DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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July 16, 2015

Ventana Medical Systems, Inc.
Yassine Labiad, MS, RAC
Regulatory Affairs Manager
203 Ravendale Drive
Mountain View, CA 94043

Re: K142965
Trade/Device Name: Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT
Regulation Number: 21 CFR § 864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Code: OEO
Dated: July 13, 2015
Received: July 14, 2015

Dear Mr. Labiad:

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 Part 801); 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 regulation (21 CFR Part 801), 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" (21CFR 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,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of *In Vitro* Diagnostics and
Radiological Health
Center for Devices and Radiological Health

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)*
K142965

Device Name

Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT

Indications for Use *(Describe)*

The Virtuoso™ system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

The Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT is for the digital read application. This particular Virtuoso system is intended for use as an aid to the pathologist in the qualitative detection of progesterone receptor (PR) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay is indicated for use as an aid in the assessment of breast cancer patients for whom endocrine treatment is being considered (but is not the sole basis for treatment).

Note: The IHC PR (1E2) Digital Read application is an adjunctive computer-assisted methodology for the qualified pathologist in the acquisition and interpretation of images from microscope glass slides of breast cancer specimens stained for the presence of PR protein. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody used to assure the validity of the Virtuoso System for IHC PR Digital Read scores. The actual correlation of CONFIRM™ anti-PR antibody to clinical outcome has not been established. This device is intended for IHC slides stained on the BenchMark XT and BenchMark ULTRA stainers. For prescription use only.

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)*

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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SECTION 5
510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92. The assigned 510(k) number is **K142965**.

807.92 (a)(1): Name: Ventana Digital Pathology
Address: 203 Ravendale Rd
Mountain View, CA 94043

Phone: (408) 585-7949
FAX: (408) 207-4299
Contact: Mr. Yassine Labiad

807.92 (a)(2): Device name- trade name and common name, and classification

Trade name: Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT

Common Name: IHC Digital pathology system for immunochemistry-stained slides

Classifications: 21 CFR § 864.1860- Immunohistochemistry reagents and kits

807.92 (a)(3): Identification of the legally marketed predicate devices

This Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT is substantially equivalent to its immediate predecessors cleared under K111869 on March 5, 2012, and K122143 on September 19, 2013. The only difference between the two is the use of a new scanner. The new iScan HT scanner is a powerful, high throughput bright field scanner that Ventana Medical Systems has decided to offer as an alternative to the iScan Coreo, which is a low to medium volume instrument currently employed for use with the Virtuoso™ System for IHC PR (1E2). Both the new and the predicate devices are digital pathology system for the consistent assessment of pathology interpretations using immunohistochemically stained slides (in this case, stained for PR expression), and both systems include slide scanner hardware, and software that both automates the procedural steps and performs the analyses.

807.92 (a)(4): Device Description

General Description

The Virtuoso™ System is an instrument-plus-software system designed to assist the qualified pathologist in the consistent assessment of protein expression in

immunohistochemically stained histologic sections from formalin-fixed, paraffin-embedded normal and neoplastic tissues. The system consists of a slide scanner, computer, monitor, keyboard, and mouse for specific immunohistochemical markers, and software with a Windows web browser-based user interface. Virtuoso is a web-based, end-to-end, digital pathology software solution that allows pathology laboratories to acquire, manage, view, analyze, share, and report digital images of pathology specimens. Using the Virtuoso software, the pathologist can view digital images, add annotations and generate reports.

Hardware: The iScan HT scanning device captures digital images of formalin-fixed, paraffin-embedded tissues that are suitable for storage and viewing. The device includes a digital slide scanner, a carousel for loading glass slides, computer, scanner software, keyboard, mouse and monitor.

Software: The Virtuoso software is designed to complement the routine workflow of a qualified pathologist in the review of immunohistochemically stained histologic slides. The software makes no independent interpretations of the data and requires competent human intervention for all steps in the process. Complete software information, following FDA's 2005 guidance document for software documentation required for regulatory submissions is being provided in Section 6 of this premarket notification.

