November 29, 2019

Phadia AB
℅ Sheryl Skinner
Associate Director RA/QA
Phadia US Inc.
4169 Commercial Avenue
Portage, Michigan 49002

Re: K190710
Trade/Device Name: EliA Symphony^{S} Immunoassay
Regulation Number: 21 CFR 866.5100
Regulation Name: Antinuclear antibody immunological test system
Regulatory Class: Class II
Product Code: LLL
Dated: March 19, 2019
Received: March 19, 2019

Dear Sheryl Skinner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal

statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Leonthena R. Carrington -S

Lea Carrington
Director
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K190710

Device Name
EliA(TM) SymphonyS Immunoassay

Indications for Use *(Describe)*
EliA SymphonyS is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (Li-heparin, EDTA). EliA SymphonyS is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and a synthetic SmD3 peptide as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/dermatomyositis, in conjunction with other laboratory and clinical findings. EliA SymphonyS uses the EliA IgG method on the instrument Phadia 250.

EliA SymphonyS is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (Li-heparin, EDTA). EliA SymphonyS is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and a synthetic SmD3 peptide as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/dermatomyositis, in conjunction with other laboratory and clinical findings. EliA SymphonyS uses the EliA IgG method on the instrument Phadia 2500/5000.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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A.6 510k Decision Summary Input

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY

A. 510(k) Number: K190710

B. Purpose for Submission:
New device

C. Measurand:
Antinuclear IgG antibodies: SmD, RNP (70, A, C), SS-A (60 kDa, 52 kDa), SS-B, Centromere B, Scl-70, Jo-1

D. Type of Test:
Qualitative immunofluorescence assays

E. Applicant:
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Rapsgatan 7P
P.O. Box 6460
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Tel: +46-18-16 50 60

510(k) Contact Person:
Sheryl Skinner
Associate Director, RA/QA
ImmunoDiagnostics US
Thermo Fisher Scientific
Phadia US Inc.
4169 Commercial Avenue
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Tel. 269.568.3603
sheryl.skinner@thermofisher.com

Date of Summary Preparation: **November 25, 2019**

F. Proprietary and Established Names:
EliA™ Symphony^{S} Immunoassay

G. Regulatory Information:
1. Regulation section:
21 CFR §866.5100, Antinuclear Antibody Immunological Test System

2. Classification:
Class II

3. Product code:
LLL Extractable Antinuclear Antibody, Antigen, Control

4. Panel:
Immunology

H. Intended Use:

1. Intended use(s):

EliA Symphony^{S} is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (Li-heparin, EDTA). EliA Symphony^{S} is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and a synthetic SmD_3 peptide as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/dermatomyositis, in conjunction with other laboratory and clinical findings. EliA Symphony^{S} uses the EliA IgG method on the instrument Phadia 250.

EliA Symphony^{S} is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (Li-heparin, EDTA). EliA Symphony^{S} is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and a synthetic SmD_3 peptide as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/dermatomyositis, in conjunction with other laboratory and clinical findings. EliA Symphony^{S} uses the EliA IgG method on the instrument Phadia 2500/5000.

2. Indication(s) for use:
Same as intended use

3. Special conditions for use statement(s):
For prescription use only

4. Special instrument requirements:
Phadia® 250 or Phadia® 2500/5000

I. Device Description:

The method specific reagents on Phadia® 250 and Phadia® 2500/5000 are identical; they are only filled in different containers. Each device consists of:

- EliA Symphony^S Wells are coated with human recombinant U1RNP (RNP70, A, C), SS-A/Ro (60 kDa, 52 kDa), SS-B/La, Centromere B, Scl-70, Jo-1 proteins and synthetic SmD_3 peptide – 4 carriers (16 wells each), ready to use;
- EliA Sample Diluent: PBS containing BSA, detergent and 0.095% sodium azide – 6 bottles, 48 mL each, ready to use; or 6 bottles, 400 mL each, ready to use;
- EliA IgG Conjugate 50 or 200: β-Galactosidase labeled anti-IgG (mouse monoclonal antibodies) in PBS containing BSA and 0.06% sodium azide – 6 wedge shaped bottles, 5 mL each, ready to use; or 6 wedge shaped bottles, 19 mL each, ready to use
- EliA ANA Positive Control 250 or 2500/5000: Human serum containing IgG antibodies to dsDNA, RNP, Sm, Ro, La, Scl-70, CENP and Jo-1 in PBS containing BSA, detergent and 0.095% sodium azide – 6 single use vials, 0.3 mL each, ready to use;
- EliA Negative Control 250 or 2500/5000: Human sera from healthy donors in PBS containing BSA, detergent and 0.095% sodium azide – 6 single-use vials, 0.3 mL each, ready to use;
- EliA IgG Calibrator Strips: Human IgG (0, 4, 10, 20, 100, 600 µg/L) in PBS containing BSA, detergent and 0.095% sodium azide – 5 strips, 6 single-use vials per strip, 0.3 mL each, ready to use;
- EliA IgG Curve Control Strips: Human IgG (20 µg/L) in PBS containing BSA, detergent and 0.095% sodium azide – 5 strips, 6 single-use vials per strip, 0.3 mL each, ready to use;
- EliA IgG Calibrator Well: Coated with mouse monoclonal antibodies – 4 carriers (12 wells each), ready to use.

