SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	VENTANA MET (SP44) RxDx Assay
Device Trade Name:	VENTANA MET (SP44) RxDx Assay
Device Procode:	SER
Applicant's Name and Address:	Ventana Medical Systems, Inc. (Roche Tissue Diagnostics) 1910 E Innovation Park Drive Tucson, AZ 85755
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P240037
Date of FDA Notice of Approval:	May 14, 2025

II. INDICATIONS FOR USE

VENTANA MET (SP44) RxDx Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-MET, clone SP44, intended for use in the assessment of MET protein in formalin-fixed paraffin embedded (FFPE) non-squamous non-small cell lung cancer (NSCLC) specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA or BenchMark ULTRA PLUS instrument.

MET protein expression clinical cut-off is ≥ 50% of tumor cells exhibiting strong membrane and/or cytoplasmic staining (3+) in non-squamous NSCLC.

VENTANA MET (SP44) RxDx Assay is indicated as an aid in identifying non-squamous NSCLC patients who may be eligible for treatment with EMRELIS™ (telisotuzumab vedotin-tllv).

The results of VENTANA MET (SP44) RxDx Assay should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information and proper controls.

This product is intended for *in vitro* diagnostic (IVD) use.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the VENTANA MET (SP44) RxDx Assay labeling (Package Insert/Method Sheet).

V. DEVICE DESCRIPTION

A. Device Kit Components

VENTANA MET (SP44) RxDx Assay contains optimized reagents required to complete the immunohistochemistry (IHC) staining procedure for FFPE specimens on the BenchMark ULTRA or BenchMark ULTRA PLUS automated staining instruments visualized using the OptiView DAB IHC Detection Kit. VENTANA MET (SP44) RxDx Assay recombinant rabbit monoclonal antibody is produced as purified cell culture supernatant. The antibody and detection reagents are provided as ready-to-use dispensers and each VENTANA MET (SP44) RxDx Assay primary antibody dispenser contains sufficient reagent for 50 tests. The VENTANA MET (SP44) RxDx Assay components and their description are provided in Tables 1 and 2, below.

Table 1. VENTANA MET (SP44) RxDx Assay Components

Components Description	Packaged Form	Description
VENTANA MET (SP44) Recombinant Rabbit Monoclonal Primary Antibody	1 Flo-Lok Dispenser: 50 tests	One 5 mL dispenser of VENTANA MET (SP44) RxDx Assay contains approximately 17.5 µg of recombinant rabbit monoclonal antibody (approximately 3.5 µg/mL). The antibody is diluted in 0.05 M Tris-HCl with carrier protein and 0.10% ProClin 300, a preservative.
OptiView DAB IHC Detection Kit	Set of 6 Flo-Lok dispensers, packaged in a kit: 250 tests	OptiView Peroxidase Inhibitor contains 3.0% hydrogen peroxide solution.
		OptiView HQ Universal Linker contains a cocktail of HQ-labeled (HQ is a proprietary hapten covalently attached to the goat antibodies) antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit) (<50 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView HRP Multimer contains a mouse monoclonal anti-HQlabeled HRP tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300, a preservative
		OptiView H_2O_2 contains 0.04% hydrogen peroxide in a phosphate-buffered saline (PBS) solution
		OptiView DAB contains 0.2% 3, 3′-diaminobenzidine tetrahydrochloride (DAB) in a proprietary stabilizer solution with a proprietary preservative.
		OptiView Copper contains copper sulfate (5.0 g/L) in an acetate buffer with a proprietary preservative
BenchMark ULTRA automated staining instrument and Ventana System Software (VSS) software	Instrument installed with the VSS host system software; Version 12.3 to 12.5.4	A personal computer (PC) that runs on Microsoft Windows controls and monitors the BenchMark ULTRA instrument via the host operating software.
BenchMark ULTRA PLUS automated staining instrument and VSS software	Instrument installed with the VSS host system software; Version 14.1	A personal computer (PC) that runs on Microsoft Windows controls and monitors the BenchMark ULTRA PLUS instrument via the host operating software.
Negative Control (Rabbit Monoclonal Ig)	1 Flo-Lok dispenser: 250 tests	Intended for laboratory use as a control for non-specific binding of the primary antibody in sections of FFPE tissue. One 25 mL dispenser contains approximately 25 µg (1 ug/mL) of rabbit monoclonal antibody. The antibody is diluted in PBS with 3% carrier protein and 0.05% ProClin 300, a preservative.

Table 2: Ancillary Reagents Required for VENTANA MET (SP44) RxDx Assay

Reagent	Description
Hematoxylin II counterstain	Modified Mayer's hematoxylin used for staining cellular nuclei on slides containing cells from frozen tissue, FFPE tissue, or cytologic preparations
Bluing Reagent	Aqueous solution of buffered lithium carbonate used for bluing hematoxylin-stained sections on glass slides
Reaction Buffer 10x	Tris based buffer solution (pH 7.6 ± 0.1) used to rinse slides between staining steps and provide a stable aqueous environment for reactions carried out on the BenchMark instrument
EZ Prep 10X	A detergent-containing reagent that removes paraffin from the tissue specimen during the IHC staining to prepare the tissue for antigen retrieval and subsequent reactions
ULTRA Liquid CoverSlip (LCS), predilute	Pre-diluted coverslip solution used as a barrier between aqueous reagents and air to prevent evaporation
ULTRA CC1 Cell Conditioning Solution	Pre-diluted solution used as a pretreatment step in the processing of FFPE tissue samples or cytologic on the BenchMark ULTRA and BenchMark ULTRA PLUS instruments

B. Device Instrumentation and Software

The VENTANA MET (SP44) RxDx Assay is performed on the BenchMark ULTRA automated staining instrument using Ventana System Software (VSS) versions 12.3 to 12.5.4 and the BenchMark ULTRA PLUS automated staining instrument using Ventana System Software (VSS) versions 14.1.

C. Specimen Preparation

Routinely processed FFPE non-squamous NSCLC tissues are suitable for use with this primary antibody when used with OptiView DAB IHC Detection Kit and BenchMark ULTRA and ULTRA PLUS instruments. The recommended tissue fixative is 10% neutral buffered formalin (NBF). The samples should be fixed in NBF for 6-72 hours. Fixation times less than 6 hours are not recommended due to loss of specific MET expression. Zinc formalin fixative may also be used using a fixation time of 6-72 hours.

Fixatives such as AFA, PREFER fixative, Z-fix, Alcohol Formalin and 95% ethanol are not recommended for use with this assay and due to significant loss of specific MET protein expression.

Tissue sections should be cut at approximately 4-5 µm thickness and mounted on positively charged glass slides. Slides should be stained immediately or store at 2-8°C for no more than 45 days before staining, as antigenicity of cut tissue sections may diminish over time. See device labeling for additional details.

D. Quality Control Procedures

Run controls are included in each staining run to establish the validity of the test results. The following controls must be run with VENTANA MET (SP44) RxDx Assay:

1. Positive/Negative Tissue Control

Gallbladder tissue is used as a positive control for this antibody. Positive and negative staining elements for the MET protein present in gall bladder tissues are used to confirm that the VENTANA MET (SP44) RxDx Assay functioned properly. Positive tissue controls should be utilized only for monitoring performance of reagents and instruments, not as an aid in determining specific diagnosis of test samples. The interpretation of the MET staining in gallbladder tissue when used as a positive/negative tissue control is given in the table below.

Table 3: Positive/Negative Control Tissue Evaluation, Gallbladder tissue

Staining Elements	Acceptable	Unacceptable
Positive	Presence of Moderate* membrane staining in the epithelium	Absence of Moderate * membrane staining in the epithelium
Negative	Absence of specific MET staining within cells of stromal tissue	Excessive background staining of the stromal tissue that interferes with interpretation

* Moderate staining intensity is characterized by rich brown thickened membranes that are detectable at low magnifications such as 4x or 10x. Refer to the interpretation guide for additional information.

2. Negative Reagent Control (NRC)

A matched NRC slide should be run for every specimen to aid in the interpretation of results. Rabbit Monoclonal Negative Control Ig, a negative reagent control antibody, is specifically matched for this VENTANA MET (SP44) RxDx Assay and is used on a separate tissue section from the same patient specimen in place of the primary antibody to evaluate nonspecific staining in the patient tissue that may result from a reaction with the detection chemistry and not the MET (SP44) primary antibody. The incubation period for the negative reagent control should equal the primary antibody incubation period. If the NRC slide is considered not acceptable, the MET (SP44) slide should not be evaluated for scoring purposes, and the assay should be repeated.

E. Principles of Operation

The VENTANA MET (SP44) RxDx Assay is fully automated for use on the BenchMark ULTRA and BenchMark ULTRA PLUS automated slide stainers from deparaffinization through counterstaining. Patient FFPE tissue specimens are cut to approximately 4-5µm thickness and mounted on positively charged glass slides. These slides are loaded into the Benchmark ULTRA or BenchMark ULTRA PLUS instrument. This system first removes the paraffin wax from the tissue (deparaffinization), and then subjects the tissue to heated antigen retrieval (cell conditioning). Endogenous peroxidases that could potentially react with the horseradish peroxidase conjugates (HRP) are blocked with OptiView Inhibitor (3% H2O2). After the endogenous peroxidase block, the VENTANA MET (SP44) Rabbit Monoclonal Primary Antibody is dispensed during the antibody incubation step and allowed to bind to its antigen. The slides are then incubated with the reagents in the OptiView DAB IHC Detection Kit, which is an indirect, biotin-free system for detecting mouse IgG, mouse IgM, and rabbit primary antibodies and which produces a visible dark brown precipitate (3,3'-Diaminobenzidine) via a horseradish peroxidase (HRP) enzymatic reaction at the antigen site. Slides are then counterstained using Hematoxylin II and Bluing Reagent to create brown/blue contrast to aid the pathologist when reviewing the slides using bright field microscopy. The VENTANA MET (SP44) RxDx Assay staining protocol is shown in the Table 4 below.

Table 4. VENTANA MET (SP44) RxDx Assay Staining Protocol with OptiView DAB Detection Kit on BenchMark ULTRA or Benchmark ULTRA PLUS Instrument

Procedure Type	Protocol Parameter
Baking	Optional*
Deparaffinization	4 minutes (default), 72°C
Cell Conditioning (Antigen Unmasking)	ULTRA Cell Conditioning 1 64 minutes, 100°C
Pre-antibody peroxidase inhibitor	4 minutes, 36°C
Antibody (Primary)	16 minutes, 36ºC
Negative Control	16 minutes, 36ºC
OptiView HQ Linker	8 minutes, 36°C
OptiView HRP Multimer	8 minutes, 36°C
Counterstain	Hematoxylin II, 4 minutes
Post Counterstain	Bluing , 4 minutes

*May be performed on-board the instrument (4-32 minutes, 60°C) or performed offline (up to 60 minutes, 60°C)

F. Slide Review and Interpretation of MET Staining

The cellular staining pattern for VENTANA MET (SP44) RxDx Assay is membranous and/or cytoplasmic in tumor cells in non-squamous NSCLC tissue with varying ranges of stain intensity. The percentage of tumor cells with strong (3+) membranous and/or cytoplasmic staining will be assessed from for specimens containing a minimum of approximately 100 viable tumor cells.

Strong (3+) signal intensity is characterized by dark brown to black hue with saturated DAB. Membranes/cytoplasm exhibiting strong signal are detectable at low power magnifications such as 2x or 4x.

1. **Hematoxylin & Eosin (H&E) Slide:**
   The pathologist will determine whether the H&E slide contains sufficient tumor tissue (which is defined as presence of a minimum of approximately 100 viable tumor cells) consistent with non-squamous NSCLC cases to allow interpretation of the case-matched IHC slides. If the H&E is not acceptable, the case-matched NRC and MET (SP44) patient case slides will not be evaluated.

2. **System-level Control Slide – Tissue Control Slide(s)**
   One system-level control (SLC) slide containing non-neoplastic gallbladder tissue should be included in each BenchMark ULTRA and Benchmark ULTRA PLUS staining run to confirm the validity of the staining run and should be evaluated by a qualified pathologist. Gallbladder tissue contains positive and negative staining elements for the MET protein and is therefore suitable for use as a tissue control. The positive and negative staining elements should be examined to ascertain that all reagents are functioning properly. If these elements fail to demonstrate appropriate staining, any results with the test specimens included in the same staining run should be considered invalid.

   Gallbladder tissue demonstrates moderate staining of the membrane in epithelial cells and absence of staining within cells of stromal tissue. The pathologist determined whether the SLC slide was acceptable or unacceptable based on criteria presented in Table 3 above.

3. **Negative Reagent Control (NRC) Slide**
   The NRC slide is evaluated based on the level of non-specific staining (background). If the NRC slide is not acceptable, slide will not be evaluated, and the assay should be repeated.

4. **Patient Tissue Slide**
   MET IHC status will only be assigned if the H&E slide, the system-level control (SLC) slide, the NRC slide, and the VENTANA MET (SP44) antibody case slide (including background, morphology, and overall staining) are all acceptable. Patient specimens should have a minimum of approximately 100 viable tumor cells identified on the H&E in order to determine MET IHC status. Non-

squamous NSCLC tissues stained with the VENTANA MET (SP44) RxDx Assay are scored for percent tumor cell with strong membrane and/or cytoplasmic staining intensity. Non-squamous NSCLC tissue cases are considered positive if ≥ 50% of tumor cells (TC) demonstrate strong membranous and/or cytoplasmic MET (SP44) staining.

The scoring algorithm for the VENTANA MET (SP44) RxDx Assay is provided in the Table 5 below along with the staining intensities description. For detailed information on the Assay scoring and algorithm, refer to the device package insert and interpretation guide.

Table 5. VENTANA MET (SP44) RxDx Assay Scoring Algorithm for non-squamous NSCLC

MET IHC Status	Staining Description
Positive*	≥ 50% of tumor cells with strong membrane and/or cytoplasmic staining intensity (3+).
Negative*	< 50% of tumor cells with strong membrane and/or cytoplasmic staining intensity (3+)
Not Evaluable (N/E)	Interpretation is not possible, e.g., no tissue present, presence of staining artifacts or poor tissue quality

*Re-reading by Additional Pathologists for MET Scoring if borderline staining (%TC or intensity)

Re-reading by Additional Pathologists for MET Scoring: To decrease variability of MET results for cases with %TC near the threshold of 50% (40% to 60%) or with staining intensity near the strong versus moderate threshold due to reader variability, re-reading of slides that fall into these categories by a second pathologist is recommended. An initial case result with %TC between 40-60% or borderline strong versus moderate intensity by a pathologist should be reviewed by another independent pathologist and the reported results should be based on a consensus score.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is currently no alternative FDA-cleared or approved assays available for detection of MET protein in FFPE non-squamous non-small cell lung cancer tissue as an aid in identifying patients who may be eligible for treatment with EMRELIS™ (telisotuzumab vedotin-tllv).

VII. MARKETING HISTORY

The VENTANA MET (SP44) RxDx Assay has not been marketed in the United States or any other foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

VENTANA MET (SP44) RxDx Assay is intended for in vitro diagnostic (IVD) use only. As with any IVD test, the potential risks are associated with an incorrect test result or incorrect interpretation of results. Failure of the device to perform as expected or failure to correctly interpret test results may lead to improper patient management decisions.

