510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k103358

B. Purpose for Submission:
New Device

C. Measurand:
ROMA (Risk of Ovarian Malignancy Algorithm) – Ovarian adnexal mass assessment score based on 2 serum analytes

D. Type of Test:
Software algorithm and 2 immunoassays

E. Applicant:
Fujirebio Diagnostics, Inc

F. Proprietary and Established Names:
ROMA™ (HE4 EIA + ARCHITECT CA 125 II™)

G. Regulatory Information:

1. Regulation section:
   21 CFR§866.6050 – Ovarian adnexal mass assessment score test system
2. Classification:
   Class II
3. Product code:
   ONX; Ovarian adnexal mass assessment score test system
4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended use(s):
   For *In Vitro* Diagnostic Use Only.
   The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA125 II™ and menopausal status into a numerical score.

   ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.

PRECAUTION: The ROMA (HE4 EIA+ARCHITECT CA125 II) should not be used without an independent clinical/radiological evaluation and is **not** intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of the ROMA (HE4 EIA+ARCHITECT CA125 II) carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

2. Indication(s) for use:
   Same as Intended Use.
3. Special conditions for use statement(s):
   Prescription use only
4. Special instrument requirements:
   ARCHITECT *i*2000SR system for the ARCHITECT CA125 II™ assay and microplate spectrophotometer at 620 nm or 405 nm for the HE4 EIA.

I. Device Description:

The ROMA is a qualitative serum test that combines the results of 2 analytes, HE4 (HE4 EIA) and CA 125 (ARCHITECT CA 125II) and menopausal status into a numerical score between 0.0 and 10.0. The premenopausal or postmenopausal status must be based on ovarian function determined with information available from clinical evaluation and medical history.

The test system consists of the manual HE4 EIA and ARCHITECT CA 125II assays, reagents, instrument and software (calculator tool) used to obtain the ROMA test result. The ROMA instructions for use and calculator tool are provided in the kit. Users are instructed to use only the assay kits identified by Fujirebio Diagnostic Inc. The immunoassays are performed according to the manufactures' directions detailed in each product insert.

Both manual HE4 EIA and ARCHITECT CA 125 II are previously cleared devices ((k072939 and k042731 respectively). The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum and was previously cleared as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. ARCHITECT CA 125 II assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of CA 125 reactive determinants in human serum and plasma on the ARCHITECT *i* System and was previously cleared as an aid in monitoring response to therapy for patients with epithelial ovarian cancer.

Using an algorithm and the value of the 2 analytes, ROMA scores (numerical score from 0.0-10.0) for both premenopausal and postmenopausal will be calculated and indicate a low likelihood or high likelihood for finding malignancy on surgery.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):
   OVA1™ Test (k081754)
2. Comparison with predicate:

Similarities		
Item	Device (ROMA (HE4 EIA + ARCHITECT CA125 II))	Predicate (OVA1™ Test)

Similarities		
Item	Device (ROMA (HE4 EIA + ARCHITECT CA125 II))	Predicate (OVA1™ Test)
Intended Use/Indication for Use	For In Vitro Diagnostic Use Only. The Risk of Ovarian Malignancy Algorithm (ROMA™) is a qualitative serum test that combines the results of HE4 EIA, ARCHITECT CA 125 II™ and menopausal status into a numerical score. ROMA is intended to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy on surgery. ROMA is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. ROMA must be interpreted in conjunction with an independent clinical and radiological assessment. The test is not intended as a screening or stand-alone diagnostic assay.	The OVA1™ Test is a qualitative serum test that combines the results of five immunoassays into a single numerical score. It is indicated for women who meet the following criteria: over age 18; ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist. The OVA1 Test is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy. The test is not intended as a screening or stand-alone diagnostic assay.
Black box warning (PRECAUTION)	Should not be used without an independent clinical /radiological evaluation and is not intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use carries the risk of unnecessary testing, surgery, and/or delayed diagnosis	Same
Sample matrix	Serum	Same
Type of test	Algorithm	Same

Differences		
Item	Device (ROMA (HE4 EIA + ARCHITECT CA125 II))	Predicate (OVA1™ Test)
Measurand	Score based on 2 analytes and menopausal status	Score based on 5 analytes and menopausal status
Analyte	Fujirebio manual HE4 EIA and ARCHITECT CA125 II	Roche Elecsys CA125 and Siemens BN II assays (Transythretin, Apolipoprotein A-1, β_2-microglobulin and Transferrin)
Equation used for test	Different equation for premenopausal and postmenopausal	One equation with two cut-offs depending on menopausal status
Clinical Cut-off	Premenopausal: ROMA score ≥ 1.31 High likelihood of finding malignancy ROMA score < 1.31 Low likelihood of finding malignancy Postmenopausal: ROMA score ≥ 2.77 High likelihood of finding malignancy ROMA score < 2.77 Low likelihood of finding malignancy	Pre-menopausal: OVA1™ Test score < 5.0 low probability for malignancy OVA1™ Test score ≥ 5.0 high probability for malignancy Post-menopausal: OVA1™ Test score < 4.4 low probability for malignancy OVA1™ Test score ≥ 4.4 high probability for malignancy
Instrument platform	ARCHITECT *i*2000SR system for CA125	Roche Elecsys 2010 and Siemens BN II

K. Standard/Guidance Document Referenced (if applicable):

CLSI guideline EP7-A "Interference Testing in Clinical Chemistry; Approved Guideline".

CLSI guideline C28-A3 "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition".

L. Test Principle:

The HE4 EIA is a solid-phase, non-competitive immunoassay based upon the direct sandwich technique using two monoclonal antibodies, 2H5 and 3D8, directed against two epitopes in the C-WFDC domain of HE4. One antibody, 2H5, serves as capture antibody, and the other antibody, 3D8, serves as detecting antibody. Calibrators, controls and patient samples are incubated together with biotinylated capture antibody in streptavidin coated microstrips. The strips are then washed and incubated with enzyme-labeled detection antibody. After washing, the buffered substrate/chromogen reagent is added to each well and the enzyme reaction is allowed to proceed. The

intensity of the color is proportional to the amount of HE4 present in the samples. The color intensity is determined in a microplate spectrophotometer at 620 nm (or optionally at 405 nm after addition of Stop Solution). Calibration curves are constructed for each assay by plotting absorbance value versus the concentration for each calibrator. The HE4 concentrations of patient samples are then read from the calibration curve. The HE4 EIA Kit measures concentrations between 15 and 900 pM.

