

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k142965

B. Purpose for Submission:

New device

C. Manufacturer and Instrument Name:

Ventana Medical Systems, Inc.

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

D. Type of Test or Tests Performed:

Manual scoring of digital images on a computer monitor of progesterone receptor (PR) (1E2) immunohistochemistry (IHC) stained slides using the VENTANA iScan HT scanner.

E. System Descriptions:

1. Device Description:

The Virtuoso™ System for IHC PR (1E2) Using the VENTANA iScan HT is an instrument-plus-software system designed to assist the qualified pathologist in the assessment of protein expression in IHC stained histologic sections from formalin-fixed, paraffin-embedded (FFPE) breast tissues.

The system consists of a slide scanner (iScan), computer, monitor, keyboard, mouse and software with a Windows web browser-based user interface. Virtuoso is a web-based, end-to-end, IHC digital pathology software solution that allows pathology laboratories to acquire, manage, view, analyze, share, and report digital images of IHC stained slides. Using the Virtuoso software, the pathologist can view digital images, add annotations, make measurements and generate reports.

The Digital Read (DR) option allows the pathologist to manually score the PR (1E2) stained slide's digital image on a computer monitor.

Hardware: The iScan HT slide scanning device captures digital images of FFPE breast 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 IHC stained breast tissue slides. It allows the user to select fields of view (FOVs) in the digital image for manual analysis. The software makes no independent interpretations of the data and requires competent human intervention for all steps in the analysis process.

2. Principles of Operation:

Glass slides with FFPE tissue sections stained using the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody are loaded into the VENTANA iScan HT scanner. The slides are then scanned and the resulting digitized images are displayed on a computer monitor. The pathologist reviews these images on the computer monitor and provides a qualitative PR IHC score based on the $\geq 1\%$ cut-off.

3. Modes of Operation:

Digital Read (DR): Manual scoring of IHC PR stained slide images on a computer monitor.

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

Yes or No

Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

Yes or No

4. Specimen Identification:

Glass tissue slides are identified by slide label or barcode (if provided by the user) by scanning the whole slide including the label or barcode.

5. Specimen Sampling and Handling:

IHC stained slides are manually loaded on to the VENTANA iScan HT slide scanner in the carousel. The slide capacity is 360 slides. Under the default setting, a thumbnail view of the slide and the area of interest (AOI) in the slide are scanned. The operator has the option of rescanning the slide after viewing the image on the computer monitor. Under the manual scanning option, the user has the ability to select the scan area for single or batch slides.

6. 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.

7. Quality Control:

Quality control is performed by the operator before releasing the images to the pathologist for review. Slides with sub-optimal images will be rescanned. Additionally, the software performs a quality check on the digital images to determine if they are suitable for further analysis using the “Image Quality Assessment” module.

8. Software:

FDA has reviewed applicant’s Hazard Analysis and Software Development processes for this line of product types:

Yes or No

F. Regulatory Information:

1. Regulation section:
21 CFR §864.1860, Immunohistochemistry reagents and kits
2. Classification:
Class II
3. Product code:
OEO - Automated Digital Image Manual Interpretation Microscope
4. Panel:
Pathology (88)

G. Intended Use:

1. Indication(s) for 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.

2. Special Conditions for Use Statement(s):

For prescription use only

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

Virtuoso™ System for IHC PR (1E2), k111869

2. Comparison with Predicate Device:

Similarities		
Item	Device	Predicate
Intended use	<p>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, size, intensity, pattern and shape.</p> <p>The Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT is for digital read. 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</p>	Same

Similarities		
Item	Device	Predicate
	<p>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).</p> <p>Note: The IHC PR (1E2) Digital Read adjunctive computer-assisted 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 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.</p>	
System Operation	Histologic observation by a pathologist through the viewer	Same

Differences		
Item	Device	Predicate
Hardware	VENTANA iScan HT slide scanner	VENTANA iScan Coreo slide scanner

I. Special Control/Guidance Document Referenced (if applicable):

None

J. Performance Characteristics:

1. Analytical Performance:

a. Accuracy:

The accuracy of the Virtuoso™ System for IHC PR (1E2) using the VENTANA iScan HT was evaluated by comparing the IHC PR score agreement between the reference manual method (MR) using a traditional microscope and the DR application of the Virtuoso system. This study was conducted in 3 sites with one pathologist at each site. The study utilized 163 cases of de-identified, archived invasive breast carcinoma slides stained for the identification of PR using the CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody (Ventana), applicable staining run control and negative reagent control slides, the ultraView™ and iVIEW™ DAB detections (Ventana), the XT and ULTRA staining platforms, and the iScan HT.

Study procedures included the selection and randomization of study cases consisting of H&E, negative reagent control, and test slides. Archived positive and negative staining run control slides of the selected test cases were also identified and included as part of each case. Cases were scanned and accessioned into the Virtuoso system to support digital read following Ventana scanning and accessioning procedures. Positive run control slides and negative control slides were also scanned. There was a minimum 7-day wash-out period between each read by each investigator and slides were re-randomized prior to each read.