Additional Materials Required:

- Ventana CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody
- Reagents for visualization, such as DAB chromogen
- Associated materials for completing immunohistochemical staining according to the appropriate package insert; this submission includes slides stained using both the Benchmark XT and Benchmark ULTRA stainers.
- Color printer if user wishes to print color copies

Device Quality Control

The quality of results depends on the laboratory following the quality control instructions recommended in the labeling of the immunohistochemistry (IHC) reagents.

Device Calibration:

The VENTANA iScan HT slide scanner is calibrated and verified at the manufacturing facility before shipment. Upon installation, calibrations are performed and verified by Roche Customer Support. No additional calibration or verification is required or performed by the end user. Annual preventive maintenance performed by Roche Customer Support is recommended to ensure that the VENTANA iScan HT slide scanner is operating as intended.

Summary of Procedure

Samples are obtained as formalin-fixed, paraffin-embedded tissue blocks. Histologic sections are prepared and mounted onto glass slides. Slides are reacted with the PR (1E2) primary antibody and are then visualized using DAB. Prepared slides are loaded into the Virtuoso system scanner and scanned. The resulting digital images are reviewed by the pathologist on a computer monitor.

807.92 (a)(5): Intended Use

The Virtuoso™ system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

The Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT is for the digital read application. This particular Virtuoso system is intended for use as an aid to the pathologist in the qualitative detection of progesterone receptor (PR) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay is indicated for use as an aid in the assessment of breast cancer patients for whom endocrine treatment is being considered (but is not the sole basis for treatment).

Note: The IHC PR (1E2) Digital Read application is an adjunctive computer-assisted methodology for the qualified pathologist in the acquisition and interpretation of images from microscope glass slides of breast cancer specimens stained for the presence of PR protein. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody used to assure the validity of the Virtuoso System for IHC PR Digital Read scores. The actual correlation of CONFIRM™ anti-PR antibody to clinical outcome has not been established. This device is intended for IHC slides stained on the BenchMark XT and BenchMark ULTRA stainers. For prescription use only.

807.92 (a)(6): Technological Similarities and Differences to the Predicate Devices

The similarities and differences between the two test systems are described below.

Characteristic	Predicate 1 Virtuoso™ System for IHC PR (1E2) [Benchmark ULTRA Stainer] K122143	Predicate 2 Virtuoso™ System for IHC PR (1E2) [Benchmark XT Stainer] K111869	New Device Virtuoso™ System for IHC PR (1E2) Using the VENTANA iScan HT
Intended Use/Indications for Use	The Virtuoso System provides automated digital slide creation, management, analysis, and viewing. It is intended for IVD use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, size, intensity, pattern and shape. The Virtuoso™ System for IHC PR (1E2) is for digital read and image analysis applications. This particular Virtuoso system is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of progesterone receptor (PR) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay is indicated for use as an aid in the assessment of breast cancer patients for whom endocrine treatment is being considered (but is not the sole basis for treatment). Note: The IHC PR (1E2) Digital Read and Image Analysis applications are adjunctive computer- assisted	SAME SAME	The Virtuoso™ system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape. The Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT is for the digital read application. This particular Virtuoso system is intended for use as an aid to the pathologist in the qualitative detection of progesterone receptor (PR) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay is indicated for use as an aid in the assessment of breast cancer patients for whom endocrine treatment is being considered (but is not the sole basis for treatment). Note: The IHC PR (1E2)