The Phadia EliA Immunodiagnostic System is an automated system for immunodiagnostic testing. The EliA reagents are available as modular packages, each purchased separately. Apart from the EliA ANA Positive Control 250 or 2500/5000 and the EliA IgG/IgM/IgA Negative Control 250 or 2500/5000, all packages listed above are required to carry out an EliA Symphony^S Test.

J. Substantial Equivalence Information:

1. Predicate device name(s) and 510(k) number(s):

EliA Symphony Immunoassay, Phadia AB	K072149

2. Comparison with predicate device:

EliA Symphony^S Immunoassay – Similarities to predicate device

Feature	Predicate Device EliA Symphony	New Device EliA Symphony^S
Intended Use	EliA Symphony is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (heparin, EDTA and citrate). EliA Symphony is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and native purified Sm proteins as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/ dermatomyositis, in conjunction with other laboratory and clinical findings. EliA Symphony uses the EliA IgG method on the instruments Phadia 100 and Phadia 250.	EliA Symphony^S is intended for the in vitro, qualitative measurement of antinuclear IgG antibodies in human serum and plasma (Li-heparin, EDTA). EliA Symphony^S is based on human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SSB/La, Centromere B, Scl-70, Jo-1 proteins and a synthetic SmD_3 peptide as antigen and is useful as an aid in the clinical diagnosis of patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, scleroderma and polymyositis/dermatomyositis, in conjunction with other laboratory and clinical findings. EliA Symphony^S uses the EliA IgG method on the instruments Phadia 250 and Phadia 2500/5000.
Internal Controls	Positive and negative Control provided with EliA ANA Positive Control 100 and 250 and EliA IgG/IgM/IgA Negative Control 100 and 250, resp.	Positive and negative Control provided with EliA ANA Positive Control 250 / 2500/5000 and EliA IgG/IgM/IgA Negative Control 250 / 2500/5000, resp.
Calibration	6-point total IgG Calibration 6 vials of human IgG at concentrations of 0 – 4 – 10 – 20 – 100 – 600 µg/L	
Assay Type	ELISA	
Type of test	qualitative	
Reported Unit	Ratio	
Antigen	human recombinant U1RNP (RNP 70, A, C), SS-A/Ro (60 kDa, 52 kDa), SS-B/La, Centromere B, Scl-70, Jo-1 proteins	
Sample Dilution	1:100	
Cut-off	Negative <0.7 Ratio Equivocal 0.7 – 1.0 Ratio Positive >1.0 Ratio	

EliA Symphony^S – Differences to predicate device

Feature	Predicate Device EliA Symphony	New Device EliA Symphony^S
Instrumentation	EliA Symphony uses the EliA IgG method on the instruments Phadia 100 and 250.	EliA Symphony^S uses the EliA IgG method on the instruments Phadia 250 and Phadia 2500/5000.
Sample type	Serum or plasma (heparin, EDTA, citrate)	Serum or plasma (Li-heparin, EDTA) No use of citrate plasma
Antigen	native purified Sm proteins	Synthetic SmD_3 peptide

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

CLSI EP07_ED3, Interference in Clinical Chemistry, April 2018

L. Test Principle:

The EliA wells are molded cups comparable to excised wells from a microtiter plate. They are made of polystyrene and are coated with the respective antigen. The wells are at the same time a holder of the coupled antigen for convenient automation and a reaction chamber with reaction/washing solution handling based on pipetting to add and aspiration to remove liquids.

The specific antigen for the antibodies to be detected is bound to the EliA solid phase component (EliA Well).

