

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

A. 510(k) Number:

k141375

B. Purpose for Submission:

New device

C. Measurand:

IgG antibodies specific for M2 protein

D. Type of Test:

Fluoroenzyme immunoassay, semi-quantitative

E. Applicant:

Phadia US Inc.

F. Proprietary and Established Names:

EliA™ M2 Immunoassay
EliA™ M2 Positive Control 100
EliA™ M2 Positive Control 250

G. Regulatory Information:

1. Regulation section:

21 CFR §866.5090, Antimitochondrial antibody immunological test system
21 CFR §862.1660, Quality control material (assayed and unassayed)

2. Classification:

Class II (Assays)
Class I (Controls)

3. Product code:

DBM, Antimitochondrial Antibody, Indirect Immunofluorescent, Antigen, Control
JJY, Multi-Analyte Controls, All Kinds (assayed)

4. Panel:

Immunology (82) (Assays)

H. Intended Use:

1. Intended use(s):

EliA M2 is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to M2 in human serum and plasma (heparin, EDTA) to aid in the clinical diagnosis of primary biliary cirrhosis in conjunction with other laboratory and clinical findings. EliA™ M2 uses the EliA™ IgG method on the instrument Phadia 100.

EliA M2 is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to M2 in human serum and plasma (heparin, EDTA) to aid in the clinical diagnosis of primary biliary cirrhosis in conjunction with other laboratory and clinical findings. EliA™ M2 uses the EliA™ IgG method on the instrument Phadia 250.

EliA M2 Positive Control 100 is intended for laboratory use in monitoring the performance of in vitro measurement of M2 antibodies with Phadia 100 using the EliA IgG method.

EliA™ M2 Positive Control 250 is intended for laboratory use in monitoring the performance of in vitro measurement of M2 antibodies with Phadia 250 using the EliA IgG method.

2. Indication(s) for use:

Same as intended use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

For use on the instruments Phadia® 100 and Phadia® 250 (k061165).

I. Device Description:

EliA™ uses a modular reagent system. The test-specific, method-specific and general reagents are packaged and purchased as separate units. The reagents on Phadia® 100 and Phadia® 250 are identical; they are only filled in different containers.

EliA™ M2 Test-Specific Reagents consist of:

- 1) EliA™ M2 wells coated with native pyruvate dehydrogenase complex from mitochondria and recombinant M2-antigen. The EliA™ wells are packed in carriers which are stored in sealed aluminum foil bags containing a desiccant.
- 2) EliA™ M2 Positive Control containing IgG antibodies to M2 in human serum.

- 3) EliA™ IgG/IgM/IgA Negative Control containing normal human serum from healthy donors. The EliA™ IgG/IgM/IgA Negative Control was cleared under k091845.

Also required for the test are EliA™ Method-Specific Reagents:

EliA™ IgG Calibrators (human IgG in PBS at measured concentrations 0, 4, 10, 20, 100, 600 µg/L), EliA™ IgG Curve Control (human IgG in PBS), EliA™ Sample Diluent (PBS containing BSA, detergent, and 0.095% sodium azide), EliA™ IgG Conjugate (β-galactosidase labeled mouse monoclonal anti- human IgG), and EliA™ IgG Calibrator Well.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):
INOVA QuantaLite™ M2 EP (MIT3) ELISA, (k052262)
2. Comparison with predicate:

Similarities		
Item	New Device EliA™ M2	Predicate QuantaLite™ M2 EP (MIT3) ELISA
Intended Use/Indications for Use	Measurement of IgG antibodies directed to M2 as an aid in the clinical diagnosis of primary biliary cirrhosis	Same
Solid Phase	Polystyrene microwells	Same
Reported Unit	U /mL	Same
Assay Format	Semi-quantitative	Same