For the specific adverse events that occurred in the EMRELIS™ clinical studies, please see the EMRELIS™ FDA approved package insert, which is available at Drugs@FDA.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Non-clinical studies were performed using the VENTANA MET (SP44) RxDx Assay to establish analytical performance of the device in NSCLC. These studies were performed using a BenchMark ULTRA instrument using the VSS software version 12.3 to 12.5.4 or BenchMark ULTRA PLUS instrument using the VSS software version 14.1. These studies were conducted to characterize the VENTANA MET (SP44) RxDx Assay, demonstrate the impact of pre-analytical variables on assay performance, verify precision and robustness of the assay, and establish assay stability. The study results detailed below establish sensitivity, specificity, precision, stability, reproducibility, and other performance characteristics of the device.

1. Analytical Sensitivity

a. Analytical sensitivity of the VENTANA MET (SP44) RxDx Assay was assessed by evaluating a commercial cohort of 100 unique NSCLC FFPE specimens (resection, core needle biopsy (CNB), and cell block [fine needle aspirate (FNA)]). The slides were read by one pathologist and were scored for the percentage of tumor cells with strong membranous and/or cytoplasmic staining intensity.

   Of the 100 cases, 91 cases had both membrane and cytoplasmic staining, 8 cases had cytoplasmic staining only, while one case had no staining. The specimens showed a percent tumor cell staining range from 0-95% and a staining intensity range of negative (0) to positive (3+). MET positive status was observed in 12% (12/100) of cases. MET negative status was observed in 88% (88/100) of cases. The results from this study are summarized below.

Table 6. Prevalence of MET in NSCLC stained with VENTANA MET (SP44) RxDx Assay

Sample Category	MET IHC % TC Bin (min. to max.)	Resection Samples n (%)	FNA Cell Block Samples n (%)	CNB Samples n (%)
Negative	0 to 49	45 (90.0%)	22 (88.0%)	21 (84.0%)
Positive	50 to 100	5 (10.0%)	3 (12.0%)	4 (16.0%)

2. Analytical Specificity

The antibody used in the VENTANA MET (SP44) RxDx Assay is a rabbit monoclonal antibody, clone SP44, produced against the carboxyl region of the human MET protein.

The following studies were conducted with MET (SP44) antibody to establish antibody specificity.

a. Western Blot Studies

Western Blot (WB) analysis was performed on whole cell lysates with varying expression levels of MET. The 6 cell lines were NCI-H441 (Lung Adenocarcinoma), NCI-H596 (Lung Adenosquamous Carcinoma), BC-3C (Bladder Carcinoma), HeLa (Cervix Epithelial Carcinoma), C-33A (Cervix Epithelial Carcinoma), and MET knockout (K/O) from HeLa (Cervix Epithelial Carcinoma). VENTANA MET (SP44) antibody reacted with a ~175kD band corresponding in size to the molecular weight (MW) of the MET precursor protein and a ~145kD band corresponding in size to the MW of the MET β chain in the MET-positive NCI-H596, which expresses high levels of MET protein by IHC staining (3+); NCI-H441 (3+); BC-3C (2.5+); and HeLa (2+) cell lines. MET (SP44) also detected a few additional protein products (40-55kD) that were likely MET protein fragments. Importantly, MET (SP44) did not detect any protein in the MET-negative C-33A cell line or in Hela cells following the knockout of the MET gene. Finally, the MET (SP44) antibody also reacted specifically with a 78 kD-fragment derived from purified recombinant MET (rMET) which includes the antibody immunogen.

b. Peptide Inhibition Study

The specificity of primary antibody binding to MET was assessed by pre-incubating the antibody with four different concentrations of the specific peptide containing the antibody binding epitope, or a non-specific peptide. The antibody was diluted 1:1 with either the peptide solutions under investigation or buffer with no peptide. One lot of antibody was used for this study. In the presence of high molar concentrations of this peptide, the MET (SP44) antibody was completely inhibited from binding to tissue expressing MET protein as determined by the absence of IHC staining. The non-specific peptide had no effect on MET staining.

c. Immunoreactivity

The purpose of this study was to assess the analytical specificity (Tour of Body and Tour of Tumor) including non-specific staining including background and cross-reactivity of VENTANA MET (SP44) antibody in non-neoplastic (TOB) and neoplastic tissue (TOT) samples. One lot each of VENTANA MET (SP44) RxDx Assay and Rabbit Monoclonal Negative Control Ig were used to stain slides containing tissue micro -arrays (TMA) and uni-blocks of non-neoplastic and neoplastic tissue. For the TOB and TOT TMAs and uni-blocks, there were 610 evaluable test samples. For the TOB and TOT, a positive case is defined as having the presence of any MET staining at any intensity. Of the evaluable test samples, 99.3% (606/610) had acceptable MET background staining. MET (SP44) off target nuclear staining was observed in four test samples out of the 610 evaluable samples (0.66%). MET (SP44) staining was observed in 94 non-neoplastic test samples out of 223 evaluable samples. Weak to moderate MET staining can occur in type II pneumocytes and the normal epithelium of bronchi and bronchioles in non-neoplastic lung tissue. MET (SP44) staining was observed in 291 neoplastic test samples out of 386 evaluable samples. Tables containing results for non-neoplastic tissues and results for neoplastic tissues are shown below.

Table 7. Specificity of VENTANA MET (SP44) RxDx Assay was Determined by Testing FFPE Non-neoplastic Tissues

Tissue	No. Positive/Total Cases	Tissue	No. Positive/Total Cases
Cerebrum	0/7	Esophagus [c]	3/4
Cerebellum	0/7	Stomach [g,h]	7/7
Adrenal gland	0/7	Small intestine [g]	5/7
Ovary	0/7	Colon [g]	5/6
Pancreas [a]	1/7	Liver [i]	2/7
Parathyroid gland	0/5	Salivary gland [j]	5/6
Pituitary gland	0/5	Kidney [k]	5/9
Testis	0/7	Prostate [c]	5/7
Thyroid [b]	3/7	Cervix [c]	3/5
Breast [c]	2/5	Skin [c]	2/5
Spleen	0/6	Mesothelium [l]	3/4
Tonsil [d]	5/6	Appendix [g]	3/3
Endometrium [c]	3/6	Bladder [m]	4/5
Skeletal muscle	0/6	Fallopian tube [c]	4/7
Nerve	0/5	Rectum [g]	3/4
Thymus [e]	0/6	Ureter [n]	2/2
Myeloid (bone marrow)	0/5	Lymph node (reactive)	0/1
Lung [f,g]	13/16	Placenta [o]	5/6
Heart	0/6	Spinal cord	0/2

[a] acinar cells (focal staining), [b] follicular cells, [c] epithelial cells (weak staining), [d] germinal center lymphocytes (weak staining), [e] epithelial cells (focal staining), [f] type 2 pneumocytes, [g] epithelial cells, [h] fundic glands, [i] focal hepatocyte staining, [j] serous glands and striated duct epithelium, [k] renal tubular epithelial cells, [l] mesothelial cells [m] urothelial cells, [n] urothelial cells (weak staining), [o] cytotrophoblastic and syncytiotrophoblastic cells

Table 8: Specificity of VENTANA MET (SP44) RxDx Assay of FFPE Neoplastic Tissues

Pathology	No. Positive/Total Cases
Adenoma, cortical (Adrenal gland)	0/1
Adrenocortical carcinoma (Adrenal gland)	0/1
Urothelial carcinoma (Bladder)	2/2
Fibroadenoma (Breast)	0/1
Osteosarcoma (Bone)	0/1
Chondrosarcoma (Bone)	0/1
Meningioma (Cerebellum)	0/2
Meningioma (Cerebrum)	1/1
Astrocytoma (Cerebrum)	0/1
Squamous cell carcinoma (Esophagus)	2/2
Adenocarcinoma (Stomach)	3/3
Adenoma (Small intestine)	1/1
Adenocarcinoma (Small intestine)	1/1
Adenoma (Colon)	1/1
Adenocarcinoma (Colon)	3/3
Adenocarcinoma (Rectum)	3/3
Clear cell carcinoma (Kidney)	2/2
Hepatocellular carcinoma (Liver)	2/4
Squamous cell carcinoma (Lung)	105/145
Adenocarcinoma (Lung)	96/116
Small cell carcinoma (Lung)	0/1
Adenosquamous carcinoma (Lung)	1/1
Adenocarcinoma in-situ (Lung)	12/13
Mucinous adenocarcinoma (Lung)	8/8
Papillary carcinoma (Lung)	5/6
Neuroendocrine tumor, typical carcinoid (Lung)	3/11
Neuroendocrine carcinoma (Lung)	5/5
Large cell carcinoma (Lung)	8/9
Large cell neuroendocrine carcinoma (Lung)	3/3
Pleomorphic carcinoma (Lung)	5/5
Mucoepidermoid carcinoma (Lung)	1/1
Hodgkin lymphoma (Lymph node)	0/1
B-cell lymphoma, NOS (Lymph node)	0/1
Anaplastic large cell lymphoma (Lymph node)	0/1
Adenocarcinoma (Oral cavity)	0/1
Squamous cell carcinoma (Oral cavity)	1/1
Nasopharyngeal carcinoma (Nasopharynx)	1/1
Granulosa cell tumor (Ovary)	0/1
Adenocarcinoma (Ovary)	1/1
Endometrioid adenocarcinoma (Ovary)	0/1
Adenocarcinoma (Pancreas)	0/1
Adenocarcinoma (Prostate)	0/2
Pleomorphic adenoma (Salivary gland)	0/1
Adenoid cystic carcinoma (Salivary gland)	1/1

Pathology	No. Positive/Total Cases
Squamous cell carcinoma (Skin)	1/1
Melanoma (Nasal cavity)	1/1
Seminoma (Testis)	0/2
Adenoma (Thyroid)	2/3
Follicular carcinoma (Thyroid)	1/1
Papillary carcinoma (Thyroid)	1/1
Squamous cell carcinoma (Cervix)	2/2
Adenocarcinoma (Endometrium)	2/2
Metastatic Colon adenocarcinoma (Liver)	1/1
Metastatic Breast ductal carcinoma (Lymph Node)	1/1
Metastatic Colon signet ring cell carcinoma (Ovary)	1/1
Metastatic Esophageal squamous cell carcinoma (Lymph Node)	1/1

3. Precision

Precision of the VENTANA MET (SP44) RxDx Assay on BenchMark ULTRA and BenchMark ULTRA PLUS was evaluated follows: Intermediate Precision and Repeatability Studies and Reader (Pathologist) Precision.

a. Intermediate Precision and Repeatability Studies

i. Between MET (SP44) Lot, Between Detection Kit Lot, Day, and ULTRA Instrument Intermediate Precision and Within Run Repeatability

Twenty-four NSCLC tissue cases (13 MET positive and 11 MET negative, including 5 borderline samples) that encompassed MET IHC staining status range of positive and negative were used in this study. This study was performed using the following design factors on a BenchMark ULTRA instrument:

- Three antibody lots of VENTANA MET (SP44) RxDx Assay
- Three lots of OptiView DAB IHC Detection Kits
- Three BenchMark ULTRA instruments
- Across three days
- One pathologist reader
- 2 replicates per condition
- Across all intermediate precision conditions (within-staining run)

All slides were blinded and randomized and evaluated using the VENTANA MET (SP44) RxDx Assay scoring algorithm specified in Table 5, above. Each case had 18 results and a majority MET (SP44) status was assigned based on 18 results. For each case, median %TC and range of %TC of 18 results were calculated. In addition, percent positive (%TC ≥50%, "Eligible" with regard to MET therapy) results were calculated. Results are summarized in the tables below.

Table 9. Median and Range of %TC for Samples in the Intermediate Precision Study (ULTRA)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results %, (n/N)	Agreement	
					Percent Agreement with Majority MET Status %, (n/N)	95% CI*
1	Negative	1	1, 2	0 (0/18)	100.0 (18/18)	82.4, 100.0
2	Negative	10	5, 15	0 (0/18)	100.0 (18/18)	82.4, 100.0
3	Negative	15	10, 30	0 (0/18)	100.0 (18/18)	82.4, 100.0
4	Negative	20	15, 30	0 (0/18)	100.0 (18/18)	82.4, 100.0
5	Negative	25	20, 40	0 (0/18)	100.0 (18/18)	82.4, 100.0
6	Negative	30	10, 45	0 (0/18)	100.0 (18/18)	82.4, 100.0
7	Negative	30	20, 35	0 (0/16)	100.0 (16/16)	80.6, 100.0
8	Negative	30	25, 45	0 (0/18)	100.0 (18/18)	82.4, 100.0
9	Negative	35	30, 40	0 (0/18)	100.0 (18/18)	82.4, 100.0
10	Negative	45	40, 60	27.8 (5/18)	72.2 (13/18)	49.1, 87.5
11	Negative	45	40, 50	5.6 (1/18)	94.4 (17/18)	74.2, 99.0
12	Positive	55	50, 60	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
13	Positive	55	50, 60	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
14	Positive	55	45, 65	88.9 (16/18)	88.9 (16/18)	67.2, 96.9
15	Positive	65	40, 70	83.3 (15/18)	83.3 (15/18)	60.8, 94.2
16	Positive	70	50, 75	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
17	Positive	70	65, 75	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
18	Positive	70	50, 75	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
19	Positive	75	30, 85	88.9 (16/18)	88.8 (16/18)	67.2, 96.9
20	Positive	80	40, 85	94.4 (17/18)	94.4 (17/18)	74.2, 99.0
21	Positive	85	65, 90	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
22	Positive	90	55, 95	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
23	Positive	90	80, 90	100.0 (18/18)	100.0 (18/18)	82.4, 100.0
24	Positive	95	80, 100	100.0 (18/18)	100.0 (18/18)	82.4, 100.0

*2-sided 95% CIs were calculated using Wilson score method.

Table 10. Precision Components for Samples in the Intermediate Precision Study (ULTRA)

				Standard Deviation					
Case ID	**Majority Call MET Result**	**Number of Results**	**Median %TC**	**Within Run**	**Between Day**	**Between Antibody Lot**	**Between Detection Kit**	**Between Instrument**	**Total**
1	Negative	18	1	0.24	0.55	0	0	0	0.6
2	Negative	18	10	1.18	5.71	0	0	0	5.83
3	Negative	18	15	4.08	4.33	0	0	0	5.95
4	Negative	18	20	2.36	2.36	4.08	0	4.08	6.67
5	Negative	18	25	5.14	2.36	2.89	0	3.82	7.41
6	Negative	18	30	6.97	0	3.91	4.41	0	9.13
7	Negative	16	30	2.67	4.63	0	0	0	5.35
8	Negative	18	30	7.17	0	6.24	5.71	3.73	11.7
9	Negative	18	35	3.12	0	0	0	0	3.12
10	Negative	18	45	2.89	7.77	0	0	0	8.29
11	Negative	18	45	1.18	0	2.76	1.18	2.76	4.25
12	Positive	18	55	1.67	0.83	0	0	0	1.86
13	Positive	18	55	1.18	2.36	3.54	2.89	2.89	6.01
14	Positive	18	55	2.64	2.2	7.07	0	4.08	8.86
15	Positive	18	65	7.82	6.82	0	8.66	0	13.51
16	Positive	18	70	6.87	0	4	0	0	7.95
17	Positive	18	70	2.04	0	3.54	0	3.54	5.4
18	Positive	18	70	5.53	0	9.32	0	0	10.83
19	Positive	18	75	5.77	21.26	0	0	0	22.03
20	Positive	18	80	6.97	0	0	15.63	0.83	17.14
21	Positive	18	85	5	0	0	5.2	0	7.22
22	Positive	18	90	10.21	6.12	0	0	0	11.9
23	Positive	18	90	1.18	0	3.73	4.93	0	6.29
24	Positive	18	95	3.91	5.07	0	0	0	6.4

In addition, a qualitative analysis of different components was performed. Results are summarized in the table below.

