510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K250816

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

ADVIA Centaur Anti-Thyroglobulin II (aTgII)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
JNL	Class II	21 CFR 866.5870 - Thyroid Autoantibody Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Autoantibodies against thyroglobulin (anti-thyroglobulin or aTg)

C Type of Test:

Quantitative, chemiluminescent immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The ADVIA Centaur Anti-Thyroglobulin II (aTgII) assay is for *in vitro* diagnostic use in the quantitative measurement of autoantibodies against thyroglobulin in human serum and plasma (EDTA, lithium heparin, sodium heparin) using the ADVIA Centaur XP system.

Anti-thyroglobulin (aTg) measurements are used, in conjunction with clinical assessment, as an aid in the diagnosis of autoimmune thyroiditis and Graves' disease.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

ADVIA Centaur XP System

IV Device/System Characteristics:

A Device Description:

The ADVIA Centaur Anti-Thyroglobulin II (aTgII) assay is available in a 1-pack (100 tests) kit and in a 5-pack (500 tests) kit. Both versions of the assay include:

- aTgII ReadyPack primary reagent pack consisting of:
  - Lite Reagent: 10.0 mL/reagent pack; Human thyroglobulin labeled with acridinium ester (~1.2 µg/mL) in buffered saline; blocker (bovine gamma globulin and bovine serum albumin); sodium azide (< 0.1%); preservative
  - Solid Phase: 20.0 mL/reagent pack; Streptavidin-coated paramagnetic particles (~0.6 mg/mL) with biotinylated human thyroglobulin in buffered saline; blocker (bovine gamma globulin and bovine serum albumin); sodium azide (< 0.1%); preservative
- ADVIA Centaur aTgII ReadyPack ancillary reagent pack: 17.5 mL/pack; Goat serum; mouse serum; sodium azide (< 0.1%); preservative
- ADVIA Centaur aTgII master curve card
- aTgII CAL low calibrator: lyophilized monoclonal mouse anti-human thyroglobulin in goat serum and mouse serum; sodium azide (< 0.1%); preservative; 1.0 mL/vial

- aTgII CAL high calibrator: lyophilized monoclonal mouse anti-human thyroglobulin in goat serum and mouse serum; sodium azide (< 0.1%); preservative; 1.0 mL/vial
- ADVIA Centaur aTgII CAL calibrator assigned value cards and barcode labels

B Principle of Operation:

The ADVIA Centaur Anti-Thyroglobulin II (aTgII) assay is a fully automated analyte-bridging immunoassay using acridinium ester chemiluminescent technology for the detection of thyroglobulin autoantibodies. This assay uses human thyroglobulin in both the Lite Reagent and the Solid Phase. In the Lite Reagent, the thyroglobulin is labeled with acridinium ester. In the Solid Phase, the thyroglobulin is biotinylated and bound to streptavidin-coated paramagnetic particles. Anti-Tg autoantibodies in the patient sample binds to the thyroglobulin in the Lite Reagent and in the Solid Phase, forming a bridge. A direct relationship exists between the amount of analyte present in the patient sample and the amount of relative light units (RLUs) detected by the system.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access Thyroglobulin Antibody II (TgAbII)

B Predicate 510(k) Number(s):

K112933

C Comparison with Predicate(s):

Device & Predicate Device(s):	K250816 (Candidate Device)	K112933 (Predicate Device)
Device Trade Name	ADVIA Centaur aTgII	Access Thyroglobulin Antibody II
General Device Characteristic Similarities		
Intended Use/ Indications For Use	The ADVIA Centaur Anti-Thyroglobulin II (aTgII) assay is for *in vitro* diagnostic use in the quantitative measurement of autoantibodies against thyroglobulin in human serum and plasma (EDTA, lithium heparin, sodium heparin) using the ADVIA Centaur XP system. Anti-thyroglobulin (aTg) measurements are used, in conjunction with clinical assessment, as an aid in the diagnosis of autoimmune thyroiditis and Graves' disease.	The Access Thyroglobulin antibody II assay is a paramagnetic chemiluminescent immunoassay for the quantitative determination of thyroglobulin antibody levels in human serum and plasma using the Access Immunoassay Systems. The measurement of thyroid autoantibodies may aid in the diagnosis of Hashimoto's disease, nontoxic goiter, and Graves' disease.

