E+06 CFU/mL	*Mobiluncus mulieris*	1.00E+06 CFU/mL
Coronavirus OC43	1.00E+05 TCID50/mL	*Moraxella catarrhalis*	1.34E+06 CFU/mL
Coxsackievirus B1	1.00E+05 TCID50/mL	*Mycoplasma orale*	1.00E+06 CFU/mL
Cutibacterium acnes	1.00E+06 CFU/mL	*Mycoplasma pneumoniae*	1.00E+06 CFU/mL
Cytomegalovirus	1.00E+05 TCID50/mL	*Neisseria gonorrhoeae*	1.00E+06 CFU/mL
Cytomegalovirus Towne	8.00E+04 TCID50/mL	*Neisseria meningitidis*	1.09E+06 CFU/mL
Echovirus 11	1.40E+05 TCID50/mL	*Prevotella melaninogenica*	1.20E+06 CFU/mL
Enterobacter cloacae	1.04E+06 CFU/mL	*Proteus mirabilis*	1.04E+06 CFU/mL
Enterococcus faecalis	1.04E+06 CFU/mL	*Rubella virus; Strain: RA 27/3*	1.00E+05 TCID50/mL
Enterovirus 70	1.00E+05 TCID50/mL	*Staphylococcus aureus*	1.15E+06 CFU/mL
Epstein Barr (EBV)	6.05E+06 cp/mL	*Staphylococcus aureus (MRSA)*	1.03E+06 CFU/mL
Escherichia coli	1.00E+06 CFU/mL	*Staphylococcus saprophyticus*	1.15E+06 CFU/mL
Fusobacterium nucleatum	1.07E+06 CFU/mL	*Streptococcus agalactiae*	1.13E+06 CFU/mL
Gardnerella vaginalis	1.03E+06 CFU/mL	*Streptococcus pneumoniae*	1.20E+06 CFU/mL
Haemophilus ducreyi	1.00E+06 CFU/mL	*Streptococcus pyogenes*	3.17E+06 CFU/mL
Haemophilus influenzae (Type A)	1.00E+06 CFU/mL	*Streptococcus salivarius*	1.00E+06 CFU/mL

b. Microbial Interference Study: The microbial interference study was performed with a list of microorganisms listed above in the Table 6 for the Cross Reactivity Study. Each potentially interfering microorganism was tested in the presence of at 3x LOD HSV-1, HSV-2 and VZV viruses, or negative matrix at clinically relevant levels of the microorganisms. All positive samples reported positive results for HSV-1, HSV-2, and VZV in the presence of these microorganisms. There was no interference observed with the 60 organisms tested with the Savanna HSV 1+2/VZV Assay.

c. Interfering Substances: The performance of the Savanna HSV 1+2/VZV Assay was evaluated with potentially interfering substances that may be present in cutaneous or mucocutaneous lesion specimens. A panel composed of thirty-six (36) substances listed

in **Table 6** was tested in the absence or presence of HSV-1, HSV-2, or VZV (Isolate 2, G strain, Ellen strain, respectively) at 2X LoD in the Savanna HSV 1+2/VZV Assay. There was no evidence of interference (false positive or false negative results) caused by the substances tested at the concentrations shown in the **Table 7** below.