Table 11. Intermediate Precision of VENTANA MET (SP44) RxDx Assay

Repeatability/ Precision	**Agreement**			
	Type	**n/N**	**%**	**95% CI***
Between- Antibody Lots	PPA	76/78	97.4	91.7, 100.0
	NPA	64/64	100.0	94.3, 100.0
	OPA	140/142	98.6	95.7, 100.0
Between-Instruments (BenchMark ULTRA)	PPA	78/78	100.0	95.3, 100.0
	NPA	65/65	100.0	94.4, 100.0
	OPA	143/143	100.0	97.4, 100.0

Repeatability/ Precision	Agreement			
	Type	n/N	%	95% CI*
Between-Detection Kits	PPA	75/78	96.2	90.3, 100.0
	NPA	61/65	93.8	83.3, 100.0
	OPA	136/143	95.1	89.5, 99.3
Between-Day	PPA	75/78	96.2	89.7, 100.0
	NPA	63/65	96.9	89.8, 100.0
	OPA	138/143	96.5	91.7, 100.0
Within-Run	PPA	230/232	99.1	97.9, 100.0
	NPA	196/198	99.0	97.5, 100.0
	OPA	426/430	99.1	98.1, 99.8

*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples except that the CIs for 100% PPA, NPA and OPA were calculated using Wilson score method.

ii. Between Day and Between ULTRA PLUS Instrument Intermediate Precision and Within Run Repeatability

Twenty-eight unique NSCLC tissue cases (12 MET positive and 16 MET negative) that encompassed the MET IHC staining status range of positive and negative, using the following design factors on a BenchMark ULTRA PLUS:

- Three BenchMark ULTRA PLUS instruments
- Across three days
- Across all intermediate precision conditions (within-staining run)
- One pathologist reader
- 2 replicates per condition

Table 12. Median and Range of %TC for Samples in the Intermediate Precision Study (ULTRA PLUS)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results % (n/N)	Agreement	
					Percent Agreement with Majority MET Status % (n/N)	95% CI*
1	Negative	0	0, 1	0	100.0 (10/10)	72.2, 100.0
2	Negative	0	0, 0	0	100.0 (10/10)	72.2, 100.0
3	Negative	0	0, 0	0	100.0 (10/10)	72.2, 100.0
4	Negative	0	0, 1	0	100.0 (10/10)	72.2, 100.0
5	Negative	0	0, 1	0	100.0 (10/10)	72.2, 100.0
6	Negative	0	0, 0	0	100.0 (10/10)	72.2, 100.0
7	Negative	0.5	0, 2	0	100.0 (10/10)	72.2, 100.0
8	Negative	1	0, 1	0	100.0 (10/10)	72.2, 100.0
9	Negative	2	1, 5	0	100.0 (10/10)	72.2, 100.0
10	Negative	5	1, 10	0	100.0 (10/10)	72.2, 100.0
11	Negative	5	2, 10	0	100.0 (10/10)	72.2, 100.0

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results % (n/N)	Agreement	
					Percent Agreement with Majority MET Status % (n/N)	95% CI*
12	Negative	17.5	10, 20	0	100.0 (10/10)	72.2, 100.0
13	Negative	17.5	5, 40	0	100.0 (10/10)	72.2, 100.0
14	Negative	17.5	15, 30	0	100.0 (10/10)	72.2, 100.0
15	Negative	20	20, 20	0	100.0 (10/10)	72.2, 100.0
16	Negative	25	25, 35	0	100.0 (10/10)	72.2, 100.0
17	Negative	30	25, 35	0	100.0 (10/10)	72.2, 100.0
18	Negative	35	30, 40	0	100.0 (10/10)	72.2, 100.0
19	Negative	35	25, 45	0	100.0 (10/10)	72.2, 100.0
20	Positive	70	50, 95	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
21	Positive	80	70, 85	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
22	Positive	80	70, 85	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
23	Positive	80	70, 90	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
24	Positive	85	75, 90	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
25	Positive	87.5	70, 95	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
26	Positive	96.5	75, 100	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
27	Positive	98	90, 100	100.0 (10/10)	100.0 (10/10)	72.2, 100.0
28	Positive	100	70, 100	100.0 (10/10)	100.0 (10/10)	72.2, 100.0

*2-sided 95% CIs were calculated using Wilson score method.

Table 13. Precision Components for Samples in the Intermediate Precision Study (ULTRA PLUS)

				Standard Deviation			
Case ID	Majority Call MET Result	Number of Results	Median %TC	Within Run	Between Day	Between Instrument	Total
1	Negative	10	0.0	0.32	0.00	0.18	0.37
2	Negative	10	0.0	0.00	0.00	0.00	0.00
3	Negative	10	0.0	0.00	0.00	0.00	0.00
4	Negative	10	0.0	0.32	0.18	0.00	0.37
5	Negative	10	0.0	0.32	0.00	0.18	0.37
6	Negative	10	0.0	0.00	0.00	0.00	0.00
7	Negative	10	0.5	0.45	0.39	0.58	0.83
8	Negative	10	1.0	0.45	0.00	0.39	0.59
9	Negative	10	2.0	0.00	0.58	2.00	2.08
10	Negative	10	5.0	2.53	4.14	0.00	4.85
11	Negative	10	5.0	0.95	2.81	1.80	3.47
12	Positive	10	17.5	3.16	1.83	5.00	6.19
13	Positive	10	17.5	11.51	0.00	0.00	11.51

				Standard Deviation			
Case ID	**Majority Call MET Result**	**Number of Results**	**Median %TC**	**Within Run**	**Between Day**	**Between Instrument**	**Total**
14	Positive	10	17.5	5.70	0.00	2.96	6.42
15	Positive	10	20.0	0.00	0.00	0.00	0.00
16	Positive	10	25.0	4.47	0.00	0.00	4.47
17	Positive	10	30.0	4.18	0.00	0.00	4.18
18	Positive	10	35.0	1.58	0.91	4.79	5.12
19	Positive	10	35.0	3.87	5.66	0.00	6.86
20	Positive	10	70.0	11.07	0.00	6.86	13.02
21	Positive	10	80.0	4.47	3.87	0.00	5.92
22	Positive	10	80.0	3.16	1.83	7.07	7.96
23	Positive	10	80.0	4.47	0.00	4.83	6.58
24	Positive	10	85.0	4.74	1.83	0.00	5.08

Table 14. Intermediate Precision of VENTANA MET (SP44) RxDx Assay

Repeatability/ Precision	**Agreement**			
	Type	**n/N**	**%**	**95% CI***
Between-Instruments (BenchMark ULTRA PLUS)	PPA	54/54	100.0	93.4, 100.0
	NPA	114/114	100.0	96.7, 100.0
	OPA	168/168	100.0	97.8, 100.0
Between-Day	PPA	54/54	100.0	93.4, 100.0
	NPA	114/114	100.0	96.7, 100.0
	OPA	168/168	100.0	97.8, 100.0
Within-Run	PPA	45/45	100.0	92.1, 100.0
	NPA	95/95	100.0	96.1, 100.0
	OPA	140/140	100.0	97.3, 100.0

*2-sided 95% confidence intervals were calculated using the Wilson score method.

iii. <u>BenchMark ULTRA and BenchMark ULTRA PLUS Between Day, and Between Platform Precision</u>

Twenty-eight unique NSCLC tissue cases (16 MET positive, 12 MET negative, including 4 borderline samples) that encompassed the MET IHC staining status range of positive and negative, using the following design factors on a BenchMark ULTRA and BenchMark ULTRA PLUS.

- Across five days
- One pathologist reader
- 2 replicates per condition

Table 15. Median and Range of %TC for Samples in the Intermediate Precision Study (ULTRA & ULTRA PLUS)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results %, (n/N)	Agreement	
					Percent Agreement with Majority MET Status %, (n/N)	95% CI*
1	Negative	0	0, 0	0	100.0 (20/20)	83.9, 100.0
2	Negative	0	0, 0	0	100.0 (20/20)	83.9, 100.0
3	Negative	0	0, 0	0	100.0 (20/20)	83.9, 100.0
4	Negative	0	0, 1	0	100.0 (20/20)	83.9, 100.0
5	Negative	1	0, 1	0	100.0 (20/20)	83.9, 100.0
6	Negative	1	1, 2	0	100.0 (20/20)	83.9, 100.0
7	Negative	5	0, 10	0	100.0 (20/20)	83.9, 100.0
8	Negative	5	0, 20	0	100.0 (19/19)	83.2, 100.0
9	Negative	5	0, 20	0	100.0 (20/20)	83.9, 100.0
10	Negative	15	10, 20	0	100.0 (20/20)	83.9, 100.0
11	Negative	15	10, 20	0	100.0 (20/20)	83.9, 100.0
12	Negative	20	10, 40	0	100.0 (18/18)	82.4, 100.0
13	Negative	20	0, 20	0	100.0 (20/20)	83.9, 100.0
14	Negative	30	10, 65	15.8 (3/19)	84.2 (16/19)	62.4, 94.5
15	Negative	40	25, 55	5.0 (1/20)	95.0 (19/20)	76.4, 99.1
16	Positive	50	50, 60	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
17	Positive	55	15, 75	85.0 (17/20)	85.0 (17/20)	64.0, 94.8
18	Positive	60	20, 75	85.0 (17/20)	85.0 (17/20)	64.0, 94.8
19	Positive	65	55, 80	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
20	Positive	65	10, 90	85.0 (17/20)	85.0 (17/20)	64.0, 94.8
21	Positive	70	60, 95	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
22	Positive	72.5	30, 90	95.0 (19/20)	95.0 (19/20)	76.4, 99.1
23	Positive	87.5	75, 95	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
24	Positive	90	75, 100	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
25	Positive	95	50, 99	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
26	Positive	95	80, 100	100.0 (20/20)	100.0 (20/20)	83.9, 100.0
27	Positive	98	10, 99	95.0 (19/20)	95.0 (19/20)	76.4, 99.1
28	Positive	100	100, 100	100.0 (20/20)	100.0 (20/20)	83.9, 100.0

*95% CIs were calculated using Wilson score method.

Table 16. Precision Components for Samples in the Intermediate Precision Study (ULTRA & ULTRA PLUS)

					Standard Deviation			
Case ID	**Majority Call MET Result**	**Number of Results**	**Median %TC**	**Range %TC (Min to Max)**	**Within Run**	**Between Day**	**Between Platform**	**Total**
1	Negative	20	0	0, 0	0	0	0	0
2	Negative	20	0	0, 0	0	0	0	0
3	Negative	20	0	0, 0	0	0	0	0
4	Negative	20	0	0, 1	0.22	0	0	0.22
5	Negative	20	1	0, 1	0.32	0.21	0.37	0.53
6	Negative	20	1	1, 2	0.22	0	0	0.22
7	Negative	20	5	0, 10	2.55	0	2.19	3.36
8	Negative	19	5	0, 20	4.29	0.31	0.66	4.35
9	Negative	20	5	0, 20	3.04	2.97	5.7	7.11
10	Negative	20	15	10, 20	2.24	1.94	1.12	3.16
11	Negative	20	15	10, 20	2.5	0	2.5	3.54
12	Negative	18	20	10, 40	5.45	0	2.89	6.17
13	Negative	20	20	0, 20	4.74	0	2.02	5.15
14	Negative	19	30	10, 65	7.82	0	16.65	18.4
15	Negative	20	40	25, 55	4.33	0	5.56	7.05
16	Positive	20	50	50, 60	2.96	0	2.68	3.99
17	Positive	20	55	15, 75	7.98	6.44	14.72	17.94
18	Positive	20	60	20, 75	5.36	10.78	13.03	17.74
19	Positive	20	65	55, 80	6.71	0	6.3	9.2
20	Positive	20	65	10, 90	12.65	0	16.59	20.86
21	Positive	20	70	60, 95	6.8	1.37	4.26	8.14
22	Positive	20	72.5	30, 90	8.94	13.28	8.86	18.3
23	Positive	20	87.5	75, 95	5.81	0	3.83	6.96
24	Positive	20	90	75, 100	7.17	0	3.61	8.03
25	Positive	20	95	50, 99	5.2	0	10.87	12.05
26	Positive	20	95	80, 100	4.28	1.63	0	4.58
27	Positive	20	98	10, 99	20.12	2.74	0	20.31
28	Positive	20	100	100, 100	0	0	0	0

Table 17. Intermediate Precision of VENTANA MET (SP44) RxDx Assay

Repeatability/ Precision	Agreement			
	Type	n/N	%	95% CI*
Between-Platform	PPA	249/260	95.8	92.1, 100.0
	NPA	292/296	98.6	96.3, 100.0
	OPA	541/556	97.3	95.1, 99.1
Between-Day (ULTRA)	PPA	120/130	92.3	85.5, 98.0
	NPA	144/147	98.0	94.7, 100.0
	OPA	264/277	95.3	91.8, 98.2
Between-Day (ULTRA PLUS)	PPA	129/130	99.2	97.7, 100.0
	NPA	148/149	99.3	97.8, 100.0
	OPA	277/279	99.3	98.2, 100.0

*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples.

iv. Between Day Intermediate Precision – Biopsy Sample Type

Twenty unique NSCLC biopsy cases (9 MET positive, 11 MET negative, including 3 borderline samples) that encompassed the MET IHC staining status range of positive and negative, using the following design factors on a BenchMark ULTRA.