The ARCHITECT CA125 II assay is a two-step sandwich technique immunoassay to determine the presence of OC 125 defined antigen in human serum and plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex. In the first step of the assay, sample and antibody (mouse monoclonal anti-OC 125) coated paramagnetic microparticles are combined. CA 125 reactive determinants present in the sample bind to the antibody coated microparticles. After washing, a second acridinium-labeled antibody conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of CA 125 reactive determinants in the sample and the RLUs detected by the ARCHITECT™ *i* optical system.

For calculation of the ROMA score, the user enters results of HE4 EIA and ARCHITECT CA 125 II into the calculator tool following the manufacturer's instruction. The calculator tool is included in the kit. Using an algorithm and the value of the 2 analytes, ROMA scores (numerical score from 0.0-10.0) for both premenopausal and postmenopausal will be calculated and indicate a low likelihood or high likelihood for finding malignancy on surgery. Both premenopausal and postmenopausal ROMA results will be reported to the ordering physician who will decide which result to use based on patient's menopausal status

M. Performance Characteristics (if/when applicable):

1. Analytical performance: Both HE4 EIA and ARCHITECT CA 125 II are previously cleared devices. Analytical performance for HE4 EIA and ARCHITECT CA 125 II were validated in k072939 and k042731 respectively. Sponsor stated that there has been no modification of assay methods for HE4 EIA and ARCHITECT CA 125 II for used in the calculation of the ROMA score. Thus, limited study was done to evaluate the analytical performance of the ROMA score.
   a. *Precision/Reproducibility:*
      Lot-to-Lot Precision: A panel of five serum samples was tested using three lots of HE4 EIA and three lots of ARCHITECT CA 125 II reagent and calibrator kits. The study was repeated for 5 days, two runs per day with the samples analyzed in two replicates per run for ARCHITECT CA 125 II and four replicates per run for the HE4 EIA. The two runs per day were separated by a minimum of 2 hours. All runs were performed according to each assay's package insert. The overall study was performed based CLSI guideline EP5-A2 entitled "Evaluation of Precision Performance of Quantitative

Measurement Methods; Approved Guideline - Second Edition (2004)". Premenopausal and postmenopausal ROMA scores were calculated using the separate algorithm both manually and by using ROMA Calculator Tool Software CD (BETA version 0.00.15). Data is summarized below.

Sample	Mean ROMA Value	Within Run		Between Runs		Between Days		Between Lots		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Premenopausal ROMA score											
1	0.66	0.03	4.98	0.01	0.93	0.03	4.64	0.02	3.52	0.05	7.72
2	1.32	0.04	2.96	0.04	2.94	0.00	0.00	0.02	1.78	0.06	4.53
3	2.81	0.07	2.40	0.08	2.81	0.10	3.65	0.00	0.00	0.15	5.20
4	1.28	0.03	2.14	0.03	2.04	0.02	1.89	0.02	1.94	0.05	4.01
5	8.66	0.04	0.42	0.06	0.69	0.01	0.09	0.00	0.00	0.07	0.82
Postmenopausal ROMA score											
1	1.05	0.03	3.01	0.00	0.45	0.03	2.40	0.01	1.33	0.04	4.10
2	2.55	0.03	1.36	0.02	0.96	0.00	0.00	0.01	0.49	0.04	1.74
3	4.83	0.06	1.18	0.03	0.63	0.06	1.15	0.01	0.14	0.09	1.77
4	2.39	0.04	1.55	0.00	0.00	0.02	0.83	0.02	0.92	0.05	1.98
5	8.73	0.03	0.29	0.03	0.33	0.00	0.00	0.02	0.21	0.04	0.49

For the ROMA score using premenopausal status, the between lots %CV for five samples was <3.52% and the total %CV was <7.72%. For the ROMA score using postmenopausal status, the between lots %CV was <1.33% for five samples and the total %CV was <4.10%. The results met the sponsor's acceptant criteria.

Site-to-site reproducibility: Three sites were involved for the site-to-site reproducibility by testing a panel of 5 serum samples with one lot of HE4 EIA and one lot of ARCHITECT CA 125 II reagent and calibrator kits. At each site, the assay was repeated for 6 days performing two runs per day with the samples analyzed in two replicates per run for ARCHITECT CA 125 II and four replicates per run for the HE4 EIA. The two runs per day were separated by a minimum of 2 hours. For HE4 EIA, two operators performed the test and each operator performed at non-consecutive days of testing. For ARCHITECT CA 125 II assay, a single operator was responsible at each site for all runs of testing. All runs were performed according to each assay's package insert. Both premenopausal and postmenopausal ROMA scores were calculated using separate algorithm both manually and by using ROMA calculator Tool Software CD (BETA version 0.00.15). The precision for

between-run, within-run, between-day, between-operators, and between-sites were evaluated. The data for between-sites and total precision for 5 samples is summarized below.

Sample	N	Mean ROMA Score	Between sites		Total*	
			SD	%CV	SD	%CV
Premenopausal ROMA score						
1	72	0.56	0.11	19.0	0.15	25.9
2	72	1.16	0.17	14.6	0.19	16.87
3	72	2.66	0.14	5.37	0.30	11.18
4	72	1.13	0.18	16.02	0.23	20.66
5	72	8.59	0.05	0.53	0.18	2.07
Postmenopausal ROMA score						
1	72	0.96	0.08	8.65	0.11	11.16
2	72	2.39	0.12	5.17	0.15	6.40
3	72	4.75	0.12	2.45	0.19	3.92
4	72	2.25	0.15	6.65	0.18	8.14
5	72	8.72	0.05	0.56	0.09	0.98

* Total precision include within-run, between-run, between-day, between operator, and between-site precision.

