510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K220265

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

ADVIA Centaur® NT-proBNPII (PBNPII)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NBC	Class II	21 CFR 862.1117 - B-Type Natriuretic Peptide Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

N-terminal pro-brain natriuretic peptide (NT-proBNP)

C Type of Test:

Quantitative, Chemiluminescence immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The ADVIA Centaur® NT-proBNPII (PBNPII) assay is for in vitro diagnostic use in the quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma (EDTA and lithium heparin) using the ADVIA Centaur® XP system.

In the Emergency Department (ED) and Outpatient (OP) populations, measurements of NT-proBNP are used as an aid in the diagnosis of heart failure (HF) in patients with clinical suspicion of new onset or worsening HF.

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 candidate device is comprised of an assay kit which includes the ADVIA Centaur PBNPII ReadyPack primary reagent pack, ADVIA Centaur PBNPII Ancillary Reagent ReadyPack, ADVIA Centaur® PBNPII Calibrators, ADVIA Centaur PBNPII CAL calibrator assigned value cards, and ADVIA Centaur PBNPII master curve card.

ADVIA Centaur® PBNPII ReadyPack primary reagent pack	ADVIA Centaur PBNPII Lite Reagent: Monoclonal sheep anti-human NT-proBNP F(ab')2 fragment antibody (~0.36 µg/mL) labeled with acridinium ester in buffer; bovine serum albumin; bovine gamma globulin; preservatives.
	ADVIA Centaur PBNPII Solid Phase Reagent: Monoclonal sheep anti-human NT-proBNP antibody (~2 µg/mL) labeled with biotin bound to streptavidin magnetic particles (~220 mg/L) in buffer; bovine serum albumin; bovine gamma globulin; sheep gamma globulin; preservatives.

ADVIA Centaur PBNPII Ancillary Reagent	Buffer with bovine serum albumin; bovine gamma globulin; sheep gamma globulin; preservatives.

ADVIA Centaur PBNPII Low and High Calibrators	After reconstitution, low or high levels of NT-proBNP antigen; buffer; bovine serum albumin; preservatives.

Materials required but not provided in the assay kit:
ADVIA Centaur Wash
ADVIA Centaur Probe Wash

B Principle of Operation:

The candidate device is an automated two-site sandwich immunoassay using chemiluminescent detection. The binding reaction relies on a biotinylated monoclonal sheep antibody specific to human NT-proBNP and conjugated to streptavidin magnetic microparticles; and an acridinium-ester-labeled monoclonal sheep F(ab')2 antibody fragment specific to NT-proBNP.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Elecsys proBNP II Immunoassay

B Predicate 510(k) Number(s):
K072437

C Comparison with Predicate(s):

Device & Predicate Device(s):	K220265	K072437
Device Trade Name	ADVIA Centaur® NT-proBNPII (PBNPII)	Elecsys proBNP II Immunoassay
General Device Characteristic Similarities		
Intended Use	Quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma	Same
General Device Characteristic Differences		
Measuring range	35 to 35,000 pg/mL	5 to 35,000 pg/mL

VI Standards/Guidance Documents Referenced:

Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers, issued on November 30, 2000.

CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

CLSI EP06 Evaluation of Linearity of Quantitative Measurement Procedures. 2nd Edition.

CLSI EP07 Interference Testing in Clinical Chemistry: Approved Guideline. 3rd Edition.

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition.

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. 1st Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

The precision performance of the ADVIA Centaur® NT-proBNPII (PBNPII) assay run on the ADVIA Centaur XP system was established in several studies following the recommendations of CLSI EP05-A3.

Within-Lab Precision
The within-lab performance was established. In the study, six native serum sample pools spanning approximately each medical decision level and three controls were assayed in replicates of two per run, two runs per day over 20 days using one reagent lot for a total of 80 measurements. The data were analyzed for repeatability and within-lab %CV using the ANOVA method consistent with the recommendations of CLSI EP05-A3. The results are summarized below.

Sample	Mean pg/mL	Repeatability		Within-Lab	
		SD	%CV	SD	%CV
Serum 1	116	6.1	5.3	7.8	6.7
Serum 2	271	9.6	3.5	10.8	4.0
Serum 3	380	5.4	1.4	8.9	2.3
Serum 4	806	15.3	1.9	16.7	2.1
Serum 5	1597	25.7	1.6	31.6	2.0
Serum 6	25073	416	1.7	690	2.8
QC 1	144	5.6	3.9	6.1	4.2
QC 2	418	8.7	2.1	12.1	2.9

Sample	Mean pg/mL	Repeatability		Within-Lab	
		SD	%CV	SD	%CV
QC 3	4778	93.0	1.9	134.7	2.8

Between-Lab reproducibility

The reproducibility performance was established with a multi-site precision evaluation. Samples for testing were comprised of 8 native patient serum pools and three controls. In the study, each sample was tested at three sites using the same three lots of reagents. Each sample was assayed in replicates of three per run, two runs per day over five days for 30 measurements per lot per site, or for a total of 270 measurements across the three sites. The data was analyzed using a random effects model to estimate the variance components of within-run, between run, between day, between lot, and between sites.

All Sites Combined:

Sample	Mean pg/mL	Between Site		Between Lot		Between Day		Between Run		Repeatability		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control	