- Across three days
- One pathologist reader
- 2 replicates per condition

Table 18. Median and Range of %TC for Samples in the Between Day Intermediate Precision Study for Biopsy Sample Types

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results, % (n/N)	Agreement	
					Percent Agreement with Majority MET Status, % (n/N)	95% CI*
1	Negative	0.0	(0, 0)	0	100.0 (6/6)	61.0, 100.0
2	Negative	0.0	(0, 1)	0	100.0 (6/6)	61.0, 100.0
3	Negative	0.0	(0, 0)	0	100.0 (6/6)	61.0, 100.0
4	Negative	1.0	(1, 2)	0	100.0 (6/6)	61.0, 100.0
5	Negative	1.5	(0, 5)	0	100.0 (6/6)	61.0, 100.0
6	Negative	5.0	(2, 5)	0	100.0 (6/6)	61.0, 100.0
7	Negative	5.0	(5, 10)	0	100.0 (6/6)	61.0, 100.0
8	Negative	5.0	(5, 5)	0	100.0 (6/6)	61.0, 100.0
9	Negative	10.0	(2, 25)	0	100.0 (6/6)	61.0, 100.0
10	Negative	15.0	(10, 25)	0	100.0 (6/6)	61.0, 100.0
11	Negative	17.5	(10, 25)	0	100.0 (6/6)	61.0, 100.0

Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results, % (n/N)	Agreement	
					Percent Agreement with Majority MET Status, % (n/N)	95% CI*
12	Negative	20.0	(15, 20)	0	100.0 (6/6)	61.0, 100.0
13	Negative	35.0	(30, 60)	16.7 (1/6)	83.3, (5/6)	43.6, 97.0
14	Positive	55.0	(50, 65)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
15	Positive	55.0	(15, 75)	66.7 (4/6)	66.7 (4/6)	30.0, 90.3
16	Positive	60.0	(55, 75)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
17	Positive	75.0	(65, 75)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
18	Positive	80.0	(75, 85)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
19	Positive	82.5	(65, 90)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
20	Positive	92.5	(50, 100)	100.0 (6/6)	100.0 (6/6)	61.0, 100.0

*95% CIs were calculated using Wilson score method.

Table 19. Components for Samples in Between Day Intermediate Precision Study for Biopsy Sample Types

				Standard Deviation	
Case ID	**Majority MET (SP44) Status**	**Number of Results**	**Median %TC**	**Between Day**	**Total**
1	Negative	6	0.0	0.00	0.00
2	Negative	6	0.0	0.00	0.41
3	Negative	6	0.0	0.00	0.00
4	Negative	6	1.0	0.00	0.58
5	Negative	6	1.5	2.55	2.58
6	Negative	6	5.0	1.73	1.73
7	Negative	6	5.0	0.00	2.89
8	Negative	6	5.0	0.00	0.00
9	Negative	6	10.0	10.23	10.43
10	Negative	6	15.0	2.89	6.77
11	Negative	6	17.5	0.00	6.45
12	Negative	6	20.0	0.00	2.04
13	Negative	6	35.0	9.90	11.81
14	Positive	6	55.0	6.45	6.77
15	Positive	6	55.0	20.10	22.91
16	Positive	6	60.0	10.41	10.41
17	Positive	6	75.0	0.00	4.08
18	Positive	6	80.0	3.54	4.08
19	Positive	6	82.5	7.64	9.57
20	Positive	6	92.5	5.00	19.04

Table 20. VENTANA MET (SP44) RxDx Assay Between Day Biopsy Intermediate Precision

Agreement Rate	n/N (Sample)	Percentage (95% Confidence Interval*)
PPA	40/42	95.2 (85.2, 100.0)
NPA	77/78	98.7 (95.8, 100.0)
OPA	117/120	97.5 (93.3, 100.0)

*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples.

1. Between Day Intermediate Precision - Cell Block Sample Type

   Twenty-one unique NSCLC cell block (FNA) cases (10 MET positive, 11 MET negative) that encompassed the MET IHC staining status range of positive and negative, using the following design factor on a BenchMark ULTRA.

- Across three days

Sixteen unique NSCLC cell block (pleural effusion) (2 MET positive, 14 MET negative, including 1 borderline sample) cases that encompassed the MET IHC staining status range of positive and negative, using the following design factor on a BenchMark ULTRA.

- Across three days

Table 21. Median and Range of %TC for Samples in the Between Day Intermediate Precision Study for Cell Block Samples

Cell Block Type	Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results, % (n/N)	Agreement	
						Percent Agreement with Majority MET Status, % (n/N)	95% CI*
FNA	1	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	2	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	3	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	4	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	5	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	6	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
FNA	7	Negative	1.5	1, 2	0	100.0 (6/6)	61.0, 100.0
FNA	8	Negative	10.0	1, 15	0	100.0 (6/6)	61.0, 100.0
FNA	9	Negative	10.0	10, 15	0	100.0 (6/6)	61.0, 100.0
FNA	10	Negative	15.0	5, 20	0	100.0 (6/6)	61.0, 100.0
FNA	11	Negative	25.0	20, 30	0	100.0 (6/6)	61.0, 100.0
FNA	12	Negative	30.0	30, 40	0	100.0 (6/6)	61.0, 100.0
FNA	13	Positive	72.5	70, 75	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	14	Positive	75.0	60, 80	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	15	Positive	85.0	85, 90	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	16	Positive	85.0	80, 85	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	17	Positive	87.5	85, 90	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	18	Positive	95.0	95, 95	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	19	Positive	95.0	90, 95	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	20	Positive	95.0	95, 95	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
FNA	21	Positive	95.0	90, 95	100.0 (6/6)	100.0 (6/6)	61.0, 100.0
Pleural effusion	22	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	23	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	24	Negative	0.0	0, 0	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	25	Negative	1.0	1, 2	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	26	Negative	1.0	1, 1	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	27	Negative	1.5	1, 2	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	28	Negative	2.0	2, 5	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	29	Negative	5.0	2, 10	0	100.0 (6/6)	61.0, 100.0

Cell Block Type	Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong Tumor Cell (Min., Max.)	Percent Positive Results, % (n/N)	Agreement	
						Percent Agreement with Majority MET Status, % (n/N)	95% CI*
Pleural effusion	30	Negative	10.0	10, 20	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	31	Negative	15.0	10, 20	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	32	Negative	17.5	15, 20	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	33	Negative	20.0	15, 20	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	34	Negative	37.5	35, 40	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	35	Negative	45.0	40, 45	0	100.0 (6/6)	61.0, 100.0
Pleural effusion	36	Positive	75.0	65, 75	100.0 (5/5)	100.0 (5/5)	56.6, 100.0
Pleural effusion	37	Positive	95.0	95, 95	100.0 (6/6)	100.0 (6/6)	61.0, 100.0

*2-sided 95% confidence intervals were calculated using the Wilson score method.

Table 22. Precision Components for Samples in Between Day Intermediate Precision Study for Cell Block Samples

					Standard Deviation	
Cell Block Type	Case ID	Majority MET (SP44) Status	Number of Results	Median %TC	Between Day	Total
FNA	1	Negative	6	0.0	0.00	0.00
FNA	2	Negative	6	0.0	0.00	0.00
FNA	3	Negative	6	0.0	0.00	0.00
FNA	4	Negative	6	0.0	0.00	0.00
FNA	5	Negative	6	0.0	0.00	0.00
FNA	6	Negative	6	0.0	0.00	0.00
FNA	7	Negative	6	1.5	0.41	0.58
FNA	8	Negative	6	10.0	4.96	5.97
FNA	9	Negative	6	10.0	0.00	2.89
FNA	10	Negative	6	15.0	5.40	7.07
FNA	11	Negative	6	25.0	1.44	3.23
FNA	12	Negative	6	30.0	0.00	4.56
FNA	13	Positive	6	72.5	2.04	2.89
FNA	14	Positive	6	75.0	0.00	8.42
FNA	15	Positive	6	85.0	2.89	2.89
FNA	16	Positive	6	85.0	2.89	2.89
FNA	17	Positive	6	87.5	2.04	2.89
FNA	18	Positive	6	95.0	0.00	0.00
FNA	19	Positive	6	95.0	2.89	2.89
FNA	20	Positive	6	95.0	0.00	0.00
FNA	21	Positive	6	95.0	2.89	2.89

					Standard Deviation	
Cell Block Type	**Case ID**	**Majority MET (SP44) Status**	**Number of Results**	**Median %TC**	**Between Day**	**Total**
Pleural effusion	22	Negative	6	0.0	0.00	0.00
Pleural effusion	23	Negative	6	0.0	0.00	0.00
Pleural effusion	24	Negative	6	0.0	0.00	0.00
Pleural effusion	25	Negative	6	1.0	0.58	0.58
Pleural effusion	26	Negative	6	1.0	0.00	0.00
Pleural effusion	27	Negative	6	1.5	0.41	0.58
Pleural effusion	28	Negative	6	2.0	0.00	1.22
Pleural effusion	29	Negative	6	5.0	1.12	2.63
Pleural effusion	30	Negative	6	10.0	0.00	4.56
Pleural effusion	31	Negative	6	15.0	3.54	4.08
Pleural effusion	32	Negative	6	17.5	2.04	2.89
Pleural effusion	33	Negative	6	20.0	0.00	2.89
Pleural effusion	34	Negative	6	37.5	2.04	2.89
Pleural effusion	35	Negative	6	45.0	0.00	2.89
Pleural effusion	36	Positive	5	75.0	5.77	5.77
Pleural effusion	37	Positive	6	95.0	0.00	0.00

Table 23. VENTANA MET (SP44) RxDx Assay Between Day Biopsy Intermediate Precision for Cell Block Samples

Precision	Agreement Rate	n/N (Sample)	Percentage (95% Confidence Interval*)
Between Day - FNA	PPA	54/54	100.0 (93.4, 100.0)
	NPA	72/72	100.0 (94.9, 100.0)
	OPA	126/126	100.0 (97.0, 100.0)
Between Day – Pleural Effusion	PPA	11/11	100.0 (74.1, 100.0)
	NPA	84/84	100.0 (95.6, 100.0)
	OPA	95/95	100.0 (96.1, 100.0)

*2-sided 95% confidence intervals were calculated using the Wilson score method.

Results from above studies (4.a.i. – 4.a.v.) are summarized in the table below.

Table 24. Summary of VENTANA MET (SP44) RxDx Assay Intermediate Precision and Repeatability

Repeatability/ Precision	Agreement		
	Type	n/N	Percentage (95% Confidence Interval)
Between-Antibody Lots	PPA	76/78	97.4% (91.7, 100.0)
	NPA	64/64	100.0% (94.3, 100.0)
	OPA	140/142	98.6% (95.7, 100.0)
Between-Detection Kit Lots	PPA	75/78	96.2% (90.3, 100.0)
	NPA	61/65	93.8% (83.3, 100.0)
	OPA	136/143	95.1% (89.5, 99.3)
Between- Instruments (BenchMark ULTRA)	PPA	78/78	100.0% (95.3, 100.0)
	NPA	65/65	100.0% (94.4, 100.0)
	OPA	143/143	100.0% (97.4, 100.0)
Between-3 non-consecutive Day (BenchMark ULTRA)	PPA	75/78	96.2% (89.7, 100.0)
	NPA	63/65	96.9% (89.8, 100.0)
	OPA	138/143	96.5% (91.7, 100.0)
Within-Run (BenchMark ULTRA)	PPA	230/232	99.1 (97.9, 100.0)
	NPA	196/198	99.0 (97.5, 100.0)
	OPA	426/430	99.1 (98.1, 99.8)
Between- Instruments (BenchMark ULTRA PLUS)	PPA	54/54	100.0% (93.4, 100.0)
	NPA	114/114	100.0% (96.7, 100.0)
	OPA	168/168	100.0% (97.8, 100.0)
Between-3 non-consecutive Day (BenchMark ULTRA PLUS)	PPA	54/54	100.0% (93.4, 100.0)
	NPA	114/114	100.0% (96.7, 100.0)
	OPA	168/168	100.0% (97.8, 100.0)
Within-Run (BenchMark ULTRA PLUS)	PPA	45/45	100.0% (92.1, 100.0)
	NPA	95/95	100.0% (96.1, 100.0)
	OPA	140/140	100.0% (97.3, 100.0)
Between-5 non-consecutive Day (BenchMark ULTRA)	PPA	120/130	92.3% (85.5, 98.0)
	NPA	144/147	98.0% (94.7, 100.0)
	OPA	264/277	95.3% (91.8, 98.2)
Between-5 non-consecutive Day (BenchMark ULTRA PLUS)	PPA	129/130	99.2% (97.7, 100.0)
	NPA	148/149	99.3% (97.8, 100.0)
	OPA	277/279	99.3% (98.2, 100.0)
Between-Platform	PPA	249/260	95.8% (92.1, 100.0)
	NPA	292/296	98.6% (96.3, 100.0)
	OPA	541/556	97.3% (95.1, 99.1)
Between-Day – Biopsy (BenchMark ULTRA)	PPA	40/42	95.2% (85.2, 100.0)
	NPA	77/78	98.7% (95.8, 100.0)
	OPA	117/120	97.5% (93.3, 100.0)
Between Day – Cell Block; FNA (BenchMark ULTRA)	PPA	54/54	100.0% (93.4, 100.0)
	NPA	72/72	100.0% (94.9, 100.0)
	OPA	126/126	100.0% (97.0, 100.0)

Repeatability/ Precision	Agreement		
	Type	n/N	Percentage (95% Confidence Interval)
Between Day – Cell Block; Pleural Effusion (BenchMark ULTRA)	PPA	11/11	100.0% (74.1, 100.0)
	NPA	84/84	100.0% (95.6, 100.0)
	OPA	95/95	100.0% (96.1, 100.0)

b. Reader Precision

i. Between and Within Reader Precision

In the Reader Precision study for VENTANA MET (SP44) RxDx Assay, Within-Reader and Between-Reader components of precision for NSCLC tissue reads were evaluated. The study included 100 unique NSCLC specimens (50 MET positive and 50 MET negative, including 12 borderline samples) that were stained with VENTANA MET (SP44) RxDx Assay. Specimens were blinded and randomized prior to evaluation for MET status using the VENTANA MET (SP44) RxDx Assay scoring algorithm specified in Table 5, above. The study included three readers (pathologists). Readers scored all specimens twice, with a minimum of two-week wash-out period between reads. Each case had 6 reads (2 reads by each of three readers). Variability of %TC values for 100 cases was evaluated and the following precision components were calculated: within-reader, between-reader, and total. Data of the Reader Precision study is presented in Table 25, below.

Table 25. Precision Components for Samples in Reader Precision of VENTANA MET (SP44) RxDx Assay

					Standard Deviation			
Sample Category	MET IHC %TC Bin (min. to max.)	n of Samples	n of reads	Range of Median %TC	Within Reader	Between Reader	Total	Percent Positive Results, % (n/N)
Negative	0 to 39	47	282	0.0 - 37.5	5.02	9.8	11.01	0.7 (2/282)
Borderline Negative	40 to 49	4	24	40.0 - 47.5	1.84	10.05	10.21	20.8 (5/24)
Borderline Positive	50 to 60	8	48	50.0 - 60.0	7.37	3.5	8.16	93.8 (45/48)
Positive	61 to 100	41	246	65.0 - 99.5	6.8	10.27	12.32	98.0 (241/246)

In addition, within-reader and between-reader precision was determined with average positive agreement (APA), average negative agreement (ANA), and overall percent agreement (OPA) across all observations. This data is summarized in Table 26, below.