Simulation precision: In order to demonstrate precision of all possible combinations of analytes, a simulation precision study for ROMA score was conducted based on the precision profiles of HE4 and CA 125 with different combinations of values of these two analytes. The statistical analysis of simulation of ROMA score precision showed acceptable precision covering the range of ROMA score from 0 to10.

b. *Linearity/assay reportable range:*
Not applicable

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Each assay uses its own calibrator and controls.

HE4 EIA calibrators and controls: Ig-HE4 is a fusion protein consisting of a human Fc antibody fragment and Human Epididymis protein HE4. The Ig-HE4 antigen is used as a calibrator protein in the HE4 assay to determine HE4 concentrations in human serum samples. The protein is produced in a stably transfected Chinese Hamster Ovary (CHO) cell line. The cell line was adapted to serum free growth medium at Fujirebio Diagnostics, Inc. Recombinant antigen is used to prepare calibrators for the HE4 EIA Kit.

ARCHITECT CA 125 II calibrators and controls: The OC125 defined antigen is used in the ARCHITECT CA 125 II Calibrators and Controls. The concentrations are specific to each calibrator and control level. This material is obtained from Fujirebio Diagnostics, Inc. proprietary human ovarian carcinoma cell line, McDonalds. OC 125 defined antigen is produced by the McDonalds cell line. The stock solution for calibrators is prepared by adding OC 125 defined antigen to a diluent to achieve the desired concentrations. The stock solution is tested to determine its actual concentration. Each Calibrator and Control is then prepared based on the actual concentration of the stock solution.

Stability:
Specimen: ROMA is intended for use with serum. The specimen stability and storage claims are limited to the HE4 EIA assay. Serum can be stored at 2–8°C for 3 days before being tested. Samples can be stored at -40°C or colder for longer periods.

Calibration Curve: For HE4 EIA, the calibration is generated with every run. For CA125 II, the calibration curve is stable up to 30 days.

Reagent Closed-Vial: Users are instructed to refer to the individual stability information in the package insert of each assay. The claimed stability for HE4 EIA is up to 18 month at 2–8°C. The claimed shelf life for ATCHITECT is 12 months at 2–8°C. Reagent stability for ROMA is limited to 2–8 °C for 12 months.

Reagent Open-Vial: Users are instructed to refer to the stability information in the package insert for reagents used in the individual assay. The stability of the opened reagents used in HE4 EIA and ARCHITECT CA125 II kit are listed below:

Component	Stability	
	Opened Vial	Opened Vial/On-board
HE4 EIA		
Streptavidin Microplate	2–8°C for 18 months	
HE4 Calibrator A, Biotin anti-HE4, HRP anti-HE4, Tracer, Tracer Diluent, Substrate, Wash Concentrate, Stop Solution	2–8°C for 18 months	
HE 4 Calibrator B-F	2–8°C for 4 weeks ≤ -20°C for 4 months	
ARCHITECT CA 125 II		

Component	Stability	
	Opened Vial	Opened Vial/On-board
CA 125 II Microparticle	2–8°C for 12 months	30 days at 2–8 °C
CA 125 II Conjugate	2–8°C for 12 months	30 days at 2–8 °C
CA 125 II Calibrators	2–8°C for 12 months	

d. Detection limit:

The limits of detection and limits of quantitation reported in each assay's package insert are incorporated into the algorithm such that results outside of the measuring interval are not imported and do not yield an ROMA score.

e. Analytical specificity:

Interference: Studies were conducted to evaluate the interference of ROMA score by hemoglobin, bilirubin (conjugated and unconjugated), lipid (triglyceride), rheumatoid factor (RF), and human anti-mouse antibodies (HAMA). CLSI guideline, EP7-A "Interference Testing in Clinical Chemistry, Approved Guideline", was used to design the interference experiments. Three pooled serum samples with ROMA score at low (~0.56 for premenopausal and ~0.98 for postmenopausal), medium (~1.32 for premenopausal and ~2.42 for postmenopausal) and high (~3.11 for premenopausal and ~5.30 for postmenopausal) were used in the studies. These samples were then supplemented with each interfering substance. The control samples were prepared without corresponding interfering substance. The control samples and test samples were tested in replicates of five (5) using both HE4 EIA and ARCHITECT CA 125 II. The ROMA score was calculated for each sample and its control sample using a mean of 5 replicates of HE4 EIA and the mean of 5 replicates of ARCHITECT CA 125 II. The effect of each interfering substance on the ROMA score was assessed by comparing the measurement of each test sample to the control. Acceptance criteria for interference were <10% difference between the sample with interferent and control. The summary of the result is shown below:

Interferent	Substance Conc.	% Difference From Control					
		ROMA (low)		ROMA (med)		ROMA (high)	
		Pre[1]	Post[2]	Pre	Post	Pre	Post
Hemoglobin	5 mg/mL	-6.7	-3.4	0.5	0.6	4.0	1.0
Bilirubin (Conjugated)	20 mg/dL	2.3	1.2	-3.9	0.0	-5.5	-1.6
Bilirubin (Unconjugated)	20 mg/dL	2.8	2.3	3.9	1.9	-4.7	-1.2
Protein	12 g/dL	-3.7	-2.0	1.4	-0.8	-0.3	-1.1
Lipid	3 g/dL	8.8	3.2	-4.0	-4.3	-1.0	-1.5
HAMA	1000 ng/mL	7.7	9.2	-3.2	-0.9	0.9	-0.3
Rheumatoid Factor	1000 IU/mL	7.7	28.2	-1.0	6.0	2.7	-0.6
	500 IU/mL	-6.9	12.6	2.6	3.6	-2.5	-1.5
	250 IU/mL	-0.6	-0.6	0.6	0.8	2.6	0.0