Test	Antigen coated to the wells
EliA Symphony^S	human recombinant U1RNP (RNP70, A, C) proteins human recombinant SS-A/Ro (60 kDa, 52 kDa) proteins human recombinant SS-B/La protein human recombinant Centromere B protein human recombinant Scl-70 protein human recombinant Jo-1 protein synthetic SmD_3 peptide

If present in the patient's specimen, antibodies to these proteins 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 assay directly measures the amount of antibody of interest bound to the antigen coating the EliA well, therefore 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:

To determine the precision of the assay on the Phadia 250 and the Phadia 2500/5000 instrument, the variability was assessed on 5 samples.
Three lots were used to determine the precision of the assay on Phadia 250 (totaling 252 replicate determinations per sample).
One lot was used to determine the precision of the assay on Phadia 2500/5000.

EliA Symphony^{S} on Phadia 250:

To determine the precision of the assay on the Phadia 250 instrument, the variability was assessed in a study with 21 runs by examining the samples in 252 replicates on 3 instruments over 7 days. The data was calculated against the calibration curve from Day 1. The results of the statistical evaluation are given in the table below.

Qualitative evaluation:

Sample	Mean Ratio	Range of Ratios	Expected Result	Repeatability	
				Positive/Equivocal/Negative	% Correct
1	0.48	0.38 – 0.59	Negative	0/0/84	100
2	0.76	0.63 – 0.96	Equivocal	0/205/47	81.3
3	1.0	0.91 – 1.13	Positive	152/100/0	60.3
4	4.4	3.8 – 5.1	Positive	252/0/0	100
5	23.2	20.8 – 26.2	Positive	252/0/0	100
6	42.9	34.4 – 54.0	Positive	250/0/0	100

EliA Symphony^S on Phadia 2500/5000:

To determine the precision of the assay on the Phadia 2500/5000 instrument, the variability was assessed in a study with 21 runs by examining the samples in 84 replicates on 3 instruments over 7 days. The data was calculated against the calibration curve from Day 1. The results of the statistical evaluation are given in the table below.

Qualitative evaluation:

Sample	Mean Ratio	Range of Ratios	Expected Result	Repeatability	
				Positive/Equivocal/Negative	% Correct
1	0.63	0.41 – 0.84	Negative	0/17/67	79.8
2	0.76	0.61 – 0.87	Equivocal	0/72/12	85.7
3	0.92	0.76 – 1.04	Equivocal	7/77/0	91.7
4	0.98	0.90 – 1.07	Equivocal	29/55/0	65.5
5	4.2	3.7 – 4.6	Positive	84/0/0	100
6	28.1	25.5 – 33.1	Positive	84/0/0	100
7	47.1	41.0 – 54.6	Positive	84/0/0	100

b. Linearity/assay reportable range:

Not applicable for a qualitative Screening assay

Hook Effect/Outside the Range Results:

n.a.

The reportable range as shown on the laboratory reports (instrument print-outs) is from 0.09 to 60 Ratio.
Results below 0.09 Ratio are reported as “below” and evaluated as “negative”, results above 60 Ratio are reported as “above” and evaluated as “positive”.

c. 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 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.

The instrument measures specific IgG concentrations in µg/L. By using a conversion factor given by the lot-specific code of the EliA™ test well, the results are automatically converted to Ratio.

Stability:

Data for **Open and closed real-time stability** and **Onboard stability** of EliA IgG reagents and general EliA reagents on Phadia 250 and Phadia 2500/5000 instrument were already cleared with several other EliA tests, e.g. under k141375 (EliA M2 on PH250). For Phadia 2500/5000 instrument, they were already cleared under k061165/A003 (EliA CCP).

Shelf life:
The stability of EliA Symphony^S Wells was evaluated with both, a real-time and accelerated/stress study. The results support stability of the test under the recommended storage of 2 – 8°C for up to 18 months.

Onboard stability:
The onboard stability EliA Symphony^S carriers (containing the antigen coated wells) was tested over 4 weeks using 3 positive and 2 negative samples only on the Phadia 250 instrument. As the storage conditions in the Phadia 2500/5000 instrument are similar, the results can also be used for stability claims for the Phadia 2500/5000. The onboard stability for the Phadia 250 instrument was determined to be 28 days at 2-8°C.

Open Stability:
Stability after first opening of the foilbag containing the EliA Symphony^S wells was tested and determined to be 9 months at 2-8°C.

d. Detection limit:

N/A for a qualitative test

e. Analytical specificity:
Endogenous Interference: A study was run to investigate whether high concentrations of potentially interfering substances in serum, like bilirubin, hemoglobin, lipemic factor and rheumatoid factor adversely affect the results of the new device. Three serum samples were prediluted in EliA Sample Diluent and spiked with the different interfering substances or their respective blank solutions, and analyzed in triplicates. A calibration curve was run in duplicate. The runs were repeated twice. One batch of EliA antigen wells and one batch of system reagents were used throughout the studies.