Table 26. Within-Reader and Between Reader Precision of VENTANA MET (SP44) RxDx Assay

Precision	Agreement			
	Type	n/N	%	95% CI*
Within-Reader	APA	288/293	98.3	91.3, 98.2
	ANA	302/307	98.4	91.9, 98.4
	OPA	295/300	98.3	92.0, 98.0
Between-Reader	APA	278/292	95.2	96.6, 99.6
	ANA	294/308	95.5	96.6, 99.7
	OPA	286/300	95.3	96.7, 99.7

Average Positive Agreement (APA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA)
*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples.

ii. Between and Within Reader Precision in Cell Block Sample Types

In the Reader Precision study for VENTANA MET (SP44) RxDx Assay, Within-Reader and Between-Reader components of precision for NSCLC cell block reads were evaluated. The study included 40 unique NSCLC cell block cases (38 FNA and 2 pleural effusion; 20 MET positive, 20 MET negative, including 3 borderline samples) that were stained with VENTANA MET (SP44) RxDx Assay. Specimens were blinded and randomized prior to evaluation for MET status using the VENTANA MET (SP44) RxDx Assay scoring algorithm specified in Table 5, above. The study included four readers (pathologists). Readers scored all specimens twice, with a minimum of two-week wash-out period between reads. Each case had 8 reads (2 reads by each of four readers). Variability of %TC values for 40 cases was evaluated and the following precision components were calculated: within-reader, between-reader, and total. Data of the Reader Precision study is presented in Table 27, below.

Table 27. Precision Components for Samples in Reader Precision Study of VENTANA MET (SP44) RxDx Assay in Cell Block Sample Types

					Standard Deviation			
Sample Category	MET IHC %TC Bin (min. to max.)	n of Samples	n of reads	Range of Median %TC	Within Reader	Between Reader	Total	Percent Positive Results, % (n/N)
Negative	0 to 39	17	136	0.0 - 35.0	4.38	9.45	10.41	1.5 (2/136)
Borderline Negative	40 to 49	3	24	42.5 - 45.0	13.32	15.13	20.16	20.8 (5/24)
Borderline Positive	50 to 60	0	0	N/A	N/A	N/A	N/A	N/A
Positive	61 to 100	20	160	70.0 - 100.0	5.88	7.29	9.37	98.8 (158/160)

Table 28. Within-Reader and Between Reader Precision of VENTANA MET (SP44) RxDx Assay in Cell Block Sample Types

Precision	Agreement			
	Type	**n/N**	**%**	**95% CI***
Within-Reader	APA	164/165	99.4	98.1, 100.0
	ANA	154/155	99.4	98.1, 100.0
	OPA	159/160	99.4	98.0, 100.0
Between-Reader	APA	222/234	94.9	89.5, 98.8
	ANA	228/240	95.0	90.0, 98.8
	OPA	2334/246	95.1	90.5, 98.8

Average Positive Agreement (APA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA)
*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples.

4. Inter-Laboratory Reproducibility and Method Comparison Studies

Inter-laboratory Reproducibility (ILR)

The Inter-laboratory Reproducibility (ILR) and Method Comparison (MC) study for the VENTANA MET (SP44) RxDx Assay was conducted to evaluate the reproducibility of the VENTANA MET (SP44) RxDx Assay on the BenchMark ULTRA and the BenchMark ULTRA PLUS platforms independently. Additionally, a method comparison between the BenchMark ULTRA and BenchMark ULTRA PLUS was performed to determine if the performance of the VENTANA MET (SP44) RxDx Assay is equivalent on both BenchMark platforms. The ILR study included 60 NSCLC specimens (30 MET Positive and 30 MET Negative, including several cases which exhibited borderline/challenging staining relative to the diagnostic cutoff) run across three BenchMark ULTRA and three BenchMark ULTRA PLUS instruments on 3 non-consecutive days at three external laboratories. For each BenchMark platform a set of 3 stained slides per sample per staining day was randomized and evaluated by a total of 6 readers (2 readers per site). Each case had 6 results per site per BenchMark platform (18 results per platform, 36 results in total for two platforms). Performance was evaluated and the following precision components were calculated: between-reader, between-site and total. The ILR study results are presented in the tables below.

Table 29. Results of the Inter-Laboratory Reproducibility Study (ULTRA)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
1	Negative	0	0, 0	0	0	0	0	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
2	Negative	0	0, 1	0	0	0	0.24	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
3	Negative	0	0, 2	0.41	0.33	0.1	0.63	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
4	Negative	2.5	0, 15	0.58	0.85	2.72	3.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
5	Negative	2.5	0, 5	1.33	0	1.65	2.26	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
6	Negative	2.5	0, 20	1.84	2.27	2.34	5.74	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
7	Negative	3.5	0, 15	2.67	1.67	2.61	4.79	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
8	Negative	4.5	0, 35	5.33	3.81	7.44	10.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
9	Negative	5	0, 15	1.08	0	4.08	5.14	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
10	Negative	5	0, 15	2.01	0	3.06	5.42	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
11	Negative	7.5	0, 20	1.99	2.79	5.32	6.8	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
12	Negative	7.5	0, 20	3.19	2.79	5.84	8	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
13	Negative	7.5	0, 35	4.58	6	6.21	10.2	0/4 (0.0)	0/6 (0.0)	0/6 (0.0)	0/16 (0.0)
14	Negative	7.5	0, 65	20.24	4.65	8.98	23.24	2/6 (33.3)	0/6 (0.0)	0/4 (0.0)	2/16 (12.5)
15	Negative	10	1, 20	3.55	3.7	3.42	7.02	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
16	Negative	10	0, 20	0	0	7.34	9.07	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
17	Negative	12.5	0, 40	6.28	3.73	12.46	15.41	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
18	Negative	17.5	5, 25	2.47	0	6.25	8.11	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
19	Negative	17.5	0, 50	9.94	0	12.73	18.06	0/6 (0.0)	0/6 (0.0)	1/6 (16.7)	1/18 (5.6)
20	Negative	20	0, 40	7.83	0	14.16	16.4	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
21	Negative	22.5	0, 45	6	5.41	9.67	15.66	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
22	Negative	25	0, 50	12.08	5.77	0	16.16	1/6 (16.7)	1/6 (16.7)	0/6 (0.0)	2/18 (11.1)
23	Negative	27.5	10, 50	8.58	0	5	12.25	1/6 (16.7)	0/6 (0.0)	0/6 (0.0)	1/18 (5.6)
24	Negative	27.5	5, 60	15.94	5.53	0	18.18	0/6 (0.0)	0/6 (0.0)	3/6 (50.0)	3/18 (16.7)
25	Negative	27.5	1, 60	0	0	7.68	22.28	2/6 (33.3)	1/6 (16.7)	2/6 (33.3)	5/18 (27.8)
26	Negative	30	5, 60	6.12	6.67	10.65	17.02	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
27	Negative	40	20, 55	7.99	5.53	0	11.96	2/6 (33.3)	0/6 (0.0)	1/6 (16.7)	3/18 (16.7)
28	Negative	40	20, 50	12.58	4.25	0	13.99	1/6 (16.7)	1/6 (16.7)	2/6 (33.3)	4/18 (22.2)
29	Negative	40	5, 70	12.47	7.55	14.73	22.7	4/6 (66.7)	0/6 (0.0)	3/6 (50.0)	7/18 (38.9)
30	Negative	40	5, 70	15.86	0	0	19.86	3/6 (50.0)	3/6 (50.0)	2/6 (33.3)	8/18 (44.4)
31	Negative	45	5, 75	12.75	8.25	13.39	22.64	3/6 (50.0)	1/6 (16.7)	3/6 (50.0)	7/18 (38.9)
32	Positive	50	10, 70	4.08	6.87	10.18	15.17	6/6 (100.0)	2/6 (33.3)	3/6 (50.0)	11/18 (61.1)
33	Positive	50	5, 90	9.43	14.85	11.67	25.33	6/6 (100.0)	3/6 (50.0)	5/6 (83.3)	14/18 (77.8)
34	Positive	50	0, 70	9.99	15.85	0	20.27	5/6 (83.3)	3/6 (50.0)	2/6 (33.3)	10/18 (55.6)
35	Positive	50	10, 70	8.38	0	9.57	20.94	5/6 (83.3)	2/6 (33.3)	2/5 (40.0)	9/17 (52.9)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
36	Positive	50	25, 90	22.82	6.97	0	25.9	4/6 (66.7)	3/6 (50.0)	4/6 (66.7)	11/18 (61.1)
37	Positive	50	1, 90	17.91	0	0	35.25	4/6 (66.7)	2/6 (33.3)	4/6 (66.7)	10/18 (55.6)
38	Positive	50	25, 75	9.35	6.01	4.71	13.39	6/6 (100.0)	1/6 (16.7)	4/6 (66.7)	11/18 (61.1)
39	Positive	50	1, 90	20.13	0	18.73	29.47	5/6 (83.3)	1/6 (16.7)	5/6 (83.3)	11/18 (61.1)
40	Positive	50	5, 80	22.42	4.08	0	23.66	5/6 (83.3)	3/6 (50.0)	5/6 (83.3)	13/18 (72.2)
41	Positive	57.5	20, 80	12.19	9.28	6.4	19.98	6/6 (100.0)	3/6 (50.0)	3/6 (50.0)	12/18 (66.7)
42	Positive	62.5	10, 90	17.32	0	6.22	23.27	6/6 (100.0)	3/6 (50.0)	5/6 (83.3)	14/18 (77.8)
43	Positive	65	25, 98	13.47	0	3.55	20.84	6/6 (100.0)	4/6 (66.7)	5/6 (83.3)	15/18 (83.3)
44	Positive	72.5	1, 95	11.53	9.4	17.36	28.86	6/6 (100.0)	3/6 (50.0)	6/6 (100.0)	15/18 (83.3)
45	Positive	82.5	20, 100	20.96	7.17	8.04	25.28	6/6 (100.0)	4/6 (66.7)	6/6 (100.0)	16/18 (88.9)
46	Positive	85	5, 99	15.65	11.9	0	23.25	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
47	Positive	90	10, 100	0	5.11	11.94	22.38	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
48	Positive	92.5	5, 100	15.86	6.95	6.9	24.98	6/6 (100.0)	4/6 (66.7)	6/6 (100.0)	16/18 (88.9)
49	Positive	95	70, 100	3.81	3.33	2.06	7.22	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
50	Positive	95	65, 100	8.23	2.79	0	10.13	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
51	Positive	95	80, 100	5.68	0	0	8.8	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
52	Positive	95	70, 100	8.64	0	0	9.92	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
53	Positive	97.5	90, 100	4.56	1.67	0	5.4	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
54	Positive	97.5	85, 100	6.01	0	0	6.67	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
55	Positive	97.5	80, 100	5.89	0	0	6.87	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
56	Positive	100	90, 100	2.53	0.75	0	3.04	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
57	Positive	100	90, 100	2.64	0	0	3.73	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
58	Positive	100	90, 100	3.91	0	0	4.56	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
59	Positive	100	90, 100	2.64	0	0	3.33	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
60	Positive	100	65, 100	5.89	6.24	0	10.74	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

Table 30. Results of the Inter-Laboratory Reproducibility Study (ULTRA PLUS)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
1	Negative	0	0, 0	0	0	0	0	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
2	Negative	0	0, 1	0	0	0	0.24	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
3	Negative	0	0, 5	0.67	0.58	0	1.22	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
4	Negative	1	0, 15	3.82	1.91	0	4.66	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
5	Negative	1	0, 15	4.62	0.53	0	4.92	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
6	Negative	1.5	0, 15	3.82	1.13	1.32	4.81	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
7	Negative	5	0, 15	4.49	1.05	4.53	7.01	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
8	Negative	5	0, 25	6.77	1.05	0	7.63	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
9	Negative	5	0, 25	6.14	0	3.69	7.86	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
10	Negative	5	0, 40	9.96	0	4.31	12	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
11	Negative	5	0, 40	10.55	3.16	3.43	13.05	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
12	Negative	5	0, 80	25.3	8.38	11.64	29.86	2/5 (40.0)	0/6 (0.0)	2/5 (40.0)	4/16 (25.0)
13	Negative	6.5	0, 25	4.81	2.53	5.43	8.17	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
14	Negative	7	2, 25	2.01	5.15	0	7.5	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
15	Negative	7.5	0, 40	8.42	4.25	2.68	11.36	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
16	Negative	10	1, 40	8.57	5.73	5.65	11.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
17	Negative	10	2, 25	5.71	2.84	3.11	7.39	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
18	Negative	10	0, 70	21.52	0	7.91	23.43	0/6 (0.0)	0/6 (0.0)	3/6 (50.0)	3/18 (16.7)
19	Negative	15	0, 40	8.03	0	12.3	15.98	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
20	Negative	19	5, 30	3.69	2.98	4.3	7.38	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
21	Negative	20	5, 50	7.26	0	9.35	15.28	0/6 (0.0)	0/6 (0.0)	2/6 (33.3)	2/18 (11.1)
22	Negative	20	1, 50	12.45	3.42	11.42	18.03	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
23	Negative	20	5, 75	17.54	5.75	0	22.98	1/6 (16.7)	1/6 (16.7)	3/6 (50.0)	5/18 (27.8)
24	Negative	24.5	1, 70	14.11	0	11.56	20.68	3/6 (50.0)	0/6 (0.0)	1/6 (16.7)	4/18 (22.2)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
25	Negative	25	1, 90	22.66	8.37	0	28.3	3/6 (50.0)	1/6 (16.7)	2/6 (33.3)	6/18 (33.3)
26	Negative	25	5, 65	14.45	8.08	14.92	23.91	4/6 (66.7)	0/6 (0.0)	3/6 (50.0)	7/18 (38.9)
27	Negative	25	5, 70	17.95	3.12	0	19.97	3/6 (50.0)	0/6 (0.0)	3/6 (50.0)	6/18 (33.3)
28	Negative	30	5, 50	9.72	9.57	0	16.29	0/6 (0.0)	2/6 (33.3)	2/6 (33.3)	4/18 (22.2)
29	Negative	32.5	20, 55	5.89	5.65	7.67	11.98	3/6 (50.0)	0/6 (0.0)	0/6 (0.0)	3/18 (16.7)
30	Negative	37.5	5, 70	19.97	7.45	0	23.57	2/6 (33.3)	3/6 (50.0)	2/6 (33.3)	7/18 (38.9)
31	Negative	40	15, 60	1.88	0	9.82	13.91	4/5 (80.0)	0/6 (0.0)	0/6 (0.0)	4/17 (23.5)
32	Negative	40	10, 90	19.22	2.89	7.98	24.88	3/6 (50.0)	1/6 (16.7)	3/6 (50.0)	7/18 (38.9)
33	Negative	42.5	20, 50	11.06	4.56	0	13.74	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
34	Positive	42.5	1, 98	30.7	9.5	11.6	35.69	4/6 (66.7)	1/6 (16.7)	4/6 (66.7)	9/18 (50.0)
35	Positive	50	5, 98	26.67	9.31	0	29.6	4/6 (66.7)	2/6 (33.3)	4/6 (66.7)	10/18 (55.6)
36	Positive	50	10, 95	13.89	10.8	5.11	24.35	5/6 (83.3)	3/6 (50.0)	4/6 (66.7)	12/18 (66.7)
37	Positive	50	15, 90	13.02	10.27	8.18	19.37	6/6 (100.0)	3/6 (50.0)	3/6 (50.0)	12/18 (66.7)
38	Positive	50	35, 70	6.35	5	5.38	10.46	6/6 (100.0)	4/6 (66.7)	3/6 (50.0)	13/18 (72.2)
39	Positive	50	15, 98	25.39	1.29	0	27.11	4/6 (66.7)	3/6 (50.0)	3/6 (50.0)	10/18 (55.6)
40	Positive	50	5, 80	17.04	0	0	28.48	3/6 (50.0)	4/6 (66.7)	3/6 (50.0)	10/18 (55.6)
41	Positive	52.5	25, 70	6.24	0	1.73	10.35	6/6 (100.0)	5/6 (83.3)	5/6 (83.3)	16/18 (88.9)
42	Positive	55	25, 90	19.4	0	0	21.21	6/6 (100.0)	5/6 (83.3)	3/6 (50.0)	14/18 (77.8)