1 ROMA score used the equation for premenopausal status;
2 ROMA score used the equation for postmenopausal status.

Except for RF, no significant interference is indicated at the concentrations evaluated for all interferent substances tested. Specimens containing levels of RF at 500 IU/mL and 1000 IU/mL showed >10% difference between the sample with RF and control with 12.6% and 28.2% respectively. The results indicated that specimens containing levels of RF above 250 IU/mL interfere with the ROMA score and are not appropriate for ROMA test.

f. Assay cut-off:
See clinical cut-off

2. Comparison studies:
   a. Method comparison with predicate device:
   Not applicable
   b. Matrix comparison:
   Serum is the only claimed matrix.
3. Clinical studies:
   a. Clinical Sensitivity/Clinical Specificity:
   Clinical study was done to validate ROMA in pre- and postmenopausal women presenting to a generalist with an adnexal mass, for whom a decision to undergo surgery has been made. The study is severed as validation set in the general population, or Pivotal Trial, of the algorithm previously developed in the Pilot Study.

   The validation study was a prospective, multi-center, blinded, clinical trial that enrolled a total of 512 patients at the 13 study sites. The patients were female patients over 18, presenting to a generalist at a general or specialty hospital with an ovarian cyst or an adnexal mass (defined as a simple, complex or a solid ovarian/pelvic mass) and were scheduled to undergo surgery. Blood samples were collected from all patients and tested on the HE4 EIA and ARCHITECT CA 125 II at Fujirebio Diagnostics AB. Menopausal status was determined for all subjects first by completing chart review and, if menopausal status was not defined, it was determined by age (≤49 pre-menopausal and ≥55 postmenopausal), 1 year post menses, and Follicle Stimulating Hormone (FSH) level. The Initial Cancer Risk Assessment (ICRA) and all clinical information relating to the surgical procedures, including imaging reports and final pathology reports, were collected. All patients underwent surgery and tissues were examined by local pathologists. An independent pathologist, Director, Division of Anatomic Pathology, from the University of Maryland School of Medicine, reviewed all imaging reports, case report forms and histopathology reports from each patient's institution pathologist, checking for discrepancies in the data. The performance of standalone use of ICRA, standalone use of ROMA and adjunctive use of ICRA and ROMA were evaluated by comparing to histopathology results for detecting the presence of ovarian malignancy.

   A total of 512 patients were enrolled at the 13 study sites and ICRA was

completed for 486 patients. Among them, ICRA of 370 patients (76.1%) were completed by general Obstetrician/Gynecologists. For the 116 remaining patients, the ICRAs were completed by other specialists including family medicine specialists (9.5%), internal medicine specialist (4.3%), and other specialists (e.g., gynecologic oncologists, medical oncologists, general surgeons) (less than 1%).

Of the 512 patients, 51 patients were excluded from analysis. The most common reason for exclusion was no surgery was performed to remove an adnexal mass. In the final total of 461 (90.0%) evaluable patients, 240 (52.1%) were premenopausal and 221 (47.9%) were postmenopausal. All of the major racial groups were represented with 85% of White, 7% of Black, 3% Hispanic, 3% Asian, and 2% of other ethnicity.

Among the 461 evaluable patients, 375 (81.3%) had a diagnosis of benign disease, 48 (10.4%) was diagnosis with epithelial ovarian cancer (EOC) and 38 (8.2%) were diagnosed with other cancers or low malignant potential (LMP) tumors. The statistics for enrolled subjects with pathology classification are summarized in the following table.

	All N=461		**Premenopausal N=240**		**Postmenopausal N=221**	
	N	**%**	**N**	**%**	**N**	**%**
Histopathology Benign	375	81.3	220	91.7	155	70.1
Borderline/LMP	18	3.9	7	2.9	11	5.0
EOC	48	10.4	9	3.7	39	17.6
Non-EOC	2	0.4	0	0.0	2	0.9
Other Gynecological Cancer	10	2.2	3	1.2	7	3.2
Other Cancer	7	1.5	1	0.4	6	2.7
Metastatic Cancer	1	0.2	0	0.0	1	0.5

The ROMA test used the following cut points to evaluate the performance of the test in pre- and postmenopausal women presenting to a generalist with an adnexal mass, for whom a decision to undergo surgery has been made:

Premenopausal:

ROMA score $\geq$ 1.31	High likelihood of finding malignancy
ROMA score < 1.31	Low likelihood of finding malignancy

Postmenopausal:

ROMA score $\geq$ 2.77	High likelihood of finding malignancy
ROMA score < 2.77	Low likelihood of finding malignancy

The information provided by the ROMA test should be used by physician only as an adjunctive test to complement, not replace, other diagnostic and clinical procedures. The ability of ROMA to contribute to the ICRA was evaluated by

comparing the sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) for standalone use of ROMA, and adjunctive use of ICRA and ROMA based on four sets of diagnosis: EOC; EOC, including LMP tumors; All Cancers; All Cancers, including LMP tumors. For each set of diagnosis, the results were cross-tabulated in a 2x2x2 table of the malignancy as determined by histopathology, test result (positive or negative) by ICRA, and test result (positive/high likelihood or negative/low likelihood) by ROMA.

The performance of ROMA evaluated for diagnosis of EOC including LMP and diagnosis of all cancer including LMP are presented below.

Performance of ROMA for Diagnosis of EOC including LMP:
Combined pre- and postmenopausal subjects:
For diagnosis of EOC including LMP, the counts for combined pre- and postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are summarized in separate tables below.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	49	9	58
	Negative	2	6	8
	Total	51	15	66

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	28	64	92
	Negative	31	252	283
	Total	59	316	375

To examine whether the ROMA test provides additional information when used in combination with ICRA, the ability of ROMA to contribute to the ICRA was analyzed.