One negative sample, one sample with a concentration around the cut-off and one high positive sample were tested. The ratio of blank/spiked sample ranged from 0.88 – 1.16 for EliA Symphony^S. No interference was observed up to the concentrations listed in the table below:

Potential Interfering Compound	Concentration in undiluted sample
Bilirubin F	19.2 mg/dL

Bilirubin C	20.1 mg/dL
Hemoglobin	496 mg/dL
Lipemic factor	1%
Rheumatoid factor	500 IU/ml

Exogenous Interference: In addition, interference by five selected exogenous substances was evaluated according to CLSI Guideline EP07-3rd Edition. The same study protocol as described above was used to analyze interference of a non-steroid anti-inflammatory drug (Ibuprofen), an oral steroid (Prednisone), an anti-malarial drug (Hydroxychloroquine), a disease-modifying anti-rheumatic drug (Azathioprine), an anti-hypertensive agent (Losartan) and a rheumatologic biologic (Infliximab) in serum samples. The concentration of the substances are based on CLSI Guideline EP37 1st Edition.

One negative sample, one sample with a concentration around the cut-off and one high positive sample were tested. The ratio of blank/spiked sample ranged from 0.83 – 1.13 for EliA Symphony^{S}. No interference was observed up to the concentrations listed in the table below:

Substance	**Concentration in undiluted serum sample**
Ibuprofen	2,19E+01 mg/dL 21.9 mg/dL
Prednisone	9,90E-03 mg/dL 0.0099 mg/dL
Hydroxychloroquine	2,25E-01 mg/dL 0.225 mg/dL
Azathioprine	2,58E-01 mg/dL 0.258 mg/dL
Losartan	1,14E+00 mg/dL 1.14 mg/dL
Infliximab	2.64E+01 mg/dl 26.4 mg/dl

Reference sera: Externally defined sera should be measured according to their target values as mentioned by the institution CDC and AMLI.
Evaluation of CDC sera on EliA Symphony^{S}:

Sample	Reactivity/IIF	Target	EliA Symphony^{S} [Ratio]
CDC ANA #1	Homogeneous, Rim Pattern (dsDNA)	Negative	**0.6**
CDC ANA #2	Speckled Pattern (SS-B/La)	Positive	**18.9**
CDC ANA #3	Speckled	Positive	**92.6**
CDC ANA #4	U1-RNP	Positive	**21.7**
CDC ANA #5	Sm	Positive	**25.9**
CDC ANA #6	nucleolar	Negative	**0.3**
CDC ANA #7	SS-A/Ro	Positive	**23.5**
CDC ANA #8	CENP	Positive	**10.6**
CDC ANA #9	Scl-70	Positive	**18.9**
CDC ANA #10	Jo-1	Positive	**14.7**
CDC ANA #11	PM-Scl	Negative	**0.2**
CDC ANA #12	Rib-P	Negative	**0.1**

Evaluation of AMLI sera on EliA Symphony^{S}:

Sample	Reactivity/IIF	Target	EliA Symphony^{S} [Ratio]
AMLI 1	Negative	Negative	**0.5**
AMLI 2	Sm / RNP	Positive	**3.4**
AMLI 3	RNP / Sm	Positive	**0.1**
AMLI 4	SS-A/Ro	Positive	**1.4**
AMLI 5	SS-B/La	Positive	**8.8**
AMLI 6	Scl-70	Positive	**0.1**
AMLI 7	Jo-1	Positive	**1.7**
AMLI 8	CENP / Sm / Scl-70 / Jo-1	Positive	**3.3**
AMLI 9	dsDNA / SS-A/Ro / SS-B/La	Positive	**49.4**
AMLI 10	Negative	Negative	**0.2**

The targets were met for AMLI Consensus Reference Panel, except for two serum samples (AMLI 3 and 6). Both samples showed negative results, while the target is positive. The defined targets could not be met by any single semi-quantitative EliA test nor by competitor screening assays. Therefore, the targets defined by AMLI could not be confirmed.

Carry-over: A study was carried out on a Phadia 250 instrument using the test EliA Ro, cleared under k082759. A serum sample was diluted 1:2 and 1:20 using instrument dilution and manual dilution. A lower dilution factor than the default one (1:100) was chosen to challenge the system. Only a few RUs difference compared to the reference pipetting could be seen, which is too low to be expressed in U/mL. The observed carry over effect is therefore negligible without any influence to assay results.