				Standard Deviation				Percent Positive Results n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
43	Positive	65	8, 99	24.03	13.11	0	29.6	5/6 (83.3)	6/6 (100.0)	4/6 (66.7)	15/18 (83.3)
44	Positive	80	50, 95	13.64	7.07	0	17.83	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
45	Positive	85	50, 100	19.87	5.06	0	21.49	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
46	Positive	90	60, 100	12.5	3.5	0	13.52	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
47	Positive	90	70, 100	9.79	0	0	10.14	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
48	Positive	90	50, 100	12.22	5.27	1.38	15.18	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
49	Positive	92.5	30, 100	7.36	1.18	4	16.69	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
50	Positive	92.5	25, 100	13.33	4.56	0	20.55	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
51	Positive	95	80, 100	6.45	0	0	6.87	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
52	Positive	95	70, 100	8.47	0	0	9.3	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
53	Positive	96.5	85, 100	5.92	1.49	0	6.35	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
54	Positive	97	10, 100	15.95	2.74	0	22.8	6/6 (100.0)	6/6 (100.0)	5/6 (83.3)	17/18 (94.4)
55	Positive	98	65, 100	5.57	1.49	0	9.02	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
56	Positive	100	80, 100	4.71	1.67	0	6.24	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
57	Positive	100	75, 100	7.73	0	0	8.42	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
58	Positive	100	90, 100	4.25	0	0	4.56	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
59	Positive	100	90, 100	2.64	1.67	0	4.08	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
60	Positive	100	85, 100	5.89	0	0	6.24	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

Table 31. Results of the Inter-Laboratory Reproducibility Study for VENTANA MET (SP44) RxDx Assay on BenchMark ULTRA and ULTRA PLUS Instrument

				Standard Deviation				Percent Positive Results			
								n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
1	Negative	0	0, 0	0	0	0	0	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
2	Negative	0	0, 1	0.10	0	0	0.24	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
3	Negative	0	0, 5	0.56	0.51	0	0.98	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
4	Negative	1.5	0, 20	2.89	0	2.28	5.33	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
5	Negative	2.0	0, 15	1.77	0	2.06	4.21	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
6	Negative	2.0	0, 15	2.52	0	1.67	3.85	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
7	Negative	4.5	0, 15	3.64	0.51	3.65	6.07	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
8	Negative	5.0	0, 25	2.65	0	4.75	6.89	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
9	Negative	5.0	0, 25	4.49	0	1.33	6.38	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
10	Negative	5.0	0, 25	4.64	1.62	5.03	7.87	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
11	Negative	5.0	0, 40	7.23	0	6.40	11.42	0/10 (0.0)	0/12 (0.0)	0/12 (0.0)	0/34 (0.0)
12	Negative	5.0	0, 40	7.99	3.59	4.42	11.85	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
13	Negative	5.0	0, 80	22.74	7.57	12.86	28.25	4/11 (36.4)	0/12 (0.0)	2/9 (22.2)	6/32 (18.8)
14	Negative	9.5	1, 25	2.75	2.25	0	6.70	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
15	Negative	10.0	0, 40	7.22	3.78	8.58	13.51	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
16	Negative	10.0	0, 25	3.48	1.24	4.85	7.31	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
17	Negative	10.0	0, 40	4.42	2.41	6.22	10.19	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)

				Standard Deviation				Percent Positive Results			
								n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
18	Negative	12.5	0, 70	16.00	0	10.91	20.85	0/12 (0.0)	0/12 (0.0)	4/12 (33.3)	4/36 (11.1)
19	Negative	19.0	5, 30	2.81	0.60	5.55	7.61	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
20	Negative	20.0	0, 40	4.81	0	13.97	16.25	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
21	Negative	20.0	0, 50	7.60	0	11.21	16.94	1/12 (8.3)	0/12 (0.0)	1/12 (8.3)	2/36 (5.6)
22	Negative	21.5	1, 75	11.29	0	5.42	21.20	3/12 (25.0)	2/12 (16.7)	5/12 (41.7)	10/36 (27.8)
23	Negative	22.5	0, 50	8.47	2.26	4.85	15.05	1/12 (8.3)	1/12 (8.3)	2/12 (16.7)	4/36 (11.1)
24	Negative	25.0	1, 70	14.38	0	7.43	19.19	3/12 (25.0)	0/12 (0.0)	4/12 (33.3)	7/36 (19.4)
25	Negative	30.0	5, 60	6.88	0	4.38	15.43	1/12 (8.3)	2/12 (16.7)	3/12 (25.0)	6/36 (16.7)
26	Negative	35.0	10, 60	6.24	0.48	7.81	13.02	5/11 (45.5)	0/12 (0.0)	0/12 (0.0)	5/35 (14.3)
27	Negative	35.0	5, 70	13.57	3.64	15.44	23.43	8/12 (66.7)	0/12 (0.0)	6/12 (50.0)	14/36 (38.9)
28	Negative	35.0	5, 75	14.31	3.44	10.30	21.54	6/12 (50.0)	1/12 (8.3)	6/12 (50.0)	13/36 (36.1)
29	Negative	37.5	20, 55	6.12	0	3.83	11.33	5/12 (41.7)	0/12 (0.0)	1/12 (8.3)	6/36 (16.7)
30	Negative	40.0	0, 90	15.18	4.70	0	23.49	8/12 (66.7)	4/12 (33.3)	4/12 (33.3)	16/36 (44.4)
31	Negative	40.0	20, 50	11.29	2.80	0	13.51	2/12 (16.7)	1/12 (8.3)	3/12 (25.0)	6/36 (16.7)
32	Negative	40.0	5, 70	17.63	3.83	0	21.32	5/12 (41.7)	6/12 (50.0)	4/12 (33.3)	15/36 (41.7)
33	Negative	45.0	10, 90	16.88	4.95	5.82	22.71	8/12 (66.7)	3/12 (25.0)	5/11 (45.5)	16/35 (45.7)
34	Positive	50.0	10, 70	5.49	0	6.85	13.14	12/12 (100.0)	7/12 (58.3)	8/12 (66.7)	27/36 (75.0)
35	Positive	50.0	5, 98	17.58	8.13	8.79	26.52	10/12 (83.3)	5/12 (41.7)	9/12 (75.0)	24/36 (66.7)

				Standard Deviation				Percent Positive Results			
								n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
36	Positive	50.0	10, 95	18.40	0	0	24.75	9/12 (75.0)	6/12 (50.0)	8/12 (66.7)	23/36 (63.9)
37	Positive	50.0	1, 98	26.39	0	0	33.93	8/12 (66.7)	3/12 (25.0)	8/12 (66.7)	19/36 (52.8)
38	Positive	50.0	25, 75	7.52	0	5.41	12.20	12/12 (100.0)	5/12 (41.7)	7/12 (58.3)	24/36 (66.7)
39	Positive	50.0	1, 98	22.88	0	8.83	27.33	9/12 (75.0)	4/12 (33.3)	8/12 (66.7)	21/36 (58.3)
40	Positive	50.0	5, 80	19.95	0	0	25.67	8/12 (66.7)	7/12 (58.3)	8/12 (66.7)	23/36 (63.9)
41	Positive	52.5	15, 90	12.43	0	9.33	19.90	12/12 (100.0)	6/12 (50.0)	6/12 (50.0)	24/36 (66.7)
42	Positive	60.0	10, 90	17.96	0	0	21.10	12/12 (100.0)	8/12 (66.7)	8/12 (66.7)	28/36 (77.8)
43	Positive	65.0	8, 99	19.02	7.19	0	25.19	11/12 (91.7)	10/12 (83.3)	9/12 (75.0)	30/36 (83.3)
44	Positive	75.0	1, 95	12.38	2.03	4.44	22.76	12/12 (100.0)	9/12 (75.0)	12/12 (100.0)	33/36 (91.7)
45	Positive	85.0	20, 100	18.68	0	0	23.44	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
46	Positive	90.0	10, 100	10.27	6.05	5.65	17.97	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)	35/36 (97.2)
47	Positive	90.0	5, 100	14.66	0	0	22.45	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
48	Positive	90.0	5, 100	14.08	0	6.41	20.94	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
49	Positive	95.0	80, 100	6.33	0.36	0	6.77	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
50	Positive	95.0	30, 100	6.41	0	3.52	13.30	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)	35/36 (97.2)
51	Positive	95.0	65, 100	9.16	2.43	0	10.16	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
52	Positive	95.0	70, 100	7.48	0	0	8.81	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
53	Positive	95.0	10, 100	11.90	0	0	17.62	12/12 (100.0)	12/12 (100.0)	11/12 (91.7)	35/36 (97.2)
54	Positive	96.5	80, 100	6.02	0	0	6.61	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
55	Positive	100.0	80, 100	3.40	0	0	5.10	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
56	Positive	100.0	75, 100	6.19	0.55	0	7.01	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)

				Standard Deviation				Percent Positive Results			
								n/N (%)			
Case ID	Majority MET (SP44) Status	Median % Strong TC	Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Overall
57	Positive	100.0	90, 100	3.50	0.36	0	4.17	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
58	Positive	100.0	65, 100	5.04	0.26	0	7.17	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
59	Positive	100.0	90, 100	2.80	1.41	0	3.78	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
60	Positive	100.0	65, 100	5.80	2.98	0	8.71	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)

The data were analyzed for positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) across all evaluable observations, and a summary is presented in the tables below.

Table 32. Inter-Laboratory Reproducibility for overall agreement rates for VENTANA MET (SP44) RxDx Assay on BenchMark ULTRA Instrument

Inter-Laboratory Reproducibility	Agreement			
	Type	n/N	%	95% CI
Overall	PPA	438/521	84.1	81.4, 86.8
	NPA	509/554	91.9	88.5, 95.1
	OPA	947/1075	88.1	86.3, 89.9
Within-Site	PPA	436/498	87.6	85.3, 89.8
	NPA	530/577	91.9	89.6, 94.1
	OPA	966/1075	89.9	88.2, 91.5
Within-Reader	PPA	445/473	94.1	92.7, 95.7
	NPA	564/602	93.7	92.2, 95.2
	OPA	1009/1075	93.9	92.9, 94.8

Table 33. Inter-Laboratory Reproducibility for overall agreement rates for VENTANA MET (SP44) RxDx Assay on BenchMark ULTRA PLUS Instrument

Inter-Laboratory Reproducibility	Agreement			
	Type	n/N	%	95% CI
Overall	PPA	424/468	87.2	83.9, 91.3
	NPA	525/591	88.8	85.8, 91.9
	OPA	949/1077	88.1	86.2, 90.1
Within-Site	PPA	441/509	86.6	83.9, 89.6
	NPA	519/568	91.4	88.9, 93.9
	OPA	960/1077	89.1	87.5, 91.0
Within-Reader	PPA	465/491	94.7	93.2, 96.2
	NPA	561/586	95.7	94.5, 97.0
	OPA	1026/1077	95.3	94.4, 96.1

In addition, pairwise comparisons were made Between-Site, Between-Reader, and Between-Day for MET clinical status. These data were analyzed for average positive agreement (APA), average negative agreement (ANA), and overall percent agreement (OPA) and are presented below.

Table 34. Inter-Laboratory Reproducibility Pairwise Agreement Rates for VENTANA MET (SP44) RxDx Assay (ULTRA)

Between-Site, Between-Reader, and Between-Day Pairwise Comparison Agreement of MET Status for BenchMark ULTRA Platform						
Rate	Between-Site		Between-Reader		Between-Day	
	% (n/N)	95% CI	% (n/N)	95% CI	% (n/N)	95% CI
APA	80.4 (4650/5785)	78.1, 82.7	81.2 (392/483)	78.0, 84.5	86.3 (832/964)	84.2, 88.4
ANA	83.9 (5920/7055)	81.6, 86.2	84.6 (500/591)	82.0, 87.3	88.8 (1044/1176)	86.9, 90.6
OPA	82.3 (5285/6420)	80.1, 84.5	83.1 (446/537)	80.4, 85.9	87.7 (938/1070)	85.8, 89.6

Table 35. Inter-Laboratory Reproducibility Pairwise Agreement Rates for VENTANA MET (SP44) RxDx Assay (ULTRA PLUS)

Between-Site, Between-Reader, and Between-Day Pairwise Comparison Agreement of MET Status for BenchMark ULTRA PLUS Platform						
Rate	**Between-Site**		**Between-Reader**		**Between-Day**	
	% (n/N)	**95% CI**	**% (n/N)**	**95% CI**	**% (n/N)**	**95% CI**
APA	80.8 (4746/5876)	77.9, 83.9	79.1 (386/488)	75.6, 82.8	89.6 (876/978)	87.5, 91.6
ANA	83.9 (5884/7014)	81.6, 86.2	82.6 (484/586)	79.8, 85.5	91.3 (1068/1170)	89.7, 92.8
OPA	82.5 (5315/6445)	80.1, 85.0	81.0 (435/537)	78.0, 84.1	90.5 (972/1074)	88.8, 92.2

Disagreements observed were caused by samples which were enrolled into the study as non-borderline samples but were considered borderline samples after study execution. Therefore, low agreement results from this study may be attributable to a high proportion of borderline samples. To mitigate this risk, a limitation is included in the labeling that states that all initial case results with %TC between 40-60% or borderline strong versus moderate intensity by a pathologist should be reviewed by another independent pathologist and the reported results should be based on a consensus score. An additional Inter-laboratory Reproducibility (ILR) study for the VENTANA MET (SP44) RxDx Assay was conducted to evaluate the reproducibility of the VENTANA MET (SP44) RxDx Assay on the BenchMark ULTRA, which showed comparable results.

Method Comparison

In this study, the performance equivalence of the VENTANA MET (SP44) RxDx Assay on the BenchMark ULTRA and BenchMark ULTRA PLUS instruments was evaluated. The method comparison (MC) study included the 60 NSCLC specimens that were used in the ILR study described above (30 MET Positive and 30 MET Negative, including several cases which exhibited borderline/challenging staining relative to the diagnostic cutoff) run across three BenchMark ULTRA and three BenchMark ULTRA PLUS instruments on 3 non-consecutive days at three external laboratories. For each BenchMark platform a set of 3 stained slides per sample per staining day was randomized and evaluated by a total of 6 readers (2 readers per site). This resulted in an 'n' of 180 reads per reader and an 'n' of 1080 total reads in the study (60 cases * 3 replicates * 3 sites * 2 readers per site). PPA and NPA of MET status (positive or negative) across all evaluable observations of cases were determined by comparing cases stained on the BenchMark ULTRA instrument compared to the same cases stained on the BenchMark ULTRA PLUS instrument. For each case, the ULTRA results and ULTRA PLUS results were matched by site, day, and reader. PPAs and NPAs were determined using each instrument platform as a reference in the MC portion of the study. Of the 1080 total possible reads, 1073 slides were evaluable for this MC analyses. The remaining 7 slides were not evaluable. MC study results are presented in the Tables 36 and 37 below.