Characteristic	Predicate 1 Virtuoso™ System for IHC PR (1E2) [Benchmark ULTRA Stainer] K122143	Predicate 2 Virtuoso™ System for IHC PR (1E2) [Benchmark XT Stainer] K111869	New Device Virtuoso™ System for IHC PR (1E2) Using the VENTANA iScan HT
	methodologies for the qualified pathologist in the acquisition and measurement of images from microscope glass slides of breast cancer specimens stained for the presence of PR protein. The pathologist should verify agreement with the Image Analysis software application score. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody used to assure the validity of the Virtuoso System for IHC PR Digital Read and Image Analysis scores. The actual correlation of CONFIRM™ anti-PR antibody to clinical outcome has not been established. This device is intended for IHC slides stained on the BenchMark XT and BenchMark ULTRA stainers. For prescription use only.		Digital Read application is an adjunctive computer-assisted methodology for the qualified pathologist in the acquisition and interpretation of images from microscope glass slides of breast cancer specimens stained for the presence of PR protein. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody used to assure the validity of the Virtuoso System for IHC PR Digital Read score. The actual correlation of CONFIRM™ anti-PR antibody to clinical outcome has not been established. This device is intended for IHC slides stained on the BenchMark XT and BenchMark ULTRA stainers. For prescription use only.
Specimen Type	Formalin-fixed, paraffin-embedded tissue stained by immunohistochemical technique	Same	Same
System Operation (Digital Read and Image Analysis)	Histologic observation by a pathologist through the image viewer and image analysis systems	Same	Histologic observation by a pathologist through the image viewer system.
Hardware and Software	Ventana iScan slide scanner, computer, color monitor, proprietary software for PR (1E2)	Same	Ventana iScan HT scanner, computer, color monitor, proprietary software for PR (1E2)
Platform	Mouse, keyboard, windows web	Same	Same

Characteristic	Predicate 1 Virtuoso™ System for IHC PR (1E2) [Benchmark ULTRA Stainer] K122143	Predicate 2 Virtuoso™ System for IHC PR (1E2) [Benchmark XT Stainer] K111869	New Device Virtuoso™ System for IHC PR (1E2) Using the VENTANA iScan HT
Components	browser.		
Primary Antibody (Assay) Reagent	Ventana CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody	Same	Same
Ancillary Reagents/Stainers	DAB universal chromogen kits, Slides stained with Benchmark ULTRA stainer	DAB universal chromogen kits, slides stained with Benchmark XT stainer	DAB universal chromogen kits, slides stained with Benchmark XT and ULTRA stainers
Localization of IHC positive stain	Nucleus	Same	Same
Interpretation	Interpretation is performed by the pathologist.	Same	Same

807.92 (b)(1/2): Brief Description of Clinical Data (Non-clinical data N/A)

The Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT was clinically validated via a method comparison (agreement/concordance) study and a precision and reproducibility study. The method comparison study evaluated overall system performance in terms of agreement between the reference manual method (with a traditional microscope) and the digital read (DR) application of the Virtuoso system. Two sets of statistical analyses were performed for the method comparison study: 1) Initial analysis: This analysis involved the primary endpoint analysis for each of the 3 pathologists participating in the study. The primary end points included the overall percent agreement (OPA), positive percent agreement (PPA), and negative percent agreement (NPA) between the Digital Read (DR) method and Manual Read (MR) method. 2) The additional analysis employed the Generalized Linear Mixed Model (GLMM) analysis methodology for the primary endpoint analysis. This additional analysis was associated with model-based results, which enabled appropriate estimation within a repeated-measures design of the average reader performance using the comparator device. The GLMM analysis included all 3 pathologists' data.

The reproducibility components of the studies involved the intra-pathologist/inter-day reproducibility evaluation as well the inter-pathologist reproducibility of the DR Virtuoso application.

The Scanner precision study involved a subset of the clinical cases (n = 40, both stainers) that were scanned two more times, and also scanned three times with two different scanners at two separate locations. This study evaluated scanner precision for both inter-scanner precision and intra-scanner/inter-day precision.

The data from both method comparison and precision/reproducibility studies are summarized below.

Method comparison (Agreement/Concordance)

Virtuoso Digital Read vs Manual Method

Each pathologist's Virtuoso digital read results were compared to their manual results. The data were categorized as "neg" and "pos" using the PR score of 0 to 0.99% positive staining to describe negative, and ≥1% positive staining to describe positive. The overall percent agreements using negative and positive, as defined above, across the three sites were: 98.7%, 88.9%, and 96.2%, respectively. The overall, negative, and positive percent agreements, with the 95% confidence intervals (CI) around the agreements are shown below.