Device & Predicate Device(s):	K250816 (Candidate Device)	K112933 (Predicate Device)
Technology	Chemiluminescence	Same
Measurement	Quantitative	Same
Sample type	Serum and Plasma (K2-EDTA, lithium heparin, sodium heparin)	Same
Traceability	Traceable to the NIBSC 65/093.	Same
General Device Characteristic Differences		
Assay Range	1.1 – 1000 IU/mL	0.9 – 2500 IU/mL
Cut-Off	4.5 IU/mL	4.0 IU/mL
Operating Principle	1-Step Sandwich immunoassay	2-Step Sandwich immunoassay
Calibration	2 levels	6 levels

VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guidelines were used:

- CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition
- CLSI EP06-Ed2, Evaluation of the Linearity of Quantitative Measurement Procedures – Second Edition
- CLSI EP07-A3, Interference Testing in Clinical Chemistry – Third Edition
- CLSI EP09c, 3rd ed., Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP12-A2, User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline - Second Edition.
- CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition
- CLSI EP25- Ed2, Evaluation of Stability of *In Vitro* Medical Laboratory Test Reagents; Approved Guideline
- CLSI EP28-A3c, Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition
- CLSI EP37, Supplemental Tables for Interference Testing in Clinical Chemistry – First Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision and reproducibility studies were conducted following the recommendations in CLSI EP05-A3.

Within-Laboratory Precision:

Within-laboratory precision was assessed using eight native human serum samples and two levels of control materials. Two replicates for each of the samples were run on one (1) ADVIA Centaur XP system for 20 days, two runs per day using one aTgII reagent lot, resulting in a total of 80 replicates per sample. The data were analyzed for repeatability (within-run), between-run, between-day, and within-laboratory precision. The mean (IU/mL), standard deviation (SD) (IU/mL) and % of coefficient of variation (%CV) are summarized in the table below:

Sample	Mean (IU/mL)	Within-Run (Repeatability)		Between-Run		Between-Day		Within-Laboratory	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum A	2.1	0.28	13.5	0.00	0.0	0.11	5.5	0.30	14.6
Serum B	4.1	0.15	3.6	0.02	0.4	0.08	1.9	0.17	4.1
Serum C	6.7	0.39	5.9	0.18	2.6	0.23	3.5	0.49	7.3
Serum D	13.0	0.77	6.0	0.64	5.0	0.00	0.0	1.00	7.7
Serum E	18.3	0.73	4.0	0.54	2.9	0.49	2.7	1.03	5.6
Serum F	50.4	1.56	3.1	0.86	1.7	1.64	3.3	2.43	4.8
Serum G	496.0	8.88	1.8	14.16	2.9	12.16	2.5	20.7	4.2
Serum H	872.0	27.9	3.2	32.36	3.7	24.66	2.8	49.3	5.7
Control 1	48.1	1.28	2.7	0.61	1.3	0.00	0.0	1.41	2.9
Control 2	448.8	11.82	2.6	4.95	1.1	6.76	1.5	14.49	3.2

Lot-to-Lot Precision:

The lot-to-lot precision was evaluated using three reagent lots on the ADVIA Centaur XP system. Seven serum samples at different concentrations and two levels of control materials were tested with five replicates per run, one run per day over five days, resulting in a total of 75 datapoints per sample on one instrument. The same study was also performed on two additional instruments. The data was analyzed for within-run, between-day, and between-reagent lot, and total precision. The lot-to-lot precision data on one representative instrument are summarized in the table below.

Sample	Mean (IU/mL)	Within-Run		Between-Day		Between-Lot		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum A	2.2	0.21	9.4	0.04	1.9	0.00	0.0	0.21	9.6
Serum B	2.5	0.20	8.1	0.19	7.7	0.04	1.7	0.28	11.3
Serum C	5.0	0.30	5.9	0.48	9.6	0.00	0.0	0.57	11.3
Serum D	14.7	0.47	3.2	0.99	6.7	0.68	4.6	1.29	8.8
Serum E	43.2	1.54	3.6	3.19	7.4	0.96	2.2	3.67	8.5
Serum F	410.7	14.99	3.6	28.32	6.9	25.72	6.3	41.09	10.0

Sample	Mean (IU/mL)	Within-Run		Between-Day		Between-Lot		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum G	689.2	24.83	3.6	43.66	6.3	33.55	4.9	60.40	8.8
Control 1	46.2	1.69	3.6	0.71	1.5	2.23	4.8	2.88	6.2
Control 2	435.4	16.67	3.8	6.93	1.6	19.23	4.4	26.38	6.1

Instrument-to-Instrument Precision:

The instrument-to-instrument precision was evaluated on three ADVIA Centaur XP systems. Seven (7) serum samples and two levels of control materials at different concentrations were tested with five replicates per run, one run per day over five days using one reagent lot on three instruments, resulting in 75 datapoints per sample. The same study was also performed on two additional lots. The data was analyzed for within-run, between-day, and between-instrument, and total precision. The instrument-to-instrument precision data on one representative lot are summarized in the table below.