Differences		
Item	New Device EliA™ M2	Predicate QuantaLite™ M2 EP (MIT3) ELISA
Assay Type	Automated fluoroenzyme immunoassay	Manual ELISA
Coating Antigens	Native pyruvate dehydrogenase complex from mitochondria and recombinant M2-antigen	Affinity-purified recombinant antigen (MIT3) containing immunodominant portions of PDC-E2, BCOADC-E2, and OGDC-E2
Sample Matrix	Serum and plasma (heparin, EDTA)	Serum
Sample Dilution	1:100 (manual or instrument dilution)	1:101 (manual dilution only)
Reaction Temperature	37°C (controlled)	Room temperature (20-26°C)

Differences		
Item	New Device EliA™ M2	Predicate QuantaLite™ M2 EP (MIT3) ELISA
Incubation times	Diluted patient samples: 30 min. Conjugate: 28 min. Development Solution: 39 min.	High positive, low positive and negative controls, diluted patient samples: 30 min. Conjugate: 30 min. Substrate: 30 min (in dark).
Detection Antibody (Conjugate)	Mouse monoclonal anti-human IgG β-Galactosidase	Goat anti-human IgG horseradish peroxidase
Substrate/Chromogen	4-Methylumbelliferyl-βD-Galactoside	Tetramethylbenzidine (TMB)
Stop Solution	Sodium Carbonate (4%)	Sulfuric Acid (0.344 M)
Signal	Fluorescence	Optical density
Instrumentation	Phadia 100 and 250 are fully automated immunoassay analyzers	Microwell plate reader (450 nm)
Calibration	Total IgG calibration	1-point calibration
Calibrators	6 vials of human IgG with assigned values of: 0, 4, 10, 20, 100, 600 µg/L	Not specified
Calibration Curve	Option to store the calibration curve for up to 28 days and run curve controls in each assay for calibration	Not specified
Internal Controls	Positive and Negative Control sera provided in a separate package	High Positive, Low Positive and Negative Control sera included in the assay kit
Limit of detection	0.5 U/mL	Not specified
Reportable Range	0.5 – 276 U/mL	Not specified
Results Interpretation	Negative: < 4 U/mL Equivocal: 4 – 6 U/mL Positive: > 6 U/mL	Negative: < 20 U/mL Equivocal: 20.1 – 24.9 U/mL Positive: > 25 U/mL

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

CSLI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

CLSI H18-A3: Procedures for the Handling and Processing of Blood Specimens; Approved Guideline

L. Test Principle:

The EliA™ M2 Wells are coated with native pyruvate dehydrogenase complex from mitochondria and recombinant M2-antigen. If present in the patient's specimen, antibodies to M2 bind to their specific antigen. After washing away non-bound antibodies, enzyme-labeled antibodies against human IgG antibodies (EliA IgG Conjugate) are added to form an antibody-conjugate complex. After incubation, non-bound conjugate is washed away and the

bound complex is incubated with a Development Solution. After stopping the reaction, the fluorescence in the reaction mixture is measured. The higher the value of fluorescent signal detected by the instrument, the higher the amount of antibody bound and detected in the sample tested. To evaluate test results, the response for patient samples is compared directly to the response for calibrators.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

At least 8 serum samples selected from different parts of the claimed assay range were tested on Phadia® 100 and Phadia® 250 instruments to establish intra- and inter-assay precision. Each sample was tested in 7 runs over 7 days in 4 replicates per run on 3 instruments. One batch was used to determine the precision of the assays on Phadia® 100 (equal to 84 replicate determinations per sample). Three batches were used to determine the precision of the assays on Phadia® 250 (equal to 252 replicate determinations per sample). Results summarized below met the manufacturer’s pre-determined percent coefficient of variation (%CV) specifications for intra-assay (<10.6% for Phadia® 100 and <10.1% for Phadia® 250), inter-assay (<11.5% for Phadia® 100 and <11.0% for Phadia® 250) and total (<16% for Phadia® 100 and Phadia® 250) imprecision.