Table: PR Clinical Status Agreement[a,b] Between DR and MR[c], By Site (Reader)

		Manual Read							
		SITE 1 (n =159)		SITE 2 (n =162)		SITE 3 (n =156)		Overall (n = 477)	
		Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Digital Read	Pos	107	1	72	7	68	0	247	8
	Neg	1	50	11	72	6	82	18	204
	Total	108	51	83	79	74	82	265	212
Overall agreement (%) (95% CI) [d]		98.7 (95.5-99.7)		88.9 (83.1-92.9)		96.2 (91.9-98.2)			
Positive Agreement (%) (95% CI) [d]		99.1 (94.9-99.8)		86.7 (77.8-92.4)		91.9 (83.4-96.2)			
Negative agreement (%) (95% CI) [d]		98.0 (89.7-99.7)		91.1 (82.8-95.6)		100.0 (95.5-100.0)			

[a] Clinical status: positive = clinical scoring category of 1-10% or >10%; negative = clinical scoring category of 0-0.99%.

[b] Only cases with evaluable results are included this analysis. For a case result to be evaluable, the investigator must have assigned a valid clinical score (status) to the case and must have confirmed that the case morphology and background staining were acceptable and that the run controls were valid.

[c] For sites that performed two independent MR scoring rounds, these data are from the first MR round.

[d] Two-sided 95% confidence interval calculated using the score method.

Reproducibility

a. Intra-Pathologist/Inter-Day (pair-wise comparisons, Session 1 vs Session 2, Session 1 vs Session 3, Session 2 vs Session 3)

Digital Read

In the primary analysis of DR intra-reader reproducibility, the PR clinical status [negative (0–0.99%) or positive (≥1%)] was compared across three individual DR evaluations of the same set of 39 cases by the Reader. The 2 × 2 comparisons for the 3 reading sessions (reads) are shown in the following table with the respective agreement values. OPA rates for the 3 pairwise comparisons ranged from 89.7% to 97.4%. During the second and third reads for the DR reproducibility evaluation, Reader 3 investigator identified one case as unevaluable.

PR clinical Status [a] Agreement Within Reader (Digital Read)

READ 1 vs READ 2		Read 2 Clinical Assessment			Read 1 vs Read 2 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI[b]
Read 1 Clinical Assessment	Pos	19	1	20	APA	38/39	97.4	90.9-100.0
	Neg	0	19	19	ANA	38/39	97.4	90.7-100.0
	Total	19	20	39	OPA	38/39	97.4	86.8-99.5
READ 1 vs READ 3		Read 3 Clinical Assessment			Read 1 vs Read 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI[b]
Read 1 Clinical Assessment	Pos	18	2	20	APA	36/40	90.0	78.0-97.9
	Neg	2	17	19	ANA	34/38	89.5	76.5-97.8
	Total	20	19	39	OPA	35/39	89.7	76.4-95.9
READ 2 vs READ 3		Read 3 Clinical Assessment			Read 2 vs Read 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI[b]
Read 2 Clinical Assessment	Pos	18	1	19	APA	36/39	92.3	81.3-100.0
	Neg	2	18	20	ANA	36/39	92.3	81.3-100.0
	Total	20	19	39	OPA	36/39	92.3	79.7-97.3

[a] Clinical assessment (ie, PR status): positive = clinical score of 1–10% or ≥ 10%; negative = clinical score of 0 – 0.99%.
[b] Two-sided 95% CIs for OPA of each read pair (not pooled for all read-pairs) are calculated using the score method. The other CIs are calculated using the percentile bootstrap method.

b. Inter-Pathologist (pair-wise comparisons, Pathologist 1 vs Pathologist 2, Pathologist 1 vs Pathologist 3, Pathologist 2 vs Pathologist 3)

The agreement of PR clinical status between sites (readers) was examined separately for DR and MR. Each investigator's results for the PR clinical status [negative (0–0.99%) or positive (≥1%)] of the study cases were compared to those of another reader using the same reading method. The agreement rates and 95% CIs are shown in the following tables, respectively, for each reading method (DR and MR).