Sample	Mean (IU/mL)	Within-Run		Between-Day		Between-Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
Serum A	2.1	0.21	10.1	0.14	6.6	0.01	0.4	0.25	12.1
Serum B	2.2	0.26	11.4	0.24	10.7	0.06	2.7	0.36	15.9
Serum C	5.2	0.26	5.0	0.09	1.6	0.37	7.1	0.46	8.9
Serum D	16.0	0.69	4.3	0.42	2.6	0.54	3.4	0.98	6.1
Serum E	44.5	1.58	3.5	0.55	1.2	0.00	0.0	1.67	3.8
Serum F	443.2	12.62	2.8	7.39	1.7	3.11	0.7	14.95	3.4
Serum G	728.5	22.53	3.1	16.32	2.2	8.75	1.2	29.17	4.0
Control 1	47.2	1.65	3.5	0.83	1.8	0.52	1.1	1.92	4.1
Control 2	443.4	15.30	3.4	4.68	1.1	15.33	3.5	22.16	5.0

2. Linearity:

The linearity of the ADVIA Centaur aTgII was determined in accordance with CLSI EP06-ED2. Linearity samples were prepared by mixing high and low samples in known ratios. Three sets of dilutions were created; Sample Set 1 was prepared to cover the range of 0.6 – 70.9 IU/mL, Sample Set 2 was prepared to cover 1.2 – 149.2 IU/mL, and Sample Set 3 was prepared to cover the range of 1.2 – 1023.8 IU/mL. The data was analyzed for weighted regression for each Set, and % deviation from linearity was calculated. The results are summarized in the table below.

Sample Set	Range (IU/mL)	Slope (95% CI)	Intercept (95% CI)	r	% Deviation from Linearity
1	0.6–70.9	1.05 (1.00–1.10)	0.24 (-0.05–0.53)	0.999	-37.9%* – 7.4%
2	1.2–149.2	1.02 (0.98–1.07)	0.42 (-0.03–0.87)	0.999	-18.6%* – 8.6%
3	1.2–1023.8	1.01 (0.96–1.05)	0.79 (-0.22–1.80)	1.000	-40.4%* – 10.7%
Combined	0.6–1023.8	0.99 (0.98–1.00)	1.06 (-1.95–4.07)	1.000	-67.1%* – 9.7%

* %Deviation from linearity of -37.9% was for sample with concentration level of 0.6 IU/mL for Set 1,-67.1% when combined. %Deviation of -18.6% was for sample 1.2 IU/mL for Set 2, and -40.4% in Set 3.

The results support the linearity of analytical measuring interval from 1.1 – 1000 IU/mL.

High Dose Hook Effect:

The ADVIA Centaur aTgII assay was evaluated for high-dose hook effect by preparing a sample spiked with anti-Thyroglobulin antibody positive plasma to approximately 65,000 IU/mL and testing serial dilutions across the assay range. Testing was performed on one ADVIA Centaur XP system using two reagent lots with six replicates each. No hook effect was observed up to 50,000 IU/mL.

3. Analytical Specificity/Interference:

Interference:

Interference studies were performed in accordance with the CLSI guidelines EP07 3rd Edition to determine if endogenous and exogenous substances interfere with the test results of the ADVIA Centaur aTgII assay. Three samples representing a low positive (~5 IU/mL), a moderate positive (~50 IU/mL), and a high positive (~500 IU/mL) were tested in triplicate for each substance with one aTgII reagent lot on one ADVIA Centaur XP analyzer. The mean results were determined from the replicates tested. Interferents were analyzed using a paired difference method. No significant interference (< 10% deviation from control) was observed for the ADVIA Centaur aTgII to the following concentration for each endogenous and exogenous substance tested:

a) Endogenous Substances:

Substance	Concentration
Bilirubin, conjugated	60 mg/dL
Bilirubin, unconjugated	60 mg/dL
Hemoglobin	1000 mg/dL
Human Immunoglobulin G (IgG)	6 g/dL
Insulin	18 mIU/L
Lipemia (Intralipid)	3,500 mg/dL
Protein (low)	3 g/dL
Protein (high)	12 g/dL
Rheumatoid Factor (RF)	750 IU/mL

b) Exogenous Substances:

Substance	Concentration
Acetaminophen	20 mg/dL
Acetylsalicylic acid (Aspirin)	65.2 mg/dL
Biotin	3500 ng/mL
Ibuprofen	50 mg/dL
Iodide	38 mg/dL
L-thyroxine (T4)	10,000 ng/mL
Methimazole	1 µg/mL

Cross-reactivity:

Cross-reactivity was determined using the ADVIA Centaur XP system in accordance with CLSI Document EP07 3rd Edition. The same three samples (low positive ~5 IU/mL, moderate positive ~50 IU/mL, and high positive ~500 IU/mL) were tested in triplicate for each substance with one aTgII reagent lot on one ADVIA Centaur XP analyzer. Cross-reactivity of samples spiked with the following substances does not exceed the specified acceptance criteria:

Substance	Test Concentration
T3 Antibodies	0.55 mg/mL
T4 Antibodies	1.01 mg/mL

4. Assay Reportable Range:

The assay reportable range for the ADVIA Centaur aTgII is 1.1 –1000.0 IU/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

a) Traceability:

The ADVIA Centaur aTgII assay is traceable to NIBSC 65/093 Human Anti-thyroglobulin serum reference standard.

b) Stability:

Kit stability:

Shelf-life Stability: A Real-Time stability study was conducted using three lots of reagents and three lots of calibrators stored at 2–8°C. For reagents, three levels of patient samples (approximately 5, 50, and 500 IU/mL) and three levels of in-house controls were tested at multiple timepoints up to 2.1 years for Lot 1, up to 3.8 years for Lot 2, and up to 2.5 years for Lot 3. For calibrators, two levels (low and high) were tested at multiple timepoints for 2.1 years for all three lots. Aged calibrators were evaluated against Time 0 concentration results to determine stability. The results support a 24-month (2 years) stability claim for both reagents and calibrators.

In-use Reagent Stability: In-use stability of the ADVIA Centaur aTgII kit was evaluated by testing two patient pools representing a moderate positive (~52-59 IU/mL) and a high positive (~473-524 IU/mL) and two controls representing a low positive (~8 IU/mL) and a high positive (~870-960 IU/mL), using multiple lots which were opened and stored on the ADVIA Centaur XP system for the duration of the study, which included at least five timepoints and at least three replicates per sample. The results support a claim for reagent on-board stability of 28 days.

Sample Stability:

The stability of specimens stored under different conditions was evaluated by testing a panel of samples collected into Serum Separator tubes (SST), glass tubes, Lithium Heparin (LiHep) tubes, dipotassium EDTA (K2 EDTA) tubes, and sodium heparin tubes spiked with anti-thyroglobulin positive samples to make samples across the assay range. The data supported the following storage conditions for all five tested sample matrices:

Sample Stability Attribute	Stability Claims
Room Temperature (RT)	8 hours
Refrigerated (2 – 8°C)	7 days
Frozen (-20°C)	6 months
On the clot - RT	8 hours
Freeze-thaw	2 cycles
Time to centrifugation	8 hours

6. Detection Limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) for the ADVIA Centaur aTgII were determined based on the CLSI guideline EP17-A2.

a) LoB: The LoB was determined by testing four (4) human samples that were known to be negative for anti-Tg and used as blank samples. Each blank sample was measured in five (5) replicates per run, one run per day, for a minimum of three days on the ADVIA Centaur XP system using three (3) lots of aTgII reagents, resulting in a total of 60 replicates per reagent lot/system combination. Analyte concentrations were calculated using Day 1 calibration. The LoB was calculated using the non-parametric method. The highest LoB among the reagent lots was chosen as the LoB. The claimed LoB is 0.6 IU/mL.