EliA™ M2 on Phadia® 100 (n = 84)						
Mean value (U/mL)	Intra-assay		Inter-assay		Total Imprecision	
	SD	CV%	SD	CV%	SD	%CV
3.4	0.1	4.2	0.2	7.0	0.3	8.2
3.9	0.2	3.9	0.3	7.3	0.3	8.4
4.9	0.1	5.2	0.3	2.5	0.3	5.7
6.7	0.2	2.8	0.4	5.3	0.5	8.1
7.1	0.3	3.5	0.3	4.0	0.5	6.4
29.1	0.5	5.9	1.7	1.8	1.8	6.1
101.1	4.6	4.5	6.8	6.7	10.5	10.4
105.2	4.2	4.0	3.9	3.7	8.9	8.4
174.8	9.8	5.3	9.3	5.6	15.0	8.6
234.6	16.1	6.8	15.4	6.6	23.8	10.2
255.5	15.7	6.2	12.7	5.0	28.7	11.2

EliA™ M2 on Phadia® 250 (n = 252)						
Mean value (U/mL)	Intra-assay		Inter-assay		Total Imprecision	
	SD	CV%	SD	CV%	SD	%CV
3.7	0.1	2.4	0.1	2.2	0.1	3.6
3.8	0.1	2.3	0.1	1.6	0.1	2.9
5.4	0.2	3.7	0.2	3.1	0.4	7.4

EliA™ M2 on Phadia® 250 (n = 252)						
Mean value (U/mL)	Intra-assay		Inter-assay		Total Imprecision	
	SD	CV%	SD	CV%	SD	%CV
28.4	1.7	5.7	1.6	5.9	2.6	9.0
115.0	3.6	3.1	5.1	4.5	6.9	6.0
149.9	6.1	5.1	7.7	4.1	18.5	12.3
265.9	10.9	4.1	11.4	4.3	16.8	6.3
267.6	9.3	3.5	10.0	3.7	15.2	5.7

The %CV for instrument-to-instrument variability on the Phadia® 100 and Phadia® 250 ranged from 0% to 8% and 0% to 3.1%, respectively. Results met the manufacturer’s pre-determined inter-instrument CV specification of 10% for Phadia® 100 and Phadia® 250. The %CV for lot-to-lot variability on the Phadia® 250 ranged from 5.6 % to 10.4 %.

b. Linearity/assay reportable range:

Four patient serum samples were serially diluted using EliA™ Sample Diluent and tested in 3 replicates with 1 batch of EliA™ M2 and 1 set of system reagents on the Phadia® 100 or Phadia® 250 instrument. The observed values were graphed against the calculated values and a linear regression was performed. Results are summarized below:

EliA™ M2 on Phadia® 100					
Sample	Dilution range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R²	%CV Range
1	0.5 – 5.5	0.97 (0.92 to 1.02)	0.09 (-0.06 to 0.23)	1.00	2.3 – 6.6
2	1.4 – 135.5	1.00 (0.99 to 1.02)	0.47 (-0.25 to 1.18)	1.00	1.0 – 6.4
3	2.5 – 239.3	0.99 (0.97 to 1.00)	-0.08 (-1.48 to 1.31)	1.00	0.7 – 5.1
4	3.9 – 281.8	1.02 (0.99 to 1.05)	0.78 (-2.93 to 4.49)	1.00	1.0 – 4.8

EliA™ M2 on Phadia® 250					
Sample	Dilution range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R²	%CV Range
1	0.5 – 5.9	1.00 (0.92 to 1.08)	0.16 (-0.08 to 0.40)	1.00	0.9 – 5.9
2	1.6 – 129.6	1.01 (0.97 to 1.04)	1.75 (0.02 to 3.48)	1.00	0.7 – 5.7
3	2.6 – 208.7	0.99 (0.98 to 1.00)	0.45 (-0.36 to 1.26)	1.00	0.2 – 4.3
4	2.5 – 246.9	1.01 (0.99 to 1.03)	0.56 (-1.35 to 2.47)	1.00	0.5 – 3.2

EliA™ M2 on Phadia® 250					
Sample	Dilution range (U/mL)	Slope (95% CI)	Intercept (95% CI)	R²	%CV Range
5	9.8 – 295.8	0.90 (0.84 to 0.96)	2.73 (-3.61 to 9.06)	1.00	0.7 – 5.2

The technical measuring range (detection limit, upper limit) for EliA™ M2 is from 0.5 to ≥ 220 U/mL. The upper limit of the reported results in EliA U/ml can vary due to a lot-specific conversion from $\mu\text{g/L}$ to EliA U/mL. Results above the upper limit are reported as “above”. Linearity was shown for the range between 0.5 – 276 U/mL. The labeling states that due to differing binding characteristics of the antibodies in patient samples, not all sera can be diluted linearly within the technical measuring range.

