510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. **510(k) Number:**
   k062583
B. **Purpose for Submission:**
   New device
C. **Measurand:**
   Anti-tissue transglutaminase (tTG) IgG antibody
D. **Type of Test:**
   Semi-quantitative fluoroenzyme immunoassay
E. **Applicant:**
   Phadia US, Inc.
F. **Proprietary and Established Names:**
   EliA™ Celikey IgG Immunoassay
G. **Regulatory Information:**
   1. Regulation section:
      21 CFR§ 866.5660 Multiple Antibodies Immunological Test System
   2. Classification:
      Class II
   3. Product code:
      MVM, Autoantibodies, endomysial (tissue transglutaminase)
   4. Panel:
      (82) Immunology
H. **Intended Use:**
   1. Intended use(s):
      EliA™ Celikey IgG is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to tissue transglutaminase (tTG) in human serum and plasma. EliA™ Celikey IgG is based on recombinant human tissue transglutaminase as antigen and is useful as an aid in the clinical diagnosis of patients with Celiac disease. EliA™ Celikey IgG uses the EliA IgG method on the instrument ImmunoCAP 100 and ImmunoCAP 250.
   2. Indication(s) for use:
      Same as above
   3. Special conditions for use statement(s):
      The device is for prescription use only.
   4. Special instrument requirements:
      ImmunoCAP 100 and ImmunoCAP 250 (k061165)
I. **Device Description:**
   The EliA reagents are available as modular packages, each purchased separately. The EliA Celikey IgG wells are coated with human recombinant tissue transglutaminase (tTG). These are packed in carriers which are stored in sealed aluminum foil bags containing a desiccant. The EliA Method-Specific reagents consists of (1) sample diluent concentrate, (2) IgG Conjugate (blue colored) β- Galactosidase anti-IgG (mouse monoclonal antibodies) in PBS, (3) ready to use 6 level IgG calibrators

(human IgG concentrations of 0,4,10,20,100 and 600 ug/L), (4) ready to use IgG Curve Control (20 µg/L), (5) IgG Calibrator well coated with mouse monoclonal antibody, (6) ready for use development solution containing 0.1% 4-methylumbelliferyl – β-D galactoside and (7) stop solution

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Celikey® Tissue Transglutaminase IgG Antibody
2. Predicate 510(k) number(s):
   k041173
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	EliA™ Celikey IgG	Celikey® Tissue Transglutaminase IgG Antibody
Intended Use	For the semi-quantitative measurement of IgG antibodies directed to tissue transglutaminase (t TG) in human serum and plasma. EliA Celikey is based on recombinant human tissue transglutaminase as the antigen and is useful as an aid in the clinical diagnosis of patients with celiac disease.	Same
Sample type	Serum and plasma	Same
Solid phase	Microwells	Same
Assay format	Semi-quantitative	Same
Assay type	Elisa	Same
Capture Antigens	Recombinant human tTG	Same

Differences		
Item	Device	Predicate
Instrumentation	ImmunoCAP 100 and 250 (fully automated)	Microplate reader with 620 nm filter
Internal controls	Positive and negative control sera available separately	Positive and negative control sera included in the kit
Calibration	Total IgG calibrators (0, 4, 10, 20, 100, 600 µg/L) Option to store curve for up to 28 days and run curve controls (provided in kit) in each assay for calibration	Analyte specific (tTG antibody concentrations of 0, 3, 7, 16, 40 and 100 U/mL) in each assay
Signal	Fluorescence	Optical density

Differences		
Item	Device	Predicate
Reaction temperature	37°C controlled	Room temperature, 18-25°C
Concept	Modular reagents concept (test-method specific and general reagents)	All reagents in a single kit
Conjugate	Anti-human IgG β-galactosidase (mouse monoclonal antibodies)	Anti-human IgG horseradish peroxidase (goat)

K. Standard/Guidance Document Referenced (if applicable):
None referenced.

L. Test Principle:
The EliA Celikey IgG wells are coated with human recombinant tTG. If present in the patient's specimen, antibodies to tTG will bind to their specific antigen in the wells. 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 response value, the more specific IgG is present in the specimen. To evaluate test results, the response for patient samples is compared directly to the response for IgG calibrators.