The following table presents the observed frequencies of malignancy tabulated according to ICRA and ROMA test results from 441 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 15% (66/441)		
ICRA alone "Positive"	46.4% (51/110)	37.3% – 55.6%
ICRA alone "Negative"	4.5% (15/331)	2.8% – 7.3%
ROMA alone "Positive"	38.7% (58/150)	31.2% – 46.7%
ROMA alone "Negative"	2.7% (8/291)	1.4% – 5.3%
ICRA "Positive" and ROMA "Positive"	63.6% (49/77)	52.5% – 73.5%
ICRA "Positive" and ROMA "Negative"	6.1% (2/33)	1.7% – 19.6%
ICRA "Negative" and ROMA "Positive"	12.3% (9/73)	6.6% – 21.8%
ICRA "Negative" and ROMA "Negative"	2.3% (6/258)	1.1% – 18.6%

The same information about the frequencies of malignancy is presented by the likelihood ratios: Likelihood ratio (Result) = Pr(Result|Malignancy) / Pr(Result|No Malignancy). Likelihood ratio is a way of quantifying how much a given test result changes the pre-test probability of malignancy in a patient.

	Likelihood Ratio	95% CI
ICRA alone "Positive"	4.91	3.38% – 5.28%
ICRA alone "Negative"	0.27	0.16% – 0.31%
ROMA alone "Positive"	3.58	2.58% – 3.78%
ROMA alone "Negative"	0.16	0.08% – 0.21%
ICRA "Positive" and ROMA "Positive"	9.94	6.25% –11.10%
ICRA "Positive" and ROMA "Negative"	0.37	0.09% – 1.04%
ICRA "Negative" and ROMA "Positive"	0.80	0.40% – 1.02%
ICRA "Negative" and ROMA "Negative"	0.14	0.06% – 0.19%

The likelihood ratio for identifying malignancy by adjunctive use of ROMA and ICRA is 9.94, almost 2 times higher than the likelihood ratio by ICRA alone (4.91). The performance of adjunctive use of ROMA and ICRA for diagnosis of EOC including LMP was further evaluated by calculating sensitivity, specificity, PPV, and NPV and compared to standalone use of ICRA. The table below shows the performance characteristics of the tests.

Performance of the Test for Diagnosis of ECO including LMP for both Pre- and Postmenopausal Subjects			
	ICRA	ROMA	ICRA and ROMA
Sensitivity (95% CI)	77.3% (51/66) (65.8% – 85.7%)	87.9% (58/66) (77.9% – 93.7%)	90.9% (60/66) (81.6% – 95.7%)
Specificity (95% CI)	84.3% (316/375) (80.2% – 87.6%)	75.5% (283/375) (70.9% – 79.5%)	67.2% (252/375) (62.3% – 71.8%)
PPV (95% CI)	46.4% (51/110) (37.3% – 55.6%)	38.7% (58/150) (31.2% – 46.6%)	32.8% (60/183) (26.4% – 39.9%)
NPV (95% CI)	95.5% (316/331) (92.7% – 97.2%)	97.3% (283/291) (94.7% – 98.6%)	97.7% (252/258) (95.0% – 98.9%)
Prevalence	15.0% (66/441)		

With adjunctive use of ICRA and ROMA, sensitivity for malignancy increased from 77.3% to 90.0%. Specificity for malignancy decreased from 84.3% to 67.2%. PPV for the adjunctive use of ICRA and ROMA decreased from 46.4% to 32.8% due to an increase in the number of false positive test added by addition of ROMA to ICRA. However, NPV of adjunctive use of ICRA and ROMA increased from 95.5% to 97.7%. The confidence interval for 2.2% increase of NPV was 0.43% to 3.98%. This observed increase in NPV was statistically significant, supporting the improved performance with adjunctive use of ICRA and ROMA compared to standalone ICRA.

Pre-menopausal subjects:

To evaluate the ROMA for diagnosis of EOC including LMP in premenopausal subject, data and statistical analysis were performed and summarized below.

The counts for premenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in the following tables.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	7	6	13
	Negative	0	3	3
	Total	7	9	16

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	9	47	56
	Negative	13	151	164
	Total	22	198	220

The performance of ICRA alone, ROMA alone and adjunctive use of ROMA and ICRA for diagnosed of EOC including LMP in premenopausal subjects are presented in the following table.

Performance of Test for Diagnosis of ECO Including LMP for Premenopausal Subjects:			
	ICRA	ROMA	ICRA and ROMA
Sensitivity (95% CI)	43.8% (7/16) (23.1% – 66.6%)	81.3% (13/16) (57.0% – 93.1%)	81.3% (13/16) (57.0% – 93.1%)
Specificity (95% CI)	90.0% (198/220) (85.3% – 93.3%)	74.5% (164/220) (70.9% – 79.5%)	68.6% (151/220) (62.2% – 74.4%)
PPV (95% CI)	24.1% (7/29) (12.2% – 42.0%)	18.8% (13/69) (11.4% – 29.6%)	15.9% (13/82) (9.5% – 25.2%)
NPV (95% CI)	95.7% (198/207) (91.9% – 97.7%)	98.2% (164/167) (94.9% – 99.4%)	98.1% (151/154) (94.4% – 99.3%)
Prevalence	6.8% (16/236)		

The prevalence of EOC including LMP for premenopausal women was 6.8%. For premenopausal subjects, comparing to ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ROMA increased from 43.8% to 81.3%, and specificity for malignancy decreased from 90.0% to 68.6%. PPV for the adjunctive use of ICRA and ROMA decreased from 24.1% to 15.9% and NPV of adjunctive use of ICRA and ROMA increased from 95.7% to 98.1%. The increase of 2.4% of NPV (95% CI: 0.07%-4.73%) by combining ICRA and ROMA is statistically significant and results in fewer False Negative tests with an increased number of women referred to oncology specialists.

Post-menopausal subjects:

To evaluate the ROMA for diagnosis of EOC including LMP in postmenopausal subject, data and statistical analysis were performed and summarized below.

The counts for postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	42	3	45
	Negative	2	3	5
	Total	44	6	50

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	19	17	36
	Negative	18	101	119
	Total	37	118	155

The performance of ICRA alone, ROMA alone and adjunctive use of ROMA and ICRA for diagnosis of EOC including LMP in postmenopausal subjects re presented in the following table.