High dose hook effect: A hook effect was not observed when analyzing a high positive serum sample with an estimated concentration more than 7 times above the upper limit of the technical measuring range.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

i) *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability – The IgG calibrators are traceable (via unbroken chain of calibrations) to the International Reference Preparation (IRP) 67/86 of Human Serum Immunoglobulins A, G and M from the World Health Organization (WHO). New batches of IgG calibrators are compared to a secondary standard (standardized with the IRP) or the IRP directly and adjusted accordingly to meet the correct concentration.

There is no international standard for IgG antibodies directed to M2. EliA M2 is calibrated against the non-WHO Reference Material Primary Biliary Cirrhosis Serum, Human NIBSC code 67/183. The instrument measures specific IgG concentration in $\mu\text{g/L}$ which is automatically converted to U/mL by using a conversion factor given by the lot-specific bar code printed on the EliA™ M2 Well package and read by the instrument during reagent loading.

Calibrators – The calibrators are human serum in standard buffer. There are 6 levels with assigned values from 0-600 $\mu\text{g/mL}$. The calibrator curve is acquired by fitting the values of the 6 calibrators and can be stored for up to 28 days by the instrument to be used on additional assays. Each additional assay includes calibrator (curve) controls that have to recover in defined ranges to ensure that the stored calibration curve is still valid.

Controls – The EliA™ M2 Positive is prepared from selected pooled human sera and contains IgG antibodies to M2. The EliA™ IgG/IgM/IgA Negative Control was cleared under k091845. EliA™ IgG/IgM/IgA Negative Control is prepared from selected pooled sera from normal, healthy donors. The controls are pre-diluted and ready for use. Each EliA™ Control package contains a Control Certificate listing predefined acceptance criteria for the EliA™ products the Controls can be used with. The target ranges of the

EliA™ Controls tested with the EliA™ M2 on the two Phadia® instruments are summarized below:

Instrument	EliA™ M2 Positive Control
Phadia® 100	24.7 – 57.7 U/mL
Phadia® 250	22.7 – 52.9 U/mL
Instrument	EliA™ IgG/IgM/IgA Negative Control
Phadia® 100	< 6 U/mL
Phadia® 250	< 6 U/mL

ii) *Kit Stability:*

Shelf-life stability – An accelerated stability study set the shelf-life stability of the EliA™ M2 Wells (from the date of manufacture when stored at recommended temperature 2-8°C) at 18 months. A real-time stability study is underway and currently available data supports a 7-month stability claim. All studies were performed on three lots of EliA M2 Wells. The sponsor notes that it is important to store the wells in dry conditions at 2-8°C.

An accelerated stability study set the shelf-life stability of the EliA™ M2 Positive Control at 15 months. A real-time stability study is underway and currently available data supported a 14-month stability claim. The shelf life is identical for the Controls for Phadia® 100 and Phadia® 250 as they contain the identical bulk material and are packaged in the same vials but just are labeled differently.

Other required components (previously reviewed) of the test method have a shelf life of 18 to 24 months.

Open stability – Stability of the foil bag containing the EliA™ M2 wells after first opening was tested and determined to be 9 months at 2-8°C.

EliA™ M2 Positive Control 100 and EliA™ M2 Positive Control 250 are for single use only. Therefore, stability after first opening study is not required.

The stability after first opening study for EliA™ IgG Calibrators and EliA™ IgG Curve Control are not required as they are for single use only.