b) LoD: The LoD was determined by testing a panel of nine (9) human serum pools targeted at concentrations of approximately 0.3 IU/mL to 6.0 IU/mL. The nine (9) low analyte samples were measured on the ADVIA Centaur XP system with five replicates per run, one run per day for three days using three lots of aTgII reagent, resulting in a total of 135 replicates per lot (9 samples × 5 replicates × 3 days = 135). The LoD was determined as LoD = LoB + 1.645 x total SD (within-laboratory SD) for each lot. The highest LoD among the reagent lots was chosen as the LoD. The claimed LoD is 1.0 IU/mL.

c) LoQ: The LoQ was determined using the same samples under the same protocol for the LoD study. The LoQ was calculated as the concentration of anti-Tg that gives a total CV of ≤20%. The highest LoQ among the reagent lots was chosen as the LoQ. The claimed LoQ is 1.1 IU/mL.

7. Assay Cut-Off:

The assay cut-off is 4.5 IU/mL.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison was conducted for the ADVIA Centaur aTgII assay (candidate device) against the Access Thyroglobulin Antibody II (TgAbII) assay (predicate device), using prospectively and retrospectively collected samples. The samples included autoimmune thyroid disease (AITD), non-autoimmune thyroid disease (NAITD), disease control samples, and pregnancy samples. Results outside the AMR (analytical measurement range) of either assay were excluded from the final analysis, and positive percent agreement (PPA) and negative percent agreement (NPA), with 95% confidence intervals were calculated:

		Predicate		Total
		Positive	Negative	
ADVIA Centaur aTgII Assay	**Positive**	117	15	132
	Negative	4	176	180
	Total	121	191	312

PPA: 96.7% (117/121) (95% CI: 91.8–98.7%)
NPA: 92.2% (176/191) (95% CI: 87.5–95.2%)

2. Matrix Comparison:

To demonstrate that Li-Heparin plasma, Na-Heparin plasma, K2-EDTA plasma, and serum samples yield the comparable results, 42 sample matched sample sets that cover the analytical measuring interval of the ADVIA Centaur aTgII assay were tested and analyzed by weighted Deming regression. The results are summarized in the following table:

	Slope (95% CI)	Intercept (95% CI)	r
SST vs. Serum	0.98 (0.96–1.00)	0.1 (-0.1–0.3)	0.999
K2-EDTA vs. Serum	0.98 (0.96–1.01)	0.2 (0.0–0.3)	0.999
Li-Heparin vs. Serum	0.98 (0.95–1.01)	0.0 (-0.3–0.3)	0.998
Na-Heparin vs. Serum	0.97 (0.94–1.00)	0.1 (-0.1–0.3)	0.997

C Clinical Studies:

1. Clinical Sensitivity and Specificity:

A total of 675 samples were evaluated in two cohorts, one with a total of 373 prospectively collected samples and one with additional retrospectively obtained 302 samples from pregnant subjects and patients with various other disease states.

For the cohort 1,373 samples, of which 216 samples were clinically confirmed autoimmune thyroiditis (also known as Hashimoto's thyroiditis) and Graves' disease (collectively, defined here as autoimmune thyroid disease, AITD), were prospectively collected across six sites in the United States. Definitive diagnoses were made by endocrinologists in accordance with

the American Thyroid Association's guidelines[1,2]. The samples were collected from subjects who presented with clinical signs or symptoms and are suspected of, or have been diagnosed with, Graves' disease or autoimmune thyroiditis or were pregnant and postpartum (within one year postpartum from pregnancy) female subjects with clinical signs or symptoms of thyroid disease. Subjects could enroll if they had not started treatment, or who started antithyroid medications or hormone replacement therapy treatment less than or equal to six (6) months from the date of collection and were ≥22 years of age. The samples were defined as AITD or not-AITD (NAITD) and not further characterized except for multinodular goiter.

		Clinical Diagnosis			
		Autoimmune Thyroiditis	**Graves' Disease**	**NAITD***	**Total**
ADVIA Centaur aTgII	**Positive**	45	29	22	96
	Negative	66	76	135	277
	Total	111	105	157	373

* The NAITD cohort included 62 multinodular goiter patients.