Table 7: Savanna HSV 1+2/VZV Assay Interference Results

Substance	Active Ingredient	Test Concentration
Blood/EDTA	N/A	0.63%
Casein	Casein Bovine Milk	7 mg/mL
Feces	N/A	2.5 mg/mL
Female Urine	Urea	7%
Leukocytes	N/A	$2.5x10^5$ cells/mL
Male Urine	Urea	3.5%
Mucus (Mucin, bovine submaxillary gland, type I-S)	Mucin	5% (w/v)
Seminal fluid	Semen	2%
Abreva Docosanol	Docosanol	3.5% (w/v)
Acetaminophen	Acetominophen	1.75% (w/v)
Anti-itch cream	Benzalkonium chloride	3.5% (w/v)
Balneol Hygienic Cleansing Lotion	N/A	3.5% (w/v)
Carmex Cold Sore Lip Balm	Benzocaine, White Petrolatum	3.5% (w/v)
Chlor-Trimeton	Chlorpheniramine maleate	1.25 mg/mL
Clotrimazole 3 Vaginal Cream	Clotrimazole	3.5% (w/v)
Cornstarch	N/A	1.25 mg/mL
Dextromethorphan hydrobromide (*i.e.* Mucinex)	Dextromethorphan, Guaifenesin, Phenylephrine	5 mg/mL
Douche	Decyl Glucoside; Octoxynol-9	7% (w/v)
K-Y Brand Jelly	Glycerol	7% (w/v)
Lanacane	3% w/w Benzocaine	3.5% (w/v)
Lip Clear Lysine+	Menthol	3.5% (w/v)
Listerine	Thymol	7% (w/v)
Miconazole 1	N/A	7% (w/v)
Miconazole 3	N/A	7% (w/v)
Monistat 1	N/A	7% (w/v)
Monistat 3	N/A	7% (w/v)
Preparation H	Witch Hazel	3.5% (w/v)
Releev	Benzalkonium chloride	3.5% (w/v)
Toothpaste	Sodium Fluoride	7% (w/v)
Triconazole 1	Tioconazole	7% (w/v)
Vagisil Cream	Benzocaine, Resorcinol	7% (w/v)
YeastGard	Sodium Borate	7% (w/v)
Acyclovir	Acyclogauanosine	7 mg/mL

Substance	Active Ingredient	Test Concentration
Cidofovir	Cidofovir Hydrate	2.5 mg/mL
Foscarnet	Foscarnet Sodium	1.25 mg/mL
Ganciclovir	Ganciclovir	2.5 mg/mL

d. Competitive Interference: A competitive interference study was conducted to evaluate the performance of the Savanna HSV 1+2/VZV Assay using samples containing 2 target analytes at different combination of high and low analyte concentrations. Each sample was prepared with one of the analytes at 3X LoD and the other analytes at 10X, 500X or 1000X LoD in negative buccal matrix. Five replicates per sample were evaluated. When competitive interference was observed (shaded in Table 8), titration of the high-level analyte was done and tested. Results are listed in **Table 8** below.

Table 8: Savanna HSV 1+2/VZV Assay Competitive Interference Results

Sample	Analyte level combination per sample evaluated		Results.		
	Low Analyte	High Analyte	HSV-1 Positivity	HSV-2 Positivity	VZV Positivity
1	HSV-1 (3x LoD)	HSV-2 (1000x LoD)	0.0% (0/5)	100.0% (5/5)	0% (0/5)*
2	HSV-1 (3x LoD)	HSV-2 (500x LoD)	0.0% (0/5)	100.0% (5/5)	0% (0/5)*
3	HSV-1 (3x LoD)	HSV-2 (250x LoD)	20.0% (1/5)	100.0% (5/5)	0% (0/5)*
4	HSV-1 (3x LoD)	HSV-2 (100x LoD)	60.0% (3/5)	100.0% (5/5)	0% (0/5)*
5	HSV-1 (3x LoD)	HSV-2 (10x LoD)	100.0% (5/5)	100.0% (5/5)	0% (0/5)*
6	HSV-1 (3x LoD)	VZV (500x LoD)	100.0% (5/5)	0% (0/5)*	100.0% (5/5)
7	HSV-2 (3x LoD)	HSV-1 (1000x LoD)	100.0% (5/5)	60.0% (3/5)	0% (0/5)*
8	HSV-2 (3x LoD)	HSV-1 (500x LoD)	100.0% (5/5)	100.0% (5/5)	0% (0/5)*
9	HSV-2 (3x LoD)	HSV-1 (250x LoD)	100.0% (5/5)	100.0% (5/5)	0% (0/5)*
10	HSV-2 (3x LoD)	HSV-1 (100x LoD)	100.0% (5/5)	100.0% (5/5)	0% (0/5)*
11	HSV-2 (3x LoD)	HSV-1 (10x LoD)	100.0% (5/5)	100.0% (5/5)	0% (0/5)*
12	HSV-2 (3x LoD)	VZV (500x LoD)	0% (0/5)*	100.0% (5/5)	100.0% (5/5)
13	VZV (3x LoD)	HSV-1 (1000x LoD)	100.0% (5/5)	0% (0/5)*	100.0% (5/5)
14	VZV (3x LoD)	HSV-2 (1000x LoD)	0% (0/5)*	100.0% (5/5)	100.0% (5/5)