Manual Read

The three manual readings across the three pathologists (sites) were compared to each other. The reproducibility in the manual readings among the three pathologists (sites) is shown below, along with the 95% CIs. The OPA rates for the 3 pairwise comparisons ranged from 81.0% to 92.9%.

PR Clinical Status Agreement[a,b] Between Sites (Readers): Manual Read

SITE 1 vs. SITE 2		Site 2 Clinical Assessment			Site 1-vs-Site 2 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI [d] (%)
Site 1 Clinical Assessment	Pos	82	25	107	APA	164/190	86.3	80.7-91.2
	Neg	1	50	51	ANA	100/126	79.4	71.1-86.6
	Total	83	75	158	OPA	132/158	83.5	77.0-88.5

SITE 1 vs. SITE 3		Site 3 Clinical Assessment			Site 1-vs-Site 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI [d] (%)
Site 1 Clinical Assessment	Pos	74	29	103	APA	148/177	83.6	77.2-89.4
	Neg	0	50	50	ANA	100/129	77.5	68.8-85.1
	Total	74	79	153	OPA	124/153	81.0	74.1-86.5

SITE 2 vs. SITE 3		Site 3 Clinical Assessment			Site 2-vs-Site 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI [d] (%)
Site 2 Clinical Assessment	Pos	70	8	78	APA	140/151	92.7	88.0-96.7
	Neg	3	74	77	ANA	148/159	93.1	88.6-96.8
	Total	73	82	155	OPA	144/155	92.9	87.7-96.0

[a] Clinical status: positive = clinical scoring category of 1–10% or ≥ 10%; negative = clinical scoring category of 0 – 0.99%.

[b] Only cases with evaluable results are included this analysis. For a case result to be evaluable, the investigator must have assigned a valid clinical score (status) to the case and must have confirmed that the case morphology and background staining were acceptable and that the run controls were valid.

[c] Two-sided 95% confidence interval for OPA of each site (reader) pair (not pooled for all sites) are calculated using the score method. The other CIs are calculated using the percentile bootstrap method.

Digital Read

The reproducibility in the Virtuoso digital readings among the three pathologists (sites) is shown below, along with the 95% CIs. The overall percent agreements ranged from 77.4% to 89.9%.

PR Clinical Status Agreement[a,b] Between Sites (Readers): Digital Read

SITE 1 vs. SITE 2		Site 2 Clinical Assessment			Site 1-vs-Site 2 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI [d] (%)
Site 1 Clinical Assessment	Pos	79	29	108	APA	158/188	84.0	78.0-89.6
	Neg	1	50	51	ANA	100/130	76.9	68.8-84.6
	Total	80	79	159	OPA	129/159	81.1	74.3-86.5
SITE 1 vs. SITE 3		**Site 3 Clinical Assessment**			**Site 1-vs-Site 3 Agreement Rates**			
		Pos	**Neg**	**Total**	**Rate**	**n/N**	**%**	**95% CI [d] (%)**
Site 1 Clinical Assessment	Pos	70	35	105	APA	140/175	80.0	73.4-86.3
	Neg	0	50	50	ANA	100/135	74.1	65.6-81.8
	Total	70	85	155	OPA	120/155	77.4	70.2-83.3
SITE 2 vs. SITE 3		**Site 3 Clinical Assessment**			**Site 2-vs-Site 3 Agreement Rates**			
		Pos	**Neg**	**Total**	**Rate**	**n/N**	**%**	**95% CI [d] (%)**
Site 2 Clinical Assessment	Pos	65	11	76	APA	130/146	89.0	83.5-93.8
	Neg	5	77	82	ANA	154/170	90.6	85.7-94.7
	Total	70	88	158	OPA	142/158	89.9	84.2-93.7

[a] Clinical status: positive = clinical scoring category of 1–10% or ≥ 10%; negative = clinical scoring category of 0 – 0.99%.