Table 36. Overall Method Comparison Results

Rate	ULTRA as Reference		ULTRA PLUS as Reference	
	% (n/N)	95% CI*	% (n/N)	95% CI*
PPA	87.2 (421/483)	84.7, 89.8	86.3 (421/488)	83.8, 88.6
NPA	88.6 (523/590)	86.3, 90.7	89.4 (523/585)	87.4, 91.6
OPA	88.0 (944/1073)	86.3, 89.5	-	-

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).
*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples

An additional analysis was performed using data from Reader 1 on Day 1 to evaluate the observations that were truly independent. The below table shows the MC for Reader 1 on Day 1 for MET status across all cases. Of the 180 total possible reads, 179 slides were evaluable for analysis. One slide was not evaluable.

Table 37. Overall Method Comparison Results (Reader 1, Day 1)

Rate	ULTRA as Reference		ULTRA PLUS as Reference	
	% (n/N)	95% CI*	% (n/N)	95% CI*
PPA	81.3 (65/80)	75.3, 87.2	85.5 (65/76)	78.7, 92.0
NPA	88.9 (88/99)	83.2, 94.0	85.4 (88/103)	80.6, 90.2
OPA	85.5 (153/179)	81.5, 89.4	-	-

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).
*2-sided 95% confidence intervals were calculated using the percentile bootstrap method from 2,000 bootstrap samples

As noted above, disagreements observed were caused by the samples which were enrolled into the study as non-borderline samples but were considered borderline samples after study execution. Therefore, low agreement results from this study may be attributable to a high proportion of borderline samples. To mitigate this risk, a limitation is included in the labeling that states that all initial case results with %TC between 40-60% or borderline strong versus moderate intensity by a pathologist should be reviewed by another independent pathologist and the reported results should be based on a consensus score.

5. Robustness

a. Tissue Thickness

To determine the impact of tissue section thickness on assay staining performance, 5 NSCLC tissue cases that encompassed MET IHC staining status range of positive and negative and 3 non-neoplastic gallbladder tissue cases, were evaluated using VENTANA MET (SP44) RxDx Assay antibody on a BenchMark ULTRA instrument. Duplicate sections at 2, 3, 4, 5, 6, and 7 µm were tested for each case. A 4 µm thick sample was used as a reference for each case.

3-, 4-, 5-, and 6 µm thick sections demonstrated concordant MET expression and acceptable background levels for VENTANA MET (SP44) antibody staining when

compared to the reference of 4 µm. Specimens should be cut at 4-5 µm for staining with the VENTANA MET (SP44) RxDx Assay.

b. Fixation Study

To evaluate the effects of fixative type and fixation time on assay performance, six HT-29 xenograft tissues were fixed for 1, 6, 12, 24, 48 and 72 hours in 6 fixatives: 10% NBF, AFA, 95% alcohol, Zinc Formalin, PREFER, and Z-5 (11 hours fixation instead of 12 hours) for a total of 36 samples. Six CALU-3 xenograft tissues were fixed for 1, 3, 6, 12, 24, 48, 72 hours in 6 fixatives: 10% NBF, Z-5, Zinc Formalin, AFA, PREFER, and Alcohol Formalin for a total of 36 samples. The samples were then compared to the reference standard of 10% NBF for 24 hours. Based on the study results, the recommended fixative is 10% NBF. Samples should be formalin fixed for 6 and 72 hours. Zinc formalin is also acceptable with a fixation time of 6 to 72 hours. Fixatives such as AFA, PREFER fixative, Z-fix, Alcohol Formalin and 95% ethanol are not acceptable for use with this assay and have demonstrated a significant loss of specific MET immunoreactivity and can lead to a false negative result. These recommendations and limitations are included in the device product labeling.

c. Ischemia Study (Time to Fixation)

The effect of delay to fixation (Ischemia) on the MET staining was evaluated using HT-29 human colorectal adenocarcinoma xenograft samples at 0, 0.5, 1, 2, 6, and 24 hours post-excision and using CALU-3 human lung adenocarcinoma xenograft samples at 0, 1, and 2-5 hours post-excision. The samples fixed immediately (0 hours of ischemia) were used as the reference condition. The HT-29 xenograft sample with an ischemia time of 24 hours failed when compared to its reference sample. The study demonstrated concordance of delay to fixation samples to their reference, except HT-29 at a 24-hour delay. It is recommended that samples are immediately fixed in 10% NBF for staining with the VENTANA MET (SP44) antibody.

d. Protocol Limitations and Failure Mode

To identify the protocol conditions (protocol parameters and simulated dispense errors) that might lead to a potential false positive, false negative, or unacceptable result and prevent these conditions from affecting the end user, the following test conditions were evaluated:

- One lot of VENTANA MET (SP44) RxDx Assay
- One lot of OptiView DAB IHC Detection Kit
- One BenchMark ULTRA instrument system
- Replicates: 1 per condition stained with VENTANA MET (SP44) RxDx
- One Negative Reagent Control per case per test condition
- One Pathologist (Reader)
- Four NSCLC samples

Serial dilutions from a single lot of antibody raw material were used: 0.125x, 0.25x, 0.5x, 2x, and 4x antibody titer. Parameters tested included offline, on instrument (online), and double baking conditions, CC1 (Cell conditioning 1) low and high incubation times (8 minutes, 24 minutes, 48 minutes, 96 minutes, 104 minutes), antibody low and high incubation times (8 minutes, 24 minutes, 32 minutes), counterstain high incubation times (8 minutes, 12 minutes), stacking (CC1, antibody, Bluing, Hematoxylin II) low and high incubation times and turnaround time. The result of each test sample was compared to its respective sample stained with the final locked staining protocol. Based on the data, the MET (SP44) staining performance on NSCLC was not affected by any of the baking test conditions and additional counterstaining incubation times (8 minutes). The final staining protocol should be followed as specified in Table 4. Refer to the device labeling for additional instructions.

5. Stability Studies

a. Real-time and Ship Stress Stability

The objective of this study was to assess the stability (shelf-life and in-use) and shipping category of the VENTANA MET (SP44) RxDx Assay antibody. Three production lots of VENTANA MET (SP44) RxDx Assay antibody were subjected to ship-stressed conditions and testing was done at specified intervals up to 26 months (Day 0, 8, 14, 24 and 26 months). The conditions tested were as follows:

i. Intended Storage (2-8°C)

ii. Hot Ship Stress Category F (37°C ± 2ºC 192 hours)

iii. Cold Ship Stress (Freeze/Thaw Cycle) (-25°C ± 5ºC 192 hours)

Based on the study results, all lots passed for all conditions and the data supports the product stability dating of 24 months when stored at 2-8°C as well as Shipping Category F (> -20°C and ≤ +35°C).

b. Cut Slide Stability

This study evaluated the stability of MET antigen in NSCLC FFPE tissue and cell block cases (5 MET positive, 5 MET negative) that had been sectioned onto positively charged glass microscope slides and stored for an extended duration of time at 30 ± 5°C with high humidity [85% relative humidity (RH) ± 10%] and with low humidity (15% RH ± 10%), at 5 ± 3°C with high humidity and with low humidity, and at ambient temperature and humidity. Slides sectioned and stained at the Day 0 time point served as the baseline comparator for 1 month, 45 day, and 2-6 months. Slides were stained at each predefined time point and staining results for each time point were compared to the Day 0 baseline slides.

Based on the results of this study, the recommended cut slide stability is 45 days at the 5 ± 3°C storage condition.

B. Animal Studies

Not applicable.

C. Additional Studies

1. Primary vs. Metastatic Tumor

This study characterized the staining performance of the VENANA MET (SP44) RxDx Assay on the primary tumor versus patient-matched metastatic tumor sample.

Of the 49 pairs of matched primary and metastatic NSCLC patient cases stained on the BenchMark ULTRA instrument, 46 (93.9%) matched pairs were concordant for MET IHC status. These data indicate that MET expression level can be different in the patient's primary and metastatic tumors stained with VENTANA MET (SP44) RxDx Assay.

2. Tissue Heterogeneity

a. Case Heterogeneity

This study characterized case heterogeneity by evaluating staining performance of the VENTANA MET (SP44) RxDx Assay on multiple blocks from the same patient case. Case Heterogeneity compares MET IHC status between multiple blocks from one patient case. Forty-five patient-matched NSCLC block pairs were used in this study. Based on the results of this study, case heterogeneity within NSCLC blocks was observed in 1 out of 45 of patient-matched pairs (2.2%). Forty-four cases (97.8%) displayed no case level heterogeneity. This suggests that case heterogeneity may change the MET IHC status in some tissue blocks of NSCLC stained with the VENTANA MET (SP44) RxDx Assay.

b. Block Heterogeneity

This study characterized within-block heterogeneity by evaluating staining outcome from multiple samples from the same tissue block. Block heterogeneity compares biomarker status between multiple slides sectioned from one block.

Eight of the thirteen (62%) NSCLC blocks maintained MET IHC status throughout the block when stained with the VENTANA MET (SP44) RxDx Assay. The remaining 5 blocks (38%) were considered borderline samples and resulted in a MET IHC status change. Based on the results of this study, block

heterogeneity within NSCLC was observed. This demonstrates that some heterogeneity may be observed in the MET expression level within each NSCLC tissue block from the same case when stained with the VENTANA MET (SP44) RxDx Assay.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of the VENTANA MET (SP44) RxDx Assay as a companion diagnostic (CDx) device to aid in the identification of patients with non-squamous non-small cell lung cancer (NSCLC) who are likely to benefit from EMRELIS™ (telisotuzumab vedotin-tllv) treatment was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the LUMINOSITY study.

A. Therapeutic Study Design

The LUMINOSITY study was a Phase 2 multicenter, open-label, non-randomized, single-arm study that evaluated the safety and efficacy of EMRELIS™ (telisotuzumab vedotin-tllv) as monotherapy in patients with locally advanced or metastatic non-squamous NSCLC with c-Met (MET) protein overexpression who had received prior systemic therapy. Patients were enrolled based on MET protein overexpression, defined as ≥ 25% of tumor cells (TC) with strong (3+ intensity) membrane staining, as determined by prospective testing of archival or recent tissue sample by immunohistochemistry (IHC), at a central laboratory prior to enrollment using the MET (SP44) clinical trial assay (CTA). However, the drug efficacy population only included patients with ≥ 50% TC with strong membrane staining. The primary efficacy endpoint was overall response rate (ORR) to EMRELIS™ (telisotuzumab vedotin-tllv) in subjects with c-Met-overexpressing NSCLC, as determined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by a blinded independent central review (BICR).The primary efficacy population included 84 patients with non-squamous, EGFR wild-type NSCLC with high MET protein overexpression, defined as ≥ 50% TC with strong membrane staining, who had received prior systemic therapy.

B. VENTANA MET (SP44) RxDx assay Clinical Bridging Study

The objectives of the clinical bridging study were to determine the concordance of results for the MET expression status between the VENTANA MET (SP44) RxDx Assay (≥ 50% TC with strong membrane and/or cytoplasmic staining) and the CTA (≥ 50% TC with strong membrane staining) and to demonstrate that the therapeutic drug efficacy was maintained when the VENTANA MET (SP44) RxDx Assay was used to identify adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with high c-Met protein overexpression [≥ 50% of tumor cells with strong (3+) staining] for treatment with EMRELIS™.

Clinical validity of the VENTANA MET (SP44) RxDx Assay was evaluated using remnant clinical study samples from LUMINOSITY study. Additionally, staining

acceptability rates for VENTANA MET (SP44) RxDx Assay were evaluated at the subject level.

1. Clinical Bridging Study Inclusion and Exclusion Criteria
   All tumor specimens submitted for the LUMINOSITY study that also satisfied the inclusion/exclusion criteria outlined below were tested with the VENTANA MET (SP44) RxDx Assay.

   Inclusion Criteria
   Specimens had to meet all of the following criteria to have been included in the clinical bridging study:

   i. FFPE tumor specimen submitted for patient enrollment screening for the LUMINOSITY study processed in accordance with current Good Clinical Practice (cGCP), consisting of:
      a. A tissue block (or at least 3 slides, but preferably 5, containing serial sections of such a block) containing resection or biopsy tumor tissue, or
      b. A cell block prepared from a cytology sample such as fine needle aspirate (FNA), bronchoalveolar lavage (BAL), bronchial brush, pleural fluid thoracentesis, or at least 3 slides, but preferably 5, containing serial sections of such a block; cytology samples must not be placed in alcohol or alcohol-based fixative/preservative prior to fixation in 10% NBF.
   ii. Tumor specimen must contain sufficient tumor tissue (100 viable tumor cells) for interpretation at the discretion of the reviewing pathologist.

   Exclusion Criteria
   Specimens were excluded from the clinical bridging study if any of the following criteria were met:

   i. Tumor specimen consisting of bone tissue including those that had been decalcified.
   ii. Tumor specimen was a cytology smear.
   iii. Tumor specimen was known to have been fixed in 95% alcohol, Alcohol Formalin Acetic acid (AFA), Alcohol Formalin, zinc formalin fixative (Z-Fix), or glyoxal fixative (PREFER), or the fixative type is unknown.
   iv. If cut slides were prepared more than 60 days prior to staining.
   v. Unstained cut slides were not shipped with cold packs or that were not stored refrigerated (2-8°C).
   vi. If the specimen was formalin-fixed for < 6 hours or > 72 hours or the fixation time was unknown.

C. Accountability of PMA Cohort

The VENTANA MET (SP44) RxDx Assay (hereafter referred to as the "CDx") clinical bridging study included a total of 37 (44%) of the 84 patient samples from the efficacy population of the LUMINOSITY study. A total of 47 (56%) subjects were missing and were excluded from the study (protocol deviations, incident events, and/or because they were screen failures for reasons other than CTA result). Of the 37 subjects that were evaluable, 32 subjects (86%) tested MET-positive by the VENTANA MET (SP44) RxDx Assay, while 5 subjects (14%) tested negative.

During the LUMINOSITY study, 830 MET-negative samples (screen fail) by CTA were also banked for assessment in the CDx clinical bridging study. Of these, 461 (56%) subjects tested MET-negative by the CDx and were included in the primary analysis set, while 42 subjects (5%) tested MET-positive. The remaining 327 patients (39%) were missing due to protocol deviations, incident events, and/or because they were screen failures for reasons other than CTA result. Patient accountability is summarized in the below table.

Table 38. Accountability of PMA Cohort for Study LUMINOSITY

Population Description	CTA MET Expression Status		Total N=914
	Positive (≥50%) N=84	Negative (<50%) N=830	
Drug Study (LUMINOSITY) Population Status, n (%)			
Primary Efficacy Analysis (239-PE) Population[1]	84	N/A	84
CDx Population Status, n (%)			
CDx Evaluable	37	503	540
CDx Unknown[2]	47	327	374
Final Bridging Study Population	37	503	540

[1] Enrolled population in the LUMINOSITY study using the CTA with a cutoff of ≥25%.