On-board stability– The on-board stability of the EliA™ M2 Wells packed in carrier storage tray without desiccant bag was tested only on the Phadia® 250 instrument since on the Phadia 100 instrument the reagents are stored outside the instrument and are only loaded as needed for an assay. The EliA™ M2 Wells can be stored open at 2-8°C for up to 28 days or at room temperature for 24 hours (1 day).

iii) *Sample Storage:*

The package insert recommends following the guidelines in CLSI H18-A3 for sample storage. Separated serum/plasma should remain at room temperature for no longer than

eight hours. If assays will not be completed within eight hours, serum/plasma should be refrigerated (2 - 8°C). If assays are not completed within 48 hours, or the separated serum/plasma will be stored beyond 48 hours, serum/plasma should be frozen at or below -20°C. Freezing and thawing should be avoided.

d. Detection limit:

The Limit of Blank (LoB) and Limit of Detection (LoD) were determined in accordance with CLSI EP17-A. On each Phadia instrument (Phadia® 100 and Phadia® 250), a immunoglobulin depleted serum (for LoB) and five low antibody samples (for LoD) were assayed in 12 replicates in each of 6 runs on 6 different days, three runs in two instruments, for a total of 432 replicates per sample. The runs were spread over three Phadia® 100 and four Phadia® 250 instruments. The values determined are presented in the table below:

EliA™ M2	LoB	LoD
Phadia® 100	0.13 U/mL	0.45 U/mL
Phadia® 250	0.13 U/mL	0.37 U/mL

The package insert states the Detection Limit as 0.5 U/mL for all instruments.

e. Analytical specificity:

i) Endogenous Interference:

Interferences were assessed by testing four samples (one negative, two with concentration levels around the cut-off, and a positive sample with concentration level around calibrator 5). Each sample was spiked with the interfering substances or substance-specific blanks, and analyzed in 2 runs, each in 3 replicates (n=6), on one lot of EliA™ M2 Well and one lot of system reagents. The data demonstrated that EliA™ M2 was not adversely affected (percent recoveries ranged from 82 to 100%) by high levels of the following substances up to the concentrations listed in the table below:

Potential Interfering Compound	Test Concentration
Bilirubin F	19.2 mg/dL
Bilirubin C	20.1 mg/dL
Hemoglobin	496 mg/dL
Lipemic factor (ClinOleic)	1%
Rheumatoid factor IgM	500 IU/mL

The package insert contains a caution not to use hemolyzed, lipemic or icteric samples.

ii) Cross-reactivity:

A panel of 20 reference NEQAS serum samples which have target specifications for mitochondrial antibodies but were without a clinical diagnosis was tested using one batch of EliA™ M2 Wells and one batch of system reagents. The EliA™ M2 test results matched the targets of the respective assessment scheme.

iii) *Carry-over:*

A study was carried out on 1 Phadia® 250 instrument using the test EliA™ Ro cleared under k082759. The sample set consisted of a high serum sample (High), a high serum sample diluted 1:2 (1:2 dilution) and 1:20 (1:20 dilution) by instrument dilution and manual dilution, and a sample containing EliA sample diluent only (Diluent). They were assayed in replicates of 5 in the following order: Diluent, High, 1:2 dilution (instrument), Diluent, 1:20 dilution (instrument), Diluent, 1:2 dilution (manual). The data demonstrate no carryover effect as the results of the Diluent sample results were not affected by the results of the previous sample.

f. *Assay cut-off:*

Based on the results of the expected values/reference range study described below in Section M.5, the 99th percentile lies below the upper limit of the equivocal range for EliA™ M2. The assay cutoffs were set as follows:

Decision point	Interpretation
<4 U/mL	Negative
4 – 6 U/mL	Equivocal
>6 U/mL	Positive

In case of equivocal results, the manufacturer recommends retesting the patient after 8-12 weeks.

2. Comparison studies:

a. *Method comparison with predicate device:*

A total of 416 serum samples were assayed in singleton on both EliA™ M2 using Phadia® 250 instrument and QuantaLite™ M2 EP (MIT3) ELISA. The samples were from the intended use population (refer to the table in section 3 Clinical studies). In addition, 30 artificial samples with antibody concentrations in the intermediate and upper assay ranges (140.6 U/mL to 255.2 U/mL) were created by mixing high positive sera with negative blood donor sera.