M. Performance Characteristics (if/when applicable):
1. Analytical performance:
    a. *Precision/Reproducibility:*
       One negative and three positive samples were measured in duplicate on one instrument in 26 runs on EliA Celikey IgG well batch together with one set of system reagent. The studies yielded the following:

ImmunoCAP 100

Sample	Mean (U/mL)	Intra-run (CV%)	Inter-run (CV%)
1	2.1	6.5	8.0
2	28.1	3.1	4.0
3	34.0	2.7	6.9
4	172.3	4.5	4.8

ImmunoCAP 250

Sample	Mean (U/mL)	Intra-run (CV%)	Inter-run (CV%)
1	4.2	7.8	5.6
2	11.6	5.2	5.8
3	55.1	3.2	2.8
4	127.9	3.4	3.0

    b. *Linearity/assay reportable range:*

Linearity was not claimed for this device.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The IgG calibrators are traceable (via an unbroken chain of calibrations) to the International Reference Preparation (IRP) 67/86 of Human Immunoglobulins A, G, and M from WHO. New batches of calibrators are compared to a secondary standard (standardized with the IRP) or the IRP directly and adjusted accordingly to meet the correct concentration (6 levels).

d. *Detection limit:*
The lower limit of the measuring range was determined by measuring dilutions (1:2, 1:4, and 1:8) of Calibrator 4 (4 µg/L) in the Calibrator Wells. The results in Response Units (RU) were compared with the result of the sample diluent on EliA Celikey Wells. The discrimination ability of the assay should be >2. All samples were measured in triplicate.

Sample ID	Results on Calibrator Wells	
	Mean Response Units (RU)	SD
Calibrator 4.0 (1:2)	161	6.7
Calibrator 4.0 (1:4)	122	2.5
Calibrator 4.0 (1:8)	90	1.8

Sample ID	Results on Celikey IgG Wells	
	Mean RU	SD
Sample Diluent	0	0.0

The 1/8 diluted calibrator 4.0 (0.5 µg/L) still can be discriminated from background given by the signal of the diluent on Celikey IgG wells. The lower limit of detection was set at 0.5 µg/L corresponding to 0.6 EliA U/mL.

e. *Analytical specificity:*
Interfering substance
The potential interferant and the corresponding blanks were added to two anti-tTG positive sera from patients with Celiac disease. The spiked samples were tested in triplicate.

Additives	Concentration in raw sample	Final concentration in diluted sample (1:100)	Normal Values
Bilirubin F	18.8 mg/dL	0.188	<1.0
Bilirubin C	20 mg/dL	0.2	<1.0
Chyle	236,000 Units/dL	2360	No data
Hemoglobin	453 mg/dL	4.5	<2.0
Rheumatoid Factor IgM	550 IU/mL	5.5	<40.0

The ratio of the result of the sample spiked with the interfering substance and the sample spiked with a buffer blank was determined:

Additive	Blank/spiked sample	Positive Sample			Low Positive Sample		
		Conc. (U/mL)	CV %	Ratio	Conc. (U/mL)	CV %	Ratio
Bilirubin C	Blank	78.0	8.8	1.01	22.4	1.3	1.00
	Sample	79.0	3.3		22.3	2.4	
Bilirubin F	Blank	74.8	4.9	1.08	22.4	3.2	1.02
	Sample	80.9	3.5		22.8	3.1	
Hemoglobin	Blank	80.9	0.9	1.01	23.6	2.3	0.95
	Sample	80.5	5.7		22.5	2.4	
Chyle	Blank	82.2	4.7	1.03	23.8	2.5	1.00
	Sample	84.7	3.6		23.7	0.2	
RF	Blank	84.1	2.3	0.97	23.9	2.9	1.03
	Sample	81.5	1.7		24.6	0.9	

Additional data on low concentration around the cut-off for each interfering substances were also tested. The results are summarized below:

Additive	blank/spiked sample	Low Positive Sample EliA Celikey IgG		
		Conc. [U/ml]	CV%	Ratio
Bilirubin F	Blank	13.8	2.6	0.95
	Sample	13.1	4.6	
Bilirubin C	Blank	13.3	1.2	1.03
	Sample	13.6	5.0	
Hemoglobin	Blank	13.6	2.8	1.03
	Sample	14.0	2.3	
Chyle	Blank	13.5	3.3	1.02
	Sample	13.8	5.0	
RF	Blank	13.9	1.3	0.97
	Sample	13.5	2.7	

The interfering substances listed did not appear to adversely affect the results of the new device.

f. *Assay cut-off:*
The purpose of the normal sera studies was to evaluate expected values in the normal population and to confirm the defined cut-off. Samples from 400 apparently healthy Caucasian adult blood donors were measured. The individuals were equally distributed by sex and age.

	EliA U/mL
Median	1.5
Mean	1.5
Mean +2SD	2.9
Mean +3SD	3.6
95th Percentile	2.6
99th Percentile	4.2

The results appeared to be equally distributed and not dependent on age or gender. The 99th percentile lies below the lower limit of the equivocal range of 7-10 U/mL.

2. Comparison studies:
   a. *Method comparison with predicate device:*
   Clinical samples:
   Two hundred forty-four patient samples were tested with the new device and the predicate device, Celikey tTG IgG antibody assay. These samples included 93 patients with a diagnosis of Celiac disease. One hundred fifty one (151) samples were from disease controls:
   101 non-CD, normal biopsy
   10 ulcerative colitis
   10 morbus crohn
   20 rheumatoid arthritis
   10 rheumatoid factor positive samples

   Equivocal results were excluded in the calculation. Results showed the following:

n = 244		Celikey® IgG in Varelisa™ format			
		positive	equivocal	Negative	Total
EliA Celikey IgG	positive	37	3	4	44
	equivocal	5	4	17	26
	negative	7	3	164	174
	Total	49	10	185	244

   Total % agreement = 94.8%
   Positive % agreement = 84.1%
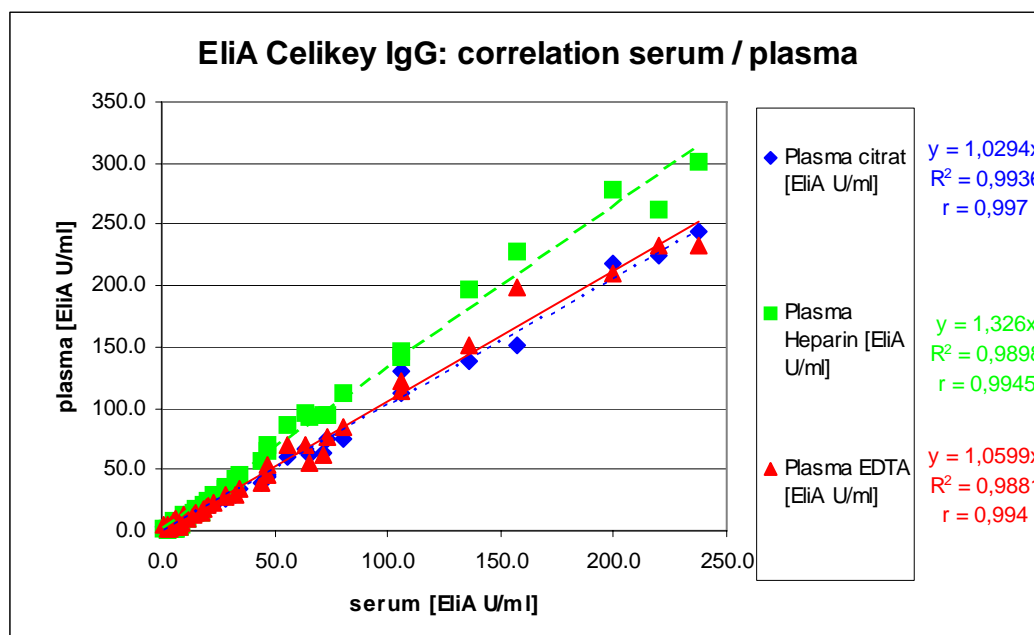   Negative% agreement = 97.6%

   An extended correlation study including 74 more samples (45 samples with celiac disease and 29 samples with suspected celiac) resulted in a positive agreement of 92.4%. No other information was provided on these banked samples. Equivocal results were excluded in the calculation. The new data is summarized below.