Autoimmune Thyroiditis	Sensitivity:	40.5% (45/111) (95% CI: 31.9–49.8%)
	Specificity:	86.0% (135/157) (95% CI: 79.7–90.6%)
Graves' Disease	Sensitivity:	27.6% (29/105) (95% CI: 20.0–36.9%)
	Specificity:	86.0% (135/157) (95% CI: 79.7–90.6%)

An additional 302 samples (cohort 2) were retrospectively obtained from pregnant subjects and patients with various other disease states that could be considered in the differential diagnosis of AITD and added to the prospective cohort, resulting a total of 675 study subject. The clinical sensitivity and specificity for the ADVIA Centaur aTgII with all samples were determined and shown in the table below:

		Clinical Diagnosis			
		Autoimmune Thyroiditis	**Graves' Disease**	**Controls**	**Total**
ADVIA Centaur aTgII	**Positive**	45	29	64	138
	Negative	66	76	395	537
	Total	111	105	459	675

Autoimmune Thyroiditis	Sensitivity:	40.5% (45/111) (95% CI: 31.9–49.8%)
	Specificity:	86.1% (395/459) (95% CI: 82.6–88.9%)
Graves' Disease	Sensitivity:	27.6% (29/105) (95% CI: 20.0–36.9%)
	Specificity:	86.1% (395/459) (95% CI: 82.6–88.9%)

[1] Ross DS et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016; 26:1343. doi: 10.1089/thy.2016.0229.
[2] Jonklaas J et al. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. Thyroid. 2014; 24:1670. doi: 10.1089/thy.2014.0028.

Distribution of target and differential disease samples and antibody positivity rates for all 675 samples are shown in the table below:

	N	ADVIA Centaur aTgII	Predicate
		n POS (%)	n POS (%)
Target conditions			
Graves' Disease	105	29 (27.6%)	33 (31.4%)
Autoimmune Thyroiditis	111	45 (40.5%)	41 (36.9%)
Total	**216**	**74 (34.3%)**	**74 (34.3%)**
Differential diagnosis controls			
Multinodular goiter	62	4 (6.5%)	4 (6.5%)
Non-autoimmune thyroid disease (NAITD)*	95	18 (18.9%)	13 (13.7%)
Thyroid Carcinoma	20	1 (5.0%)	1 (5.0%)
Silent Painless Thyroiditis	20	7 (35.0%)	5 (25.0%)
Subacute Thyroiditis	10	1 (10.0%)	1 (10.0%)
Hepatitis C virus (HCV)	20	0 (0.0%)	0 (0.0%)
Hepatitis B virus (HBV)	20	10 (50.0%)	8 (40.0%)
Human immunodeficiency virus (HIV)	20	0 (0.0%)	0 (0.0%)
Diabetes Type 1	10	1 (10.0%)	1 (10.0%)
Sjogren's Syndrome	10	1 (10.0%)	1 (10.0%)
Primary Biliary Cholangitis	10	3 (30.0%)	3 (30.0%)
Systemic Sclerosis	10	2 (20.0%)	2 (20.0%)
Pernicious Anemia	10	2 (20.0%)	2 (20.0%)
Rheumatoid Arthritis	10	0 (0.0%)	0 (0.0%)
Systemic Lupus Erythematosus (SLE)	10	1 (10.0%)	1 (10.0%)
Addison's Disease	10	0 (0.0%)	0 (0.0%)
Miscarriage	20	13 (65.0%)	13 (65.0%)
Pregnancy – 1st Trimester	31	0 (0.0%)	0 (0.0%)
Pregnancy – 2nd Trimester	30	0 (0.0%)	1 (3.3%)
Pregnancy – 3rd Trimester	31	0 (0.0%)	0 (0.0%)
Total	**459**	**64 (13.9%)**	**56 (12.2%)**

* *Prospective cohort not further diagnosed*

D Clinical Cut-Off:

The clinical cut-off is 4.5 IU/mL.

E Expected Values/Reference Range:

A reference interval of the ADVIA Centaur aTgII for apparently healthy adults was established non-parametrically in accordance with CLSI Document EP28-A3c. Samples were collected prospectively from 123 apparently healthy male and female adult subjects aged 27-69 years with normal TSH levels, no personal or family history of thyroid disease, and absence of non-thyroid autoimmune disease. Each sample was tested in one replicate over the course of five days on one ADVIA Centaur XP system using one reagent lot. The 97.5th percentile was 1.2 IU/mL (90%

LCI: 0.5 IU/mL, 90% UCI: 2.7 IU/mL). The reference range claim for the ADVIA Centaur aTgII is defined as <1.2 IU/mL.

It is recommended that each laboratory should determine its own reference interval for the diagnostic evaluation of patient results.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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