The results are summarized below:

		QuantaLite™ M2 EP (MIT3) ELISA (U/mL)			Total
		Positive >25	Equivocal: 20.1 - 24.9	Negative ≤ 20	
EliA™ M2 (U/mL)	Positive: >6	105	3	11	119
	Equivocal: 4 - 6	2	1	12	15
	Negative: <4	9	3	270	282
Total		116	7	293	416

For the calculation of agreement, 58 results (42 samples below and 16 samples above the measuring range limits) were excluded. Agreements were calculated by grouping EliA™ M2

equivocal results with its test negative results, and then agreements were calculated again by grouping EliA™ M2 equivocal results with the test positive results:

Equivocal EliA™ M2 results considered as negative				
		QuantaLite™ M2 EP (MIT3) ELISA (U/mL)		Total
		Positive: >25	Negative: ≤25	
EliA™ M2 (U/mL)	Positive: > 6	89	14	103
	Negative: ≤ 6	10	245	255
Total		99	259	358
Positive percent agreement: 89.9% (89/99) 95% CI: 82.5 – 95.0%				
Negative percent agreement: 94.6% (245/259) 95% CI: 91.1 – 97.0%				
Total percent agreement: 93.3% (334/358) 95% CI: 90.2 – 95.7%				

Equivocal EliA™ M2 results considered as positive				
		QuantaLite™ M2 EP (MIT3) ELISA (U/mL)		Total
		Positive: >20	Negative: ≤20	
EliA™ M2 (U/mL)	Positive: ≥ 4	95	23	118
	Negative: < 4	11	229	240
Total		106	252	358
Positive percent agreement: 89.6% (95/106) 95% CI: 82.2 – 94.7%				
Negative percent agreement: 90.9% (229/252) 95% CI: 86.6 – 94.1%				
Total percent agreement: 90.5% (324/358) 95% CI: 87.0 – 93.3%				

b. Matrix comparison:

A study was performed to demonstrate that heparin plasma and EDTA plasma matrices yield comparable values as serum in the EliA™ M2 immunoassay. A total of 62 matrix-matched samples spread across the assay range were assayed in duplicates on Phadia 250. Negative samples did not switch to positive in any serum/plasma combination. Passing & Bablok regression plots were generated and the corresponding slopes of regression and coefficient determination are summarized in the tables below:

	Range tested (U/mL)	Slope (95% CI)	Intercept (95% CI)	R²
Serum vs. EDTA plasma	0.5 – 240.8	1.00 (0.99 to 1.02)	-0.08 (-0.10 to -0.06)	0.998
Serum vs. Heparin plasma	0.5 – 222.7	1.01 (1.00 to 1.03)	-0.06 (-0.11 to -0.02)	0.997

c. Instrument comparison:

A study was performed to demonstrate that the performance of EliA™ M2 was equivalent on the Phadia® 100 and Phadia® 250 instruments. A total of 36 samples

(27 positive, 5 equivocal and 4 negative) spanning the assay range were analyzed in 6 runs in single replicates on 3 Phadia®100 and 3 Phadia® 250 instruments, with 2 runs (a single measurement per run) on each instrument. The results of a Weighted Deming regression analysis are shown below:

EliA™ M2 weighted Deming Regression: Phadia®100 vs. Phadia® 250		
	Slope (95% CI)	Intercept (95% CI)
Phadia®100 vs. Phadia® 250	0.94 (0.92 – 0.96)	-0.12 (-0.28 – 0.03)

3. Clinical studies:

a. *Clinical sensitivity and specificity:*

The performance of EliA™ M2 was compared to a clinical diagnosis of Primary Biliary Cirrhosis. The validation set consisted of clinically characterized sera from Primary Biliary Cirrhosis and various disease controls for a total of 386 patient samples. The results of EliA™ M2 for each disease category are shown below:

Diagnostic groups	Number of samples	% Positive EliA™ M2	% Positive QuantaLite™ M2 EP (MIT3) ELISA
Primary biliary cirrhosis	100	81 (81%)	78 (78%)
Autoimmune Hepatitis	29	4 (13.8%)	1 (3.5%)
Primary sclerosis cholangitis	6	0 (0%)	0 (0%)
Hepatitis C	20	0 (0%)	1 (5%)
Cirrhosis of the liver	10	0 (0%)	0 (0%)
Crohn's Disease	30	1 (3.3%)	0 (0%)
Ulcerative Colitis	30	0 (0%)	1 (3.3%)
CREST syndrome	10	0 (0%)	0 (0%)
Sjögren's syndrome	20	1 (5%)	2 (10%)
Systemic Sclerosis	10	0 (0%)	0 (0%)
Rheumatoid arthritis	20	0 (0%)	1 (5%)
Poly-/Dermato-Myositis	5	0 (0%)	0 (0%)
Autoimmune Thyroiditis*	20	0 (0%)	0 (0%)
Osteoporosis	10	0 (0%)	0 (0%)
Celiac Disease	30	1 (3.3%)	1 (3.3%)
Diabetes mellitus Type I	5	0 (0%)	0 (0%)
Biliary obstruction / gallstones	10	0 (0%)	0 (0%)
Cancers**	20	1 (5%)	1 (5%)
Chronic fatigue syndrome	1	0 (0%)	0 (0%)
Fibromyalgia	10	0 (0%)	Not tested

* 10 Graves' disease and 10 Hashimoto's
** 17 Breast and 3 renal cancers

Clinical performance with equivocal samples considered negative is summarized in the following tables:

		Diagnosis		Total
		Positive	Negative	
EliA™ M2 (U/mL)	Positive: >6	81	4	85
	Negative: ≤6	19	263	282
Total		100	267	367
Clinical sensitivity:		81.0% (81/100)	95% CI: 71.9 – 88.2%	
Clinical specificity:		98.4% (263/267)	95% CI: 96.2 – 99.6%	

Due to documented overlap, 29 Autoimmune Hepatitis (AIH) sera were excluded from the Negative (control) group for the calculation of the specificity above. The calculation of specificity that includes 29 AIH sera in the Negative (control) group is shown below. Four AIH samples were found with a positive and four with an equivocal EliA M2 test result.

		Diagnosis		Total
		Positive	Negative	
EliA™ M2 (U/mL)	Positive: >6	81	8	89
	Negative: ≤6	19	288	307
Total		100	296	396
Clinical sensitivity:		81.0% (81/100)	95% CI: 71.9 – 88.2%	
Clinical specificity:		97.3% (288/296)	95% CI: 94.7 – 98.8%	

Clinical performance with equivocal samples considered positive is summarized in the following two tables. The first table excludes the 29 AIH sera from the Negative (control) group for the calculation of the specificity while the second table includes the 29 AIH samples in the specificity calculation.

		Diagnosis		Total
		Positive	Negative	
EliA™ M2 (U/mL)	Positive: >4	82	13	95
	Negative: ≤4	18	254	272
Total		100	267	367
Clinical sensitivity:		82.0% (82/100)	95% CI: 73.1 – 89.0%	
Clinical specificity:		95.1% (254/267)	95% CI: 91.8 – 97.4%	

		Diagnosis		Total
		Positive	Negative	
EliA™ M2 (U/mL)	Positive: >6	82	22	104
	Negative: ≤6	18	274	292

Total	100	296	396
Clinical sensitivity:	82.0% (82/100)	95% CI: 73.1 – 89.0%	
Clinical specificity:	92.6% (274/296)	95% CI: 89.0 – 95.3%	

b. Other clinical supportive data (when a. is not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

A total of 411 apparently healthy blood donor samples from a Caucasian population were measured on the Phadia® 250 instrument. There was no significant difference between male and female. Expected values may vary depending on the population tested. The results are summarized below:

	U/mL
Mean	1.0
Median	0.9
Range	0.5 -5
95th percentile	1.7
99th percentile	3.4

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.