Phadia 2500/5000 instruments use disposable tips for pipetting samples and a separate pipette for the conjugate, therefore carry-over from samples to conjugate is impossible.

f. Assay cut-off:

A study was performed on 70 apparently healthy blood donor samples from Caucasian individuals equally distributed by sex and age in order to evaluate expected values for EliA Symphony^{S} in the normal population and to confirm the defined cut-off. The samples were measured on the Phadia 250 instrument. The 95th percentile was taken into account for setting the cut-off.
Additionally, 30 ANA positive samples with known reactivities against all antigens contained in EliA Symphony^{S} were tested and should be found positive with the proposed test evaluation.
The following values were selected for the cut-off:

EliA Symphony^{S}	
<0.7 Ratio	Negative
0.7 – 1.0 Ratio	Equivocal
>1.0 Ratio	Positive

In case of equivocal results, it is recommended to retest the patient after 8-12 weeks.
In the case of a positive result, it is suggested that further confirmatory testing on individual antigen(s) be performed.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 633 serum samples were collected with a diagnosis from patients with Mixed Connective Tissue Disease (n = 46), Poly-/ Dermatomyositis (n = 78), Systemic Sclerosis (n = 87), SLE (n = 97), Sjögren's Syndrome (n = 96), Bacterial Infection (n = 20), HIV Infection (n = 27), HCV Infection (n = 36), HBV Infection (n = 36), Rheumatoid Arthritis (n = 85), Cancer (n = 25).

Samples were analyzed with the EliA Symphony^{S} and EliA Symphony assays. The results are summarized in the tables below:

EliA Symphony^S - equivocal results considered negative

N = 633	**EliA Symphony** positive: > 1.0 Ratio	**EliA Symphony** negative: **≤ 1.0 Ratio**	Total
EliA Symphony^S positive: > 1.0 Ratio	279	6	285
EliA Symphony^S negative: ≤ 1.0 Ratio	7	341	348
Total	286	347	633

	Calculation	Agreement (%)	95% CI
Positive Percent Agreement	100% x 279/286	97.6	95.0 – 99.0
Negative Percent Agreement	100% x 341/347	98.3	96.3 – 99.4
Total Agreement	100% x (279+341)/633	97.9	96.5 – 98.9

EliA Symphony^S - equivocal results considered positive

N = 633	**EliA Symphony** positive: > 0.7 Ratio	**EliA Symphony** negative: ≤ 0.7 Ratio	Total
EliA Symphony^S positive: > 0.7 Ratio	287	6	293
EliA Symphony^S negative: ≤ 0.7 Ratio	24	316	340
Total	311	322	633

	Calculation	Agreement (%)	95% CI
Positive Percent Agreement	100% x 287/311	92.3	88.7 – 95.0
Negative Percent Agreement	100% x 316/322	98.1	96.0 – 99.3
Total Agreement	100% x (287+316)/633	95.3	93.3 – 96.8

b. Matrix comparison:

Serum, lithium heparin plasma and EDTA plasma were collected from the same patients (n = 62) to demonstrate that the plasma results do not deviate from the corresponding serum results and are within the pre-defined specifications. Samples were spiked with a serum sample of high antibody titer to generate a range of reactivity. Samples were tested in duplicates. Passing & Bablok regression plots were generated using the first replicate only and by plotting the concentration observed from the control tube (serum) versus the concentration for each test collection tube. The corresponding slopes of regression and coefficient determination are summarized in the tables below:

	Range tested [Ratio]	Slope (95% CI)	Intercept (95% CI)	R^2
Serum vs. Li-heparin plasma	0.09 – 72.0	**1.03** (0.98 to 1.05)	**-0.02** (-0.03 to -0.00)	0.994
Serum vs EDTA plasma	0.09 – 68.5	**0.98** (0.96 to 1.00)	**-0.03** (-0.04 to -0.01)	0.997

c. *Instrument comparison*

Performance of EliA Symphony^S was evaluated on the Phadia 250 and Phadia 2500/5000 instruments using 81 positive, 10 equivocal and 19 negative samples. The samples were analyzed in single replicates on one Phadia 250 and one Phadia 2500/5000 instrument giving a total of two measurements per sample. The regression analysis results are summarized as follows:

	Intercept	Slope	R
Estimate	0.06	1.01	0.992
95% CI	0.01 – 0.12	0.99 – 1.03	

3. Clinical studies:

a. Clinical sensitivity and specificity:

444 clinically defined samples with a diagnosis from patients with Mixed Connective Tissue Disease (n = 22), Poly-/ Dermatomyositis (n = 10), Systemic Sclerosis (n = 32), SLE (n = 83), SLE/Lupus nephritis (n=19), Sjögren's Syndrome (n = 28), Bacterial Infection (n = 30), Viral Infection (n = 30), Rheumatoid Arthritis (n = 40), Celiac Disease (n=28), Crohn's Disease (n=22), Ulcerative Colitis (n=22), Graves' Disease (n=28), Hashimoto's Disease (n=10), primary Antiphospholipid Syndrome (n=28), PBC (n=5), Autoimmune hepatitis (n=6), Granulomatosis with Polyangiitis (n=1), were used to determine sensitivity and specificity of the assay. The results are summarized in the tables below.

EliA Symphony^S – equivocal results evaluated as negative:

n=444	Diagnostic Group	Disease Controls	Total
Positive test > 1.0 Ratio	102	13	115
Negative test ≤ 1.0	92	237	329
Total	194	250	444

Sensitivity (95% CI): 52.6% (45.3% - 59.8%)
Specificity (95% CI): 94.8% (91.3% - 97.2%)

EliA Symphony^S – equivocal results evaluated as negative:

n=444	Diagnostic Group	Disease Controls	Total
Positive test > 0.7 Ratio	107	14	121
Negative test ≤ 0.7	87	236	323
Total	194	250	444

Sensitivity (95% CI): 55.2% (47.9% - 62.3%)
Specificity (95% CI): 94.4% (90.8% - 96.9%)

The table below shows the results for each clinical subgroup where the equivocal results evaluated as negative

Diagnostic groups	n	No (%) Positive EliA Symphony^S	No (%) Positive EliA Symphony
Systemic lupus erythematosus (SLE)	83	37 (44.6%)	39 (47.0%)
SLE (Lupus Nephritis)	19	13 (68.4%)	13 (68.4%)
Mixed connective tissue disease (MCTD)	22	16 (72.7%)	14 (63.6%)
Systemic sclerosis (SSC)	32	16 (50.0%)	16 (50.0%)
Sjögren's syndrome (SS)	28	17 (60.7%)	17 (60.7%)
Poly-/Dermatomyositis (PM/DM)	10	3 (30.0%)	3 (30.0%)
Rheumatoid arthritis (RA)	40	0 (0%)	0 (0%)
Celiac disease	28	0 (0%)	0 (0%)
Crohn's disease	22	0 (0%)	0 (0%)
Ulcerative colitis	22	1 (4.5%)	0 (0%)
Graves' disease	28	1 (3.6%)	1 (3.6%)
Hashimoto's disease	10	1 (10.0%)	1 (10.0%)
Primary antiphospholipid syndrome (pAPS)	28	4 (14.3%)	4 (14.3%)
Primary Biliary Cirrhosis (PBC)	5	0 (0%)	0 (0%)
Autoimmune hepatitis (AIH)	6	3 (50.0%)	3 (50.0%)
Granulomatosis with Polyangiitis (GPA, formerly called Wegener's Granulomatosis)	1	0 (0%)	0 (0%)
Bacterial Infections	30	2 (6.7%)	2 (6.7%)

Viral infections (EBV, HBV, HCV, etc.)	30	1 (3.3%)	1 (3.3%)

b. Other clinical supportive data: Not applicable

4. Clinical cut-off:
Same as assay cut-off

5. Expected values/Reference range:

Antibody prevalence in autoimmune patients varies widely depending on disease area. The proportion of sera from a normal population found positive for the antinuclear antibodies covered by the EliA Symphony^S test is below 1%. Expected values may vary depending on the population tested.

The frequency distribution for antinuclear antibodies was investigated in a group of apparently healthy subjects equally distributed by age and gender, using sera from Caucasian, African American, Hispanic and Asian population obtained from a blood bank.

The results are given in the table below:

Test	n =	Range Min-Max (Ratio)	No. of pos./ equivocal results	Median (Ratio)	Mean (Ratio)	95th percentile	99th percentile
EliA Symphony^S	558	0.0 – 25.9	7 / 5	0.1	0.3	0.3	1.1

N. Proposed Labeling:

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

O. Conclusion:

All available data support that both immunoassays, the new device EliA Symphony^S and its predicate device EliA Symphony perform substantially equivalent.

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