n = 318		Celikey® IgG in Varelisa™ format			
		positive	equivocal	negative	Total
EliA Celikey IgG	positive	85	3	5	93
	equivocal	5	5	23	33
	negative	7	5	180	192
	Total	97	13	208	318

	Agreement (%)	95% CI (confidence interval)
Overall	95.7	Not provided
positive	92.4	84.9 – 96.9%
negative	97.3	93.8 – 99.1%

b. *Matrix comparison:*
Twenty five sets of samples from different donors were tested in double determinations. Each set contained serum, EDTA, heparin and citrate plasma samples. All samples tested were found to be negative for celiac. Positive samples were spiked into these samples to create positive sets. Linear regression comparing the quotas between serum and each type of plasma for the positive samples was performed and showed:

EliA Celikey IgG: correlation serum / plasma

Plasma citrat [EliA U/ml]: $y = 1,0294x$, $R^2 = 0,9936$, $r = 0,997$

Plasma Heparin [EliA U/ml]: $y = 1,326x$, $R^2 = 0,9898$, $r = 0,9945$

Plasma EDTA [EliA U/ml]: $y = 1,0599x$, $R^2 = 0,9881$, $r = 0,994$
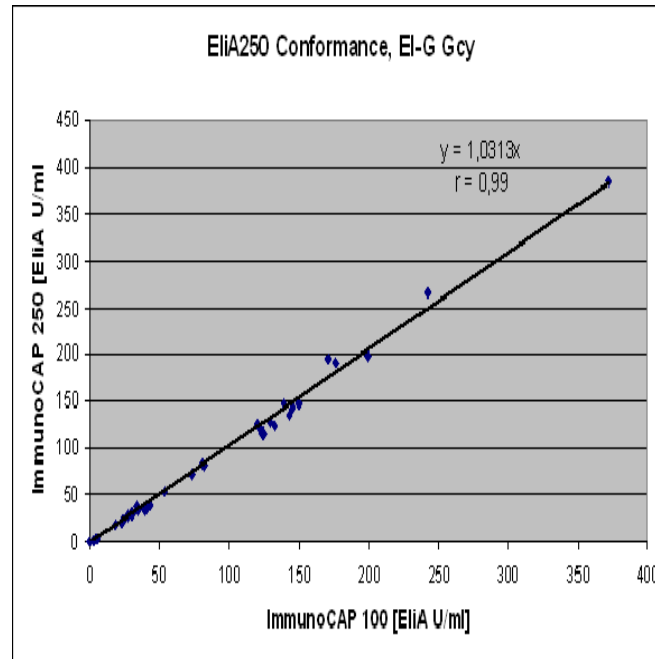
The specifications for this study are fulfilled for EDTA and citrate plasma, but not for heparin samples. This information is specified on the Specimen Collection section of the Package Insert.

c. *Instrument Platform comparison:*
For this comparison study, a total of 36 samples distributed over the

measuring range were assayed: 4 negative samples, 1 equivocal sample and 31 positive samples. All samples were run on three ImmunoCAP 100 instruments and three ImmunoCAP 250 instruments in two runs and in single replicates. Results of the conformance study are summarized in the figure below:

3. Clinical studies:
   a. *Clinical Sensitivity and Clinical Specificity:*
      Ninety three (93) patients with known diagnosis of Celiac disease and 101 non-CD patients with normal biopsy were tested for this study. Results showed clinical sensitivity of 43.0% (95% CI 32.8-53.7%) and clinical specificity of 96.0% (95% CI 90.2-98.9%) (see table below).

n = 194	EliA Celikey IgG		
	>10 U/mL	≤10 U/mL	
CD (93)	40	53	**Sensitivity (95%CI)** 43.0 (32.8-53.7%)
Disease Controls (101)	4	97	**Specificity (95%CI)** 96.0 (90.2-98.9%)

   b. *Other clinical supportive data (when a. is not applicable)*:
      Not applicable.
4. Clinical cut-off**:**
   See assay cut-off.

5. Expected values/Reference range:
   Expected value in the normal population is negative.

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.