[b] Only cases with evaluable results are included this analysis. For a case result to be evaluable, the investigator must have assigned a valid clinical score (status) to the case and must have confirmed that the case morphology and background staining were acceptable and that the run controls were valid.

[c] Two-sided 95% confidence interval for OPA of each site (reader) pair (not pooled for all sites) are calculated using the score method. The other CIs are calculated using the percentile bootstrap method.

Scanner Precision

Forty (40) cases representing the useful categories of <1%, 1-10%, and 10% positive staining for PR were scanned on three different scanners at three different sites to assess inter-scanner precision, and three FOVs were captured (total = 120) and evaluated. Similarly, these same 40 cases were scanned on three different days by the same scanner, and the same FOVs were applied to the appropriate cases to assess intra-scanner/inter day precision.

Pairwise comparisons were performed between each of the three sites (inter-scanner), and between each of the three days (sessions, intra-scanner). The precision tables are found below.

PR Clinical Scoring Category [a] Agreement Between Scanners (Between Sites): All FOVs Combined

SITE 1 vs SITE 2 [b]		Site 2 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Site 1 Clinical Scoring Category	>10%	113	8	0	121	324/360	90.0	86.5-92.7
	1–10%	3	30	15	48			
	0–0.99%	0	10	181	191			
	Total	116	48	196	360			
SITE 1 vs SITE 3 [b]		Site 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Site 1 Clinical Scoring Category	>10%	119	2	0	121	337/360	93.6	90.6-95.7
	1–10%	4	34	10	48			
	0–0.99%	0	7	184	191			
	Total	123	43	194	360			
SITE 2 vs SITE 3 [b]		Site 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Site 2 Clinical Scoring Category	>10%	115	1	0	116	325/360	90.3	86.8-92.9
	1–10%	8	28	12	48			
	0–0.99%	0	14	182	196			
	Total	123	43	194	360			

[a] PR clinical scoring categories of: 0 – 0.99% (negative), 1–10% (positive), and ≥ 10% (positive).
[b] This analysis is based on the results of pooling all days.
[c] Two-sided 95% CIs for OPA of each site (reader) pair (not pooled for all site-pairs) are calculated using the score method. Two-sided 95% CIs for OPA with all site-pairs pooled are calculated using the percentile bootstrap method.

PR Clinical Scoring Category [a] Agreement Within Scanners (Between Days): All FOVs Combined

DAY 1 vs DAY 2 [b]		Day 2 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Day 1 Clinical Scoring Category	>10%	117	4	0	121	332/360	92.2	89.0-94.6
	1–10%	1	33	11	45			
	0–0.99%	1	11	182	194			
	Total	119	48	193	360			
DAY 1 vs DAY 3 [b]		Day 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Day 1 Clinical Scoring Category	>10%	118	3	0	121	327/360	90.8	87.4-93.4
	1–10%	2	29	14	45			
	0–0.99%	0	14	180	194			
	Total	120	46	194	360			
DAY 2 vs DAY 3 [b]		Day 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI [c]
Day 2 Clinical Scoring Category	>10%	115	3	1	119	327/360	90.8	87.4-93.4
	1–10%	5	31	12	48			
	0–0.99%	0	12	181	193			
	Total	120	46	194	360			

[a] PR clinical scoring categories of: 0 – 0.99% (negative), 1–10% (positive), and ≥ 10% (positive).
[b] This analysis is based on the results of pooling all FOVs and all sites.
[c] Two-sided 95% CIs for OPA of each day pair (not pooled for all day-pairs) are calculated using the score method. Two-sided 95% CIs for OPA with all day-pairs pooled are calculated using the percentile bootstrap method.

807.92 (b)(3): Conclusions from Clinical Testing

Concordance, reproducibility, and precision studies were performed for the Virtuoso System for IHC PR (1E2) using the VENTANA iScan HT. The test system was shown to be as safe and effective (therefore substantially equivalent) as the predicate devices for its intended use.