Performance for the Test for Diagnosis of EOC including LMP for Postmenopausal Subjects:			
	ICRA	ROMA	ICRA and ROMA
Sensitivity (95% CI)	88.0% (44/50) (76.2% – 94.3%)	90.0% (45/50) (78.6% – 95.6%)	94.0% (47/50) (83.8% – 97.8%)
Specificity (95% CI)	76.1% (118/155) (68.8% – 82.1%)	76.8% (119/155) (69.5% – 82.7%)	65.2% (101/155) (57.4% – 72.2%)
PPV (95% CI)	54.3% (44/81) (43.5% – 64.7%)	55.6% (45/81) (44.7% – 65.9%)	46.5% (47/101) (37.1% – 56.2%)
NPV (95% CI)	95.2% (118/124) (89.8% – 97.7%)	96.0% (119/124) (90.9% – 98.2%)	97.1% (101/104) (91.9% – 99.0%)
Prevalence	24.4% (50/205)		

The prevalence of EOC including LMP for postmenopausal women was 24.4%. Comparing to use of ICRA only, the sensitivity for malignancy by

adjunctive use of ICRA and ROMA increased 6% (from 43.8% to 81.3%) and specificity decreased 10.9% (from 54.3% to 46.5%). PPV of addition of ROMA to ICRA decreased from 54.3% to 46.5% compared to ICRA alone, and NPV increased from 95.2% to 97.1%. The confidence interval for observed increase of NPV (1.95%) was -0.75% to 4.66%.

Performance of ROMA for Diagnosis of All Cancers including LMP:
Combined pre- and postmenopausal subjects:
To evaluate the ROMA for diagnosis of All Cancers including LMP, data and statistical analysis were performed for total 461 subjects including both pre- and postmenopausal subjects.

The counts including both pre- and postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	58	13	71
	Negative	5	10	15
	Total	63	23	86

No Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	28	64	92
	Negative	31	252	283
	Total	59	316	375

The following table presents the observed frequencies of malignancy tabulated according to ICRA and ROMA test results from the 461 patients.

	Frequency of Malignancy	95% CI
Prevalence of malignancy among patients with adnexal mass assessed: 18.7% (86/461)		
ICRA alone "Positive"	51.6% (63/122)	42.9% – 60.3%
ICRA alone "Negative"	6.8% (23/339)	4.6% – 10.0%
ROMA alone "Positive"	43.6% (71/163)	36.2% – 51.2%
ROMA alone "Negative"	5.0% (15/298)	3.1% – 8.1%
ICRA "Positive" and ROMA "Positive"	67.4% (58/86)	57.0% – 76.4%
ICRA "Positive" and ROMA "Negative"	13.9% (5/36)	6.1% – 28.7%
ICRA "Negative" and ROMA "Positive"	16.9% (13/77)	10.1% – 26.8%
ICRA "Negative" and ROMA "Negative"	3.8% (10/262)	2.1% – 6.9%

The same information about the frequencies of malignancy is presented by the observed likelihood ratio.

	Likelihood Ratio	95% CI
ICRA alone "Positive"	4.66	3.26% – 4.97%
ICRA alone "Negative"	0.32	0.21% – 0.35%
ROMA alone "Positive"	3.37	2.47% – 3.53%
ROMA alone "Negative"	0.23	0.14% – 0.27%
ICRA "Positive" and ROMA "Positive"	9.03	5.75% – 10.02%
ICRA "Positive" and ROMA "Negative"	0.70	0.27% – 1.11%
ICRA "Negative" and ROMA "Positive"	0.89	0.49% – 1.06%
ICRA "Negative" and ROMA "Negative"	0.17	0.09% – 0.21%

The likelihood ratio for identifying malignancy is 9.03 by ROMA (+) and ICRA (+) and 4.66 by ICRA alone. The performance of adjunctive use of ROMA and ICRA for diagnosis of All Cancers including LMP was further evaluated by calculating sensitivity, specificity, PPV, and NPV and compared to standalone use of ICRA. The table below shows the performance characteristics of the tests.

Performance of the Test for Diagnosis of All Cancers including LMP for both Pre- and Postmenopausal Subjects:			
	ICRA	**ROMA**	**ICRA and ROMA**
Sensitivity (95% CI)	73.3% (63/86) (63.1% – 81.4%)	82.6% (71/86) (73.2% – 89.1%)	88.4% (76/86) (79.9% – 93.5%)
Specificity (95% CI)	84.3% (316/375) (80.2% – 87.6%)	75.5% (283/375) (70.9% – 79.5%)	67.2% (252/375) (62.3% – 71.8%)
PPV (95% CI)	51.6% (63/122) (42.9% – 60.3%)	43.6% (71/163) (36.2% – 51.2%)	38.2% (76/199) (31.7% – 45.1%)
NPV (95% CI)	93.2% (316/339) (90.0% – 95.4%)	95.0% (283/298) (91.9% – 96.9%)	96.2% (252/262) (93.1% – 97.9%)
Prevalence	18.7% (86/461)		

Compared to use of ICRA alone, sensitivity of addition of ROMA to ICRA increased 15.1% (from 73.3% to 88.4%) and specificity decreased from 84.3% to 67.2%. PPV for the adjunctive use of ICRA and ROMA decreased from 46.4% to 32.8% due to an increase in the number of false positive test added by addition of ROMA to ICRA. NPV of adjunctive use of ICRA and ROMA increased 2.97% (from 95.5% to 97.7%) with 95% of the confidence interval of 0.91%-5.03%. Such observed increase in NPV with addition of ROMA to ICRA was statistically significant, supporting the improved performance with adjunctive use of ICRA and ROMA comparing to ICRA only.

Premenopausal Subjects:

To evaluate the ROMA for diagnosis of All Cancers including LMP in premenopausal subject, data and statistical analysis were performed and summarized below.