Slides were excluded from analysis for the following reasons: one or more case slides missing, duplicated slides, broken or cracked slides or no invasive carcinoma identified. All pathologists read all the slides under the manual method and the digital read mode. The data were categorized as “negative” and “positive” using PR scoring criteria of less than 1% of tumor cells staining as negative and 1% or more tumor cells staining as positive. The percent agreements across the 3 sites with the 95% confidence intervals (CI) around the agreements are shown below.

Agreement: Digital Read vs Manual (manual = reference score)

		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)		98.7 (95.5-99.7)		88.9 (83.1-92.9)		96.2 (91.9-98.2)			
Positive Agreement (%) (95% CI)		99.1 (94.9-99.8)		86.7 (77.8-92.4)		91.9 (83.4-96.2)			
Negative agreement (%) (95% CI)		98.0 (89.7-99.7)		91.1 (82.8-95.6)		100.0 (95.5-100.0)			

b. *Precision/Reproducibility:*

i. Intra-reader reproducibility:

In this study, the assessment of the PR clinical status was compared across three individual DR evaluations of the same set of 39 cases by one study pathologist-investigator (reader) at site 3. Images from the scanning sessions were accessioned into the Virtuoso application. Three image sets each were evaluated for PR clinical status [negative (0-0.99%) or positive ($\geq 1\%$)] by one reader using the DR mode. All study cases were also evaluated for morphologic adequacy, background staining, and overall evaluability. Results were compared between scoring sessions by the same reader to demonstrate the intra-reader reproducibility of the DR application of the Virtuoso System for PR (1E2) used with the iScan HT scanner. During the second and third reads one case was determined to be unevaluable. The 2×2 comparisons for the 3 reading sessions (reads) are shown in the following table:

PR Clinical Status Agreement Intra-Reader: Digital Read

READ 1 vs READ 2		Read 2			Read 1 vs Read 2 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI
Read 1	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			Read 1 vs Read 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI
Read 1	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			Read 2 vs Read 3 Agreement Rates			
		Pos	Neg	Total	Rate	n/N	%	95% CI
Read 2	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

ii. Inter-reader Reproducibility:

The agreement of PR clinical status between sites (readers) was examined separately for DR and MR. Only cases with evaluable results are included in 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. Each investigator's results for the PR clinical status [negative (0-0.99%) or positive ($\geq 1\%$)] 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).

PR Clinical Status Agreement Inter-Readers: Manual Read

SITE 1 vs. SITE 2		Site 2			Site 1-vs-Site 2 Agreement Rates			
Manual Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 1	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			Site 1-vs-Site 3 Agreement Rates			
Manual Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 1	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			Site 2-vs-Site 3 Agreement Rates			
Manual Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 2	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

PR Clinical Status Agreement Inter-Reader: Digital Read

SITE 1 vs. SITE 2		Site 2			Site 1-vs-Site 2 Agreement Rates			
Digital Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 1	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			Site 1-vs-Site 3 Agreement Rates			
Digital Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 1	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			Site 2-vs-Site 3 Agreement Rates			
Digital Read		Pos	Neg	Total	Rate	n/N	%	95% CI (%)
Site 2	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

iii. Scanner Precision

Forty (40) cases representing the categories of <1%, 1-10%, and >10% positive staining for PR were scanned on 3 different scanners at 3 different sites to assess inter-scanner precision. Three FOVs per case were captured (total = 120) and evaluated. Similarly, these same 40 cases were scanned on 3 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 3 sites (inter-scanner), and between each of the 3 days (sessions, intra-scanner). The precision study results are given in the tables below.

PR Clinical Scoring Category Agreement Between Scanners (Between Sites)
All FOVs Combined

SITE 1 vs SITE 2		Site 2 Clinical Scoring Category				OPA		
		>10%	1-10%	0-0.99%	Total	n/N	%	95% CI
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		Site 3 Clinical Scoring Category				OPA		
		>10%	1-10%	0-0.99%	Total	n/N	%	95% CI
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		Site 3 Clinical Scoring Category				OPA		
		>10%	1-10%	0-0.99%	Total	n/N	%	95% CI
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			

PR Clinical Scoring Category Agreement Within Scanners (Between Days)
All FOVs Combined

DAY 1 vs DAY 2		Day 2 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI
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		Day 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI
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		Day 3 Clinical Scoring Category				OPA		
		>10%	1–10%	0–0.99%	Total	n/N	%	95% CI
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			

c. Linearity:

Not applicable

d. Carryover:

Not applicable

e. Interfering Substances:

Not applicable

2. Other Supportive Instrument Performance Data Not Covered Above:

Not applicable

K. Proposed Labeling:

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

L. Conclusion:

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