[2] CDx unknown includes: 1) protocol deviations, incident events, and/or screen failures for reasons other than CTA result, 2) CDx not evaluable.

Given that the sample ascertainment rate for CDx-retesting in the clinical bridging study is low (44%; 37/84), a post-market study is planned to gather additional data supporting the clinical validity of the VENTANA MET (SP44) RxDx Assay (See section XV).

D. Study Population Demographics and Baseline Parameters

The key patient demographics and baseline clinical characteristics of VENTANA MET (SP44) RxDx Assay evaluable and unevaluable primary efficacy population are shown below (Table 39).

Table 39. Patient and Sample Characteristics by CDx Missing / Not Evaluable Status in Primary Efficacy Population

Characteristic	CDx Status		Total (N=84)	P-Value
	Evaluable (N=37)	Missing (N=47)		
Age (years)				0.470
Mean ± SD	62.2 ± 9.99	63. ± 8.88	63.0 ± 9.36	
Median	62	65	64	
25th, 75th Percentile	56, 69	57, 70	57, 70	
Range	38-81	45-83	38-83	
Sex, n (%)				0.616
Female	8 (21.6)	13 (27.7)	21 (25.0)	
Male	29 (78.4)	34 (72.3)	63 (75.0)	
Ethnicity, n (%)				-
Hispanic or Latino	0	0	0	
Not Hispanic or Latino	37 (100)	47 (100)	84 (100)	
Race, n (%)				0.211
Asian	11 (29.7)	21 (44.7)	32 (38.1)	
Black or African American	1 (2.7)	0	1 (1.2)	
White	25 (67.6)	26 (55.3)	51 (60.7)	
Baseline ECOG, n (%)				1.000
Grade 0	9 (24.3)	12 (25.5)	21 (25.0)	
Grade 1	28 (75.7)	34 (72.3)	62 (73.8)	
Grade 2	0	1 (2.1)	1 (1.2)	
Overall Staging at Diagnosis, n (%)				0.004**
Stage IA	1 (2.7)	0	1 (1.2)	
Stage IIB	1 (2.7)	0	1 (1.2)	
Stage IIIA	3 (8.1)	0	3 (3.6)	
Stage IIIB	0	6 (12.8)	6 (7.1)	
Stage IV	32 (86.5)	40 (85.1)	72 (85.7)	
Unknown	0	1 (2.1)	1 (1.2)	

Characteristic	CDx Status		Total (N=84)	P-Value
	Evaluable (N=37)	Missing (N=47)		
Region, n (%)				0.394
North America	3 (8.1)	6 (12.8)	9 (10.7)	
Asia	11 (29.7)	20 (42.6)	31 (36.9)	
Europe	14 (37.8)	15 (31.9)	29 (34.5)	
Rest of the World	9 (24.3)	6 (12.8)	15 (17.9)	
Screening Sample Collection Method, n (%)				0.244
Biopsy	30 (81.1)	37 (78.7)	67 (79.8)	
Cytology	1 (2.7)	4 (8.5)	5 (6.0)	
Excision/ Resection	6 (16.2)	3 (6.4)	9 (10.7)	
Unknown	0	3 (6.4)	3 (3.6)	
Screening Sample Specimen Type, n (%)				0.009**
Paraffin block	25 (67.6)	18 (38.3)	43 (51.2)	
Unstained slide	12 (32.4)	29 (61.7)	41 (48.8)	
Screening Sample Tumor Type, n (%)				0.661
Primary	20 (54.1)	22 (46.8)	42 (50.0)	
Metastasis	17 (45.9)	24 (51.1)	41 (48.8)	
Unknown	0	1 (2.1)	1 (1.2)	
Screening Sample Condition, n (%)				0.650
Archival	22 (59.5)	31 (66.0)	53 (63.1)	
Fresh	15 (40.5)	16 (34.0)	31 (36.9)	

***, **, * statistically significant at 0.001, 0.01, and 0.05 level, respectively.

E. Safety and Effectiveness Results

1. Safety Results

No adverse events were reported for the use of VENTANA MET (SP44) RxDx Assay in connection with the bridging study used to support this PMA as these involved retrospective testing of banked specimens only.

Data regarding the safety of EMRELIS™ (telisotuzumab vedotin-tllv) therapy were presented in the original drug approval and are summarized in the drug label. Refer to the EMRELIS™ United States Prescribing Information (USPI) for more information.

2. Effectiveness Results

Concordance Results
Concordance between VENTANA MET (SP44) RxDx Assay (CDx) and MET CTA is shown in Table 39 below. For concordance analyses, MET positives from both the efficacy population and biomarker-negative population were included (please refer to the Table 40 footnotes for details). The PPA was 86.5% (32/37) with two-sided 95% confidence interval (71.23%, 95.46%) and NPA was 91.7% (461/503) with two-sided 95% confidence interval (88.88%, 93.92%).

Table 40. Concordance Between VENTANA MET (SP44) RxDx Assay and CTA Testing

LUMINOSITY Study		MET CTA Status		
		Positive	**Negative**	**Total**
MET CDx Status	**Positive**	32	42	74
	Negative	5	461	466
	Unknown[1]	47	327	374
	Total	84	830	914
	PPA: 86.5% (32/37) [95% CI: 71.23, 95.46]			
	NPA: 91.7% (461/503) [95% CI: 88.88, 93.92]			
	OPA: 91.3% (493/540) [95% CI: 88.59, 93.53]			

[1] CDx unknown includes: 1) protocol deviations, incident events, and/or screen failures for reasons other than CTA result, 2) CDx not evaluable.

CDx = VENTANA MET (SP44) assay; CI = confidence interval; CTA = clinical trial assay; NPA = negative percent agreement; PPA = positive percent agreement; OPA = overall percent agreement

Note: Concordance was estimated in only those patients who had an evaluable CDx result.

The discordance between the CTA and the VENTANA MET (SP44) RxDx Assay (CDx) were evaluated. Of the 5 CTA+/CDx- samples 3 were negative by the CDx and 2 were borderline. Furthermore, of the 5 discordant cases, only one patient had a confirmed treatment response. Given that the sample ascertainment rate for CDx-retesting in the clinical bridging study is low (44%; 37/84), a post-market study will be performed to gather additional data supporting the clinical validity of the VENTANA MET (SP44) RxDx Assay (See section XV).

Overall Efficacy
The efficacy of EMRELIS™ (telisotuzumab vedotin-tllv) was evaluated in the LUMINOSITY clinical study in those subjects positive for MET protein by VENTANA MET (SP44) RxDx Assay (Table 41). The efficacy results for the CDx+/CTA+ population (ORR: 34.4%) is comparable to that for the CTA+ patients (ORR: 34.5%). The median duration of response (DoR) for VENTANA

MET (SP44) RxDx Assay clinical efficacy population was 7.2 months, which is comparable to the DoR for the CTA+ population (7.2 months).

Table 41. Clinical Benefit of MET Patient Population in LUMINOSITY

	CTA+ (n=84)	CTA+/CDx+ (n=32)	CTA+/CDx- (n=5)	CTA+/CDx unevaluable (n=47)
ORR (95% CI)	34.5 (24.5, 45.7)	34.4 (18.6, 53.2)	20 (0.5, 71.6)	36.2 (22.7, 51.5)
Complete response (CR), n (%)	0	0	0	0
Partial response (PR), n (%)	29 (34.5)	11 (34.4)	1 (20)	17 (36.2)
Duration of Response (DOR)				
Median DoR, months (95% CI)	7.2 (4.2, 12.0)	7.2 (2.8, 13.0)	4.2 (-, -)	10.0 (3.8, 18.9)
% with DoR ≥6 months, n (%)	17 (58.6)	7 (63.6)	0	10 (58.8)
% with DoR ≥12 months, n (%)	6 (20.7)	2 (18.2)	0	4 (23.5)

Given that the CTA exclusively assessed the presence of membrane staining, there is a lack of prevalence and efficacy data for patients with strong (3+) cytoplasmic staining only. As the VENTANA MET (SP44) RxDx Assay incorporates an assessment of cytoplasmic staining into the interpretation algorithm, a post-market study is planned to gather additional prevalence and efficacy data for patients whose cytoplasmic cellular compartment drives their MET positivity.

Sensitivity Analysis

Sensitivity analysis with regard to the missing CDx test results were conducted to evaluate the robustness of the ORR estimates considering VENTANA MET (SP44) RxDx Assay (CDx) unevaluable patients enrolled in the LUMINOSITY trial. Samples's CDx results were considered missing if the samples were not tested by the CDx, or if they were tested but returned an invalid result, or if they were excluded from the analysis due to protocol deviations, incident events, and/or because they were screen failures for reasons other than CTA result. Under the reasonable assumption of missing at random (MAR), the missing CDx results will be imputed. A multiple imputation approach was utilized to impute the missing CDx MET status by multiple imputation. The CTA MET result, treatment outcome variable, patient characteristics variables, and sample characteristics variables were included. Amongst all CTA+ patients, 56% did not have VENTANA MET (SP44) RxDx Assay result (47/84).

The imputed ORR was estimated to be 32.4% (95% CI: 24.23, 40.51), which is comparable to the ORR for the CTA-positive population [34.5% (24.5, 45.7)]. Thus, the sensitivity analysis demonstrated the robustness of the clinical efficacy estimate to the missing VENTANA MET (SP44) RxDx Assay results.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

Patients that were 18 years or older were eligible for enrollment into the LUMINOSITY study if they fulfilled other inclusion criteria. The youngest age enrolled in the study was 38 years. For the LUMINOSITY study, data from adult patients 38 years or older is generalizable to the pediatric population (18-21 years) and can be relied on to establish safety and effectiveness within the 18-21 years age group.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The diagnostic clinical bridging study included two investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XIII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA did not raise any new safety and effectiveness questions compared with information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the VENTANA MET (SP44) RxDx Assay as a CDx device for identifying non-squamous non-small cell lung cancer (NSCLC) patients with MET expression who may be eligible for treatment with EMRELIS™ (telisotuzimab vedotin-tllv) is based on the clinical performance assessed in the LUMINOSITY study. Overall, data show clinically meaningful efficacy for this patient population.

The performance of the VENTANA MET (SP44) RxDx Assay was also supported by the analytical validation studies.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above.

The VENTANA MET (SP44) RxDx Assay is an in vitro diagnostic device, which tests FFPE tumor specimens collected from patients with non-squamous NSCLC. The risks of the device are based on data collected in the clinical study, and no adverse events associated with the diagnostic testing procedure were reported during the LUMINOSITY study. The process of testing on FFPE tumor specimens does not present additional significant safety concerns, as the required biopsies are obtained using a medically routine sampling procedure that does not present a significant risk to the patient.

As the VENTANA MET (SP44) RxDx Assay is intended to identify non-squamous NSCLC patients for treatment with EMRELIS™ (telisotuzumab vedotin-tllv), failure of the device to perform as expected may lead to incorrect or false results and applicable NSCLC patients may not receive the proper treatment. Patients with false positive results may undergo treatment with EMRELIS™ (telisotuzumab vedotin-tllv) without much clinical benefit and may experience adverse reactions associated with EMRELIS™ (telisotuzumab vedotin-tllv) therapy. Patients with false negative results may not be considered for treatment with EMRELIS™ (telisotuzumab vedotin-tllv), and therefore, may receive other treatment options that do not offer the same clinical benefit.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the LUMINOSITY clinical study, the analytical validation, and the clinical bridging study conducted to support PMA approval as described above. Treatment with telisotuzumab vedotin-tllv is anticipated to provide meaningful clinical benefit to previously treated adult patients with locally advanced or metastatic non-squamous NSCLC selected for therapy based on the results of testing with the VENTANA MET (SP44) RxDx Assay. Based on the data provided in the clinical concordance study which compared the agreement between results of the VENTANA MET (SP44) RxDx Assay with those of the CTA MET assay and the efficacy analysis, the VENTANA MET (SP44) RxDx Assay has sufficiently comparable and clinically acceptable performance in the selection of patients for treatment as compared to the CTA.

The probable risks of the device are also based on data collected from the described studies as conducted to support PMA approval. The risks associated with the use of this device are mainly due to 1) false negatives, false positives, and failure to provide a result and 2) incorrect interpretation of test results. Erroneous device results could adversely influence clinical interpretation and consultation for patients. Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in treatment of patients with non-squamous NSCLC. Patients with false positive

results may be treated with telisotuzumab vedotin-tllv without clinical benefit, and may experience adverse reactions associated with the therapy. A false negative result may prevent a patient from accessing appropriate treatment. There is also a risk of delayed results /failure to provide a result, which may lead to delay of treatment with indicated therapy. These risks are partially mitigated by the analytical and clinical performance of the device and device labeling; therefore, the risk of this device is considered to be clinically acceptable for the indication listed.

Additional factors to be considered in determining probable risks and benefits for the VENTANA MET (SP44) RxDx Assay included variability in interpretation of %TC scores during replicate testing, changes to the DAB detection kit, and modification of the interpretation algorithm. Confirmatory testing will be performed in the post approval setting as described above.

This submission did not include specific information on patient perspectives.

In conclusion, when taking into account the totality of data and the additional mitigations provided by the labeling, the probable benefits of this device outweigh the probable risk for selecting non-squamous NSCLC patients for treatment with telisotuzumab vedotin-tllv.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The data from the LUMINOSITY study support the use of the VENTANA MET (SP44) RxDx Assay as a companion diagnostic to identify adult patients with locally advanced or metastatic non-squamous NSCLC with MET protein overexpression [≥ 50% of tumor cells with strong (3+) membrane and/or cytoplasmic staining] who may be eligible for treatment with EMRELIS™ (telisotuzumab vedotin-tllv) in accordance with approved therapeutic labeling as the probable benefits outweigh the probable risks.

XV. CDRH DECISION

CDRH issued an approval order on May 14, 2025. The final conditions of approval cited in the approval order are described below.

1. Ventana Medical Systems, Inc. must provide supplementary clinical data (i.e., efficacy data from non-NDA population) in the post-market setting to confirm the clinical effectiveness of VENTANA MET (SP44) RxDx Assay as a companion diagnostic (CDx) device for the identification of NSCLC patients with MET protein who may benefit from treatment with telisotuzumab vedotin. This supplementary study should also evaluate the prevalence and efficacy of telisotuzumab vedotin for patients whose MET-positivity is driven by the

different cellular compartments (i.e., membrane-only, membrane and cytoplasm, and cytoplasm-only).

A complete study protocol must be submitted within 30 days after approval. The data, conclusions, and labeling revisions from this study should be submitted within 30 months of the PMA approval date.

2. Ventana Medical Systems, Inc. must provide results from a cell block (e.g., cell blocks prepared from fine needle aspiration biopsy samples, pleural fluid samples, etc.) sample fixative study which demonstrates the impact of collection media commonly used to stabilize cytology specimens prior to cell block preparation on the performance of the VENTANA MET (SP44) RxDx Assay, which is indicated for the use in the assessment of MET protein in FFPE NSCLC tissue specimens by light microscopy.

   A complete study protocol must be submitted within 30 days after approval. The data, conclusions, and labeling revisions from this study should be submitted within 12 months of the PMA approval date.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.