The counts for premenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	**Negative**	**Total**
ROMA	**Positive**	7	8	15
	Negative	0	5	5
	Total	7	13	20

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	9	47	56
	Negative	13	151	164
	Total	22	198	220

The frequencies of malignancy and likelihood ratio were analyzed. The performance characteristics of ICRA alone, ROMA alone and adjunctive use of ROMA and ICRA for diagnosed of All Cancers including LMP in premenopausal subjects are presented in the following table.

Performance of the Test for Diagnosis of All Cancers including LMP in Premenopausal Subjects:			
	ICRA	ROMA	ICRA and ROMA
Sensitivity (95% CI)	35.0% (7/20) (18.1% – 56.5%)	75.0% (15/20) (53.1% – 88.6%)	75.0% (15/20) (53.1% – 88.6%)
Specificity (95% CI)	90.0% (198/220) (85.3% – 93.3%)	74.5% (164/220) (68.4% – 79.8%)	68.6% (151/220) (62.2% – 74.4%)
PPV (95% CI)	24.1% (7/29) (12.2% – 42.0%)	21.1% (15/71) (13.2% – 31.9%)	17.9% (15/84) (11.1% – 27.4%)
NPV (95% CI)	93.8% (198/211) (89.7% – 96.4%)	97.0% (164/169) (93.3% – 98.7%)	96.8% (151/156) (92.7% – 98.6%)
Prevalence	8.3% (20/240)		

The prevalence of All Cancers including LMP for premenopausal women was 8.3%. Comparing to ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ROMA increased from 35.0% to 75.0%, and specificity decreased from 90.0% to 68.6%. PPV for the adjunctive use of ICRA and ROMA decreased from 24.1% to 17.9% and NPV of adjunctive use of ICRA and ROMA increased from 93.8% to 96.8%. The increase of 2.96% by combining ICRA and ROMA results in fewer False Negative tests with an increased number of women referred to oncology specialists. The 95% confidence interval for observed increase of NPV (2.96%) was 0.33% to 5.58%. The observed increase in NPV with addition of ROMA to ICRA was statistically significant, supporting the improved performance of addition of ROMA to ICRA.

Postmenopausal subjects:
To evaluate the ROMA for diagnosis of All Cancers including LMP in

postmenopausal subjects, data and statistical analysis were performed and summarized below.
The counts for postmenopausal subjects with malignancy by pathology and with no malignancy by pathology are shown in tables below.

Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	51	5	56
	Negative	5	5	10
	Total	56	10	66

No Malignancy by Pathology				
		ICRA		
		Positive	Negative	Total
ROMA	Positive	19	17	36
	Negative	18	101	119
	Total	37	118	155

The performance of ICRA alone, ROMA alone and adjunctive use of ROMA and ICRA for diagnosis of All Cancers including LMP in postmenopausal subjects presented in the following table.

Performance of the Test for Diagnosis of All Cancers including LMP for Postmenopausal Subjects:			
	ICRA	ROMA	ICRA and ROMA
Sensitivity (95% CI)	84.8% (56/66) (74.3% – 91.5%)	84.8% (56/66) (74.3% – 91.5%)	92.4% (61/66) (83.5% – 96.7%)
Specificity (95% CI)	76.1% (118/155) (68.8% – 82.1%)	76.8% (119/155) (69.5% – 82.7%)	65.2% (101/155) (57.4% – 72.2%)
PPV (95% CI)	60.2% (56/93) (50.1% – 69.5%)	60.9% (56/92) (50.7% – 70.2%)	53.0% (61/115) (44.0% – 61.9%)
NPV (95% CI)	92.2% (118/128) (86.2% – 95.7%)	92.2% (119/129) (86.3% – 95.7%)	95.3% (101/106) (89.4% – 97.9%)
Prevalence	29.9% (66/221)		

The prevalence of All Cancers including LMP for postmenopausal women was 29.9%. Comparing to use of ICRA only, the sensitivity for malignancy by adjunctive use of ICRA and ROMA increased 7.6% (from 84.8% to 92.4%). Compared to use ICRA alone, PPV of the adjunctive use of ROMA and ICRA decreased from 60.2% to 53.0% and NPV increased from 92.2% to 95.3%. The confidence interval for observed increase of NPV (3.10%) was –0.22% to 6.42%.

Ability of Adjunctive Use of ROMA and ICRA to Identifying Additional Malignancies:

The Table below shows the counts of cancers identified by adjunctive use of ROMA and ICRA compared to by ICRA alone.

Cancers	Premenopausal	Postmenopausal	Combined
EOC	4	0	4
EOC + LMP	6	3	9
All Cancers	6	2	8
All Cancers + LMP	8	5	13

According to sponsor, addition of ROMA to ICRA detected 13 additional cancers missed by the ICRA with an acceptable rate of concomitant false positives.

Association between the ROMA Score and Likelihood of Malignancy:

Summary statistics for the ROMA scores, for subjects who had a primary ovarian malignancy are given by cancer stage in the table below.

		Stage I	Stage II	Stage III
Pre-menopausal	N	7	1	8
	Mean	3.81	9.37	8.36
Post-menopausal	N	19	4	33
	Mean	4.39	5.49	8.51

To demonstrate whether higher ROMA is associated with an increased likelihood of cancer, additional analysis was conducted by splitting the patients at the cut-off point and finding the median ROMA score within each split gives two balanced groups below the cutoff and additional groups above. The results were summarized below.