*Analyte not present in the sample, the negative results are not due to competitive interference. The negative results are true negative.

4. Assay Reportable Range:

Not Applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):
Not Applicable.

6. Detection Limit:

The limits of detection (LoD) for the Savanna HSV 1+2/VZV Assay were determined using two types/strains of HSV-1, two types/strains of HSV-2 and two types/strains of VZV, serially diluted in negative matrix. The LOD is defined as the lowest concentration at which at least 95% of all replicates tested positive. The LoD for each pathogen are listed below in **Table 9**.

Table 9: Savanna HSV 1+2/VZV Assay Limit of Detection Results

Analyte	Analyte Strain/Isolate	Concentration ($TCID_{50}$/mL)	Concentration (cp/mL)
HSV-1	Isolate 2	1.16E+02	6.65E+02
	Macintyre	1.08E-03	2.86E+02
HSV-2	Strain G	2.50E+01	1.27E+04
	MS	8.51E+00	7.64E+01
VZV	Ellen	N/A	3.32E+03
	Strain 82	N/A	1.02E+03

Analytical Reactivity (Inclusivity): The inclusivity of the Savanna HSV 1+2/VZV Assay was further evaluated by functional testing of clinically relevant strains/isolates, in addition to those strains used in the LOD study. The clinical panel consisted of 4 strains of HSV-1, 4 strains of HSV-2, and 5 strains of VZV at concentrations near the level of detection (LOD) of the assay. The evaluated strains and the lowest concentration that achieved 100% reactivity are shown in **Table 10**.

Table 10: Savanna HSV 1+2/VZV Assay Inclusivity

Analyte(s) Strain/Isolate	Analyte(s) Concentration ($TCID_{50}$/mL)	Analyte(s) Concentration (cp/mL)
HSV-1 Isolate 3	4.00E+00	8.56E+02
HSV-1 Isolate 7	1.72E+01	Not Available
HSV-1 Isolate 11	2.53E+01	Not Available
HSV-1 Isolate 20	5.45E+01	1.40E+02
HSV-2 Isolate 6	2.94E+00	2.54E+03
HSV-2 Isolate 9	2.94E+00	3.26E+02
HSV-2 Isolate 10	2.94E+00	1.34E+02
HSV-2 Isolate 20	2.94E+00	Not Available
VZV Isolate AV923L	Not Available	4.00E+02
VZV Isolate 9939	1.05E+01	1.09E+03
VZV Isolate B	Not Available	8.20E+02
VZV Isolate 275	Not Available	2.88E+02

Analyte(s) Strain/Isolate	Analyte(s) Concentration ($TCID_{50}$/mL)	Analyte(s) Concentration (cp/mL)
VZV Isolate D	Not Available	1.65E+03

7. Assay Cut-Off:
   Not Applicable.

8. Accuracy (Instrument):
   Not Applicable

9. Sample Stability Studies- Transport Media (Swab) Compatibility and Stability:

   Cutaneous or mucocutaneous lesion specimens collected in transport medium (Copan UTM, Remel M4RT, Remel M5, Remel M6) were stable when stored according to the conditions specified in **Table 11**.

   Table 11: Savanna HSV 1+2/VZV Assay Transport Medium and Sample Storage Results

Transport Media	Room Temperature (15-30°C)	Refrigerated (2° to 8°C)
Copan UTM	Upto 24 hours .	Upto 48 hours
Remel M4RT	Upto 96 hours	Upto 96 hours
Remel M5	Upto 48 hours	Upto 96 hours
Remel M6	Upto 72 hours	Upto 72 hours

Lead Reviewer or Consulting Reviewer Comments for Internal Discussion Only

The transport media compatibility and stability study results are acceptable.

HSV-1 2, HSV-2, and VZV virus stocks (HSV-1 McIntyre, HSV-2 G and VZV Ellen) were diluted to 2x LoD and 4x LoD concentrations in each of the 4 transport medium pooled negative matrix (Copan UTM, Remel M4RT, Remel M5, and Remel M6) to create positive samples. The negative sample consisted of negative buccal matrix.

The transport media systems containing the contrived samples were stored at three different conditions: Condition 1) = room temperature (15°C) for 120 hours, Condition 2) = 30°C for 120 hours, and Condition 3) = 2-8°C ± 3°C for 120 hours.

The data support that the Savanna HSV 1+2/VZV Assay can be used with the evaluated viral transport media types.

10. Carry-Over:

Potential carry-over and cross-contamination for the Savanna HSV 1+2/VZV Assay was evaluated by alternate testing replicates of negative and high positive samples. The negative samples consisted of negative buccal matrix. Positive samples consisted of HSV-1, HSV-2, and VZV in pooled negative buccal matrix at concentrations greater or equal to 10x LoD each analyte. All negative samples reported negative results, resulting in an overall carryover rate of 0.0% . No carry over or cross contamination was observed.

B Comparison Studies:

1. Method Comparison:
See Section C below.

C Clinical Studies:

1. Clinical Sensitivity:
Not Applicable.

2. Clinical Specificity:
Not Applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Performance characteristics of the Savanna HSV 1+2/VZV Assay were established through 2 clinical studies, as described below. Clinical Study 1 evaluated assay performance from fresh samples while clinical study 2 evaluated performance after samples were stored frozen.

Clinical Study #1
A multi-site study was performed in the United States to evaluate the Savanna HSV 1+2/VZV Assay using freshly collected cutaneous and mucocutaneous lesion samples in transport media. Five hundred and ninety (590) residual specimens were randomly selected from all comers for standard of care testing of patients with signs and symptoms of HSV-1, HSV-2 or VZV infection. Testing was split across three clinical sites and 44 Savanna instruments. Savanna HSV 1+2/VZV Control Sets were tested each day by the clinical sites during sample testing.

The specimens have been categorized as cutaneous (skin lesion, genital), or mucocutaneous (anorectal, genital, nares, ocular, oral and urethral). The gender and age demographics for each category are listed in **Table 12** below.

Table 12: Subject Demographics – Clinical Study #1

Specimen	Age	Female	Male	Total
Cutaneous Lesion	<= 5 years	5	10	15
	6 to 21 years	13	10	23
	22 to 59 years	57	39	96
	>= 60 years	50	23	73
	Total	**125**	**82**	**207**
Mucocutaneous Lesion	<= 5 years	8	3	11
	6 to 21 years	50	24	74
	22 to 59 years	185	56	241
	>= 60 years	43	14	57
	Total	**286**	**97**	**383**
Total	<= 5 years	13	13	26
	6 to 21 years	63	34	97
	22 to 59 years	242	95	337
	>= 60 years	93	37	130
	Total	**411**	**179**	**590**

The Clinical Study #1 clinical performance results compared to commercially available RT-PCR comparator method are shown in Tables 13 to 15. The clinical performance of the Savanna HSV 1+2/VZV Assay was established by comparing to an FDA-cleared nucleic acid amplification test in freshly collected cutaneous and mucocutaneus specimens analyzed separately.

Table 13: **HSV1** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **fresh** specimens

		HSV1 Results			
		Cutaneous (N=207)		Mucocutaneous (N=383)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	23	1	81	11
	Negative	2	181	0	291
	Total	25	182	81	302
Point Estimate & 95% CI		PPA= 92.00% (23/25) (75.04% - 97.78%)	NPA= 99.45% (181/182) (96.95% - 99.90%)	PPA= 100.00% (81/81) (95.47% - 100.00%)	NPA= 96.36% (291/302) (93.60% - 97.95%)

Table 14: **HSV2** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **fresh** specimens

		HSV2 Results			
		Cutaneous (N=207)		Mucocutaneous (N=383)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	13	0	50	3
	Negative	1	193	3	327
	Total	14	193	53	330
Point Estimate & 95% CI		PPA= 92.86% (13/14) (68.53% - 98.73%)	NPA= 100.00% (193/193) (98.05% - 100.00%)	PPA= 94.34% (50/53) (84.63% - 98.06%)	NPA= 99.09% (327/330) (97.36% - 99.69%)

Table 15: **VZV** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **fresh** specimens

		VZV Results			
		Cutaneous (N=207)		Mucocutaneous (N=383)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	37	1	5	0
	Negative	0	169	0	377
	Total	37	170	5	377
Point Estimate & 95% CI		PPA= 100.00% (37/37) (90.60% - 100.00%)	NPA= 99.41% (169/170) (96.74% - 99.90%)	PPA= 100.00% (5/5) (56.56% - 100.00%)	NPA= 100.00% (377/377) (98.99% - 100.00%)

Clinical Study #2

Analysis of residual frozen cutaneous and mucocutaneous swab samples in transport medium was performed to supplement Clinical Study #1. The samples were residual specimens left over from testing of patients with signs and symptoms of HSV-1, HSV-2 or VZV infection. The total number of evaluable samples was 154. The clinical performance of the Savanna HSV 1+2/VZV Assay was established by comparing to an FDA-cleared nucleic acid amplification test in frozen residual cutaneous and mucocutaneus specimens separately. Results are shown in Table 16.

Table 16: **HSV1** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **frozen residual** specimens

		HSV1 Results			
		Cutaneous (N=90)		Mucocutaneous (N=64)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	27	2	29	0
	Negative	0	61	0	35
	Total	27	63	29	35
Point Estimate & 95% CI		PPA= 100.00% (27/27) (87.55% - 100.00%)	NPA= 96.83% (61/63) (89.14% - 99.13%)	PPA= 100.00% (29/29) (88.31% - 100.00%)	NPA= 100.00% (35/35) (90.11% - 100.00%)

Table 17: **HSV2** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **frozen residual** specimens

		HSV2 Results			
		Cutaneous (N=90)		Mucocutaneous (N=64)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	30	0	15	1
	Negative	0	60	0	48
	Total	30	60	15	49
Point Estimate & 95% CI		PPA= 100.00% (30/30) (88.65% - 100.00%)	NPA= 100.00% (60/60) (93.98% - 100.00%)	PPA= 100.00% (15/15) (79.62% - 100.00%)	NPA= 97.96% (48/49) (89.31% - 99.64%)

Table 18: **VZV** Clinical performance for the Savanna HSV 1+2/VZV Assay in cutaneous and mucocutaneous **frozen residual** specimens

		VZV Results			
		Cutaneous (N=90)		Mucocutaneous (N=64)	
		Comparator		Comparator	
		Positive	Negative	Positive	Negative
Savanna HSV 1+2/VZV Assay Results	Positive	17	0	4	0
	Negative	0	73	0	60
	Total	17	73	4	60
Point Estimate & 95% CI		PPA= 100.00% (17/17) (81.57% - 100.00%)	NPA= 100.00% (73/73) (95.00% - 100.00%)	PPA= 100.00% (4/4) (51.02% - 100.01%)	NPA= 100.00% (60/60) (93.98% - 100.00%)

D Clinical Cut-Off:
Not Applicable.

E Expected Values/Reference Range:

Not Applicable

F Other Supportive Instrument Performance Characteristics Data:

Not applicable.

VIII Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.