Premenopausal (cut-off: 1.31)						
ROMA Score		0-0.77	0.77-1.31	1.31-2.20	2.20-3.50	3.50-10
Benign	Observed	87	78	36	16	4
	Expected	81.61	74.28	33.01	16.51	15.59
Cancer	Observed	2	3	0	2	13
	Expected	7.39	6.72	2.99	1.49	1.41
	Total	89	81	36	18	17
Cancer %		2.2% (2/89)	3.7% (3/81)	0% (0/36)	11.1% (2/18)	76.5% (13/17)

Postmenopausal (cut-off: 2.77)					
ROMA Score		0-1.50	1.50-2.77	2.77-6.16	6.16-10
Benign	Observed	64	59	31	4
	Expected	47.26	46.55	32.45	31.7
Cancer	Observed	3	7	15	41
	Expected	19.74	19.45	13.55	13.26
	Total	67	66	46	45
Cancer %		4.5% (3/67)	10.6% (7/66)	32.6% (15/46)	91.1% (41/45)

b. Other clinical supportive data:
According to the sponsor, algorithm for ROMA was developed by using a training set obtained by pooling data across two separate Pilot Studies at two sites and combined CA 125 and HE4 concentrations in a logistic model and provides a probability of finding cancer in a given patient. In that study, the cut-off was determined to achieve a specificity of 75%. Also, 80% sensitivity was set as the required minimum sensitivity for the score for premenopausal and postmenopausal women combined as the threshold for acceptance of this analysis. The cut-points defined by 75% specificity were 1.31 for premenopausal patients and 2.77 for postmenopausal patients.

4. Clinical cut-off**:**
The following cut-offs are used to interpret the result. The ROMA score is between 0.0 and 10.0.
Premenopausal women:
ROMA score ≥1.31 High likelihood of finding malignancy
ROMA score <1.31 Low likelihood of finding malignancy

Postmenopausal women:
ROMA score ≥2.77 High likelihood of finding malignancy
ROMA score <2.77 Low likelihood of finding malignancy

5. Expected values/Reference range:
In order to determine the normal and reference ranges of ROMA score in healthy women, 120 premenopausal samples and 120 postmenopausal samples (total = 240 samples) were tested. Samples covered age ranging from 20 to 87 and represented whites (96.7%), African American (2.5%) and Hispanic (0.8%) subjects. The results for ROMA score obtained from the pre- and post-menopausal populations are presented below:

	All Tested Subjects	Premenopausal Healthy Subjects	Postmenopausal Healthy Subjects
N	240	120	120
ROMA Score			
Mean (SD)	1.19 (0.76)	0.94 (0.75)	1.44 (0.68)
Median	0.98	0.72	1.30
Range (min, max)	0.22-4.58	0.22-4.51	0.39-4.58
Reference Interval (5^{th}, 95^{th} percentile)	0.39, 2.75	0.33, 2.36	0.61, 2.75
ROMA Score (n, %)			
High Likelihood	25 (10.4%)	19 (15.8%)	6 (5.0%)
Low Likelihood	215 (89.6%)	101 (84.2%)	114 (95.0%)

Overall, 95% of the premenopausal healthy women had a ROMA score equal to or below 2.36. 95% of the postmenopausal healthy women had a ROMA score equal to or below 2.75. It is recommended that each laboratory establish its own reference value for the population of interest.

Expected values in Non-Ovarian Malignancy Condition: To evaluate the performance of ROMA in subjects with other benign and other malignant conditions, the ROMA was evaluated in women with benign conditions (benign gynecological disease, congestive heart failure (CHF), hypertension, pregnant, and other benign disease) and in women with other malignant conditions (bladder cancer, breast caner, endometrial cancer, gastrointestinal cancer, and lung cancer). A total of 978 subjects were analyzed. The table below summarized the results analyzed for premenopausal and postmenopausal samples.

	Bladder Cancer (N=40)		Breast Cancer (N=40)		Endometrial Cancer (N=40)		GI Cancer (N=39)		Lung Cancer (N=40	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
N	5	35	12	28	4	36	11	28	0	40
ROMA										
Mean (SD)	3.60 (4.24)	5.72 (2.87)	4.36 (3.34)	4.59 (3.00)	1.70 (0.81)	5.85 (2.85)	1.56 (0.63)	4.34 (2.95)	-	4.70 (2.45)
Median	1.15	5.38	2.80	3.75	1.88	5.62	1.75	2.91	-	4.60
Range (min-max)	0.38-10.0	0.78-9.89	0.60-9.93	1.18-9.92	0.67-2.39	1.17-9.99	0.55-2.40	1.00-9.24	-	0.74-9.63
5^{th}, 95^{th} percentile	0.42, 9.18	1.58, 9.78	1.00, 9.85	1.42, 9.76	0.79, 2.38	1.83, 9.91	0.66, 2.36	1.22, 9.04	-	0.98, 9.14
ROMA Likelihood (n, %)										
High Likelihood	2 (40%)	29 (83%)	11 (92%)	15 (54%)	3 (75%)	30 (83%)	6 (54.5%)	15 (54%)	-	31 (77.5%)
Low Likelihood	3 (60%)	6 (17%)	1 (8%)	13 (46%)	1 (25%)	6 (17%)	5 (45.5%)	13 (46%)	-	9 (22.5%)

	Benign Gynecological Disease (N=381)		Other Benign Disease (N=30)		CHF (N=40)		Hypertension (N=40)		Pregnant (N=38)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
N	222	159	13	27	0	40	4	36	38	-
ROMA										
Mean (SD)	1.12 (0.73)	2.15 (1.44)	1.29 (0.86)	2.41 (1.58)	-	3.09 (1.82)	0.85 (0.40)	2.50 (1.73)	1.01 (0.59)	-
Median	0.92	1.71	0.96	1.97	-	2.53	0.89	1.99	0.88	-
Range (min-max)	0.19-3.82	0.40-8.56	0.15-2.65	0.57-6.97	-	0.83-7.93	0.33-1.29	0.83-8.38	0.28-3.47	-
5^{th}, 95^{th} percentile	0.40, 2.81	0.70, 4.82	0.27, 2.56	0.77, 5.92	-	1.08, 5.95	0.40, 1.24	0.91, 5.69	0.34, 1.94	-
ROMA Likelihood (n, %)										
High Likelihood	57 (26%)	37 (23%)	6 (46%)	9 (33%)	-	17 (42.5%)	0 (0%)	12 (33%)	7 (18%)	-
Low Likelihood	165 (74%)	122 (77%)	7 (54%)	18 (67%)	-	23 (57.5%)	4 (100%)	24 (67%)	31 (82%)	-

N. Proposed Labeling:

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

O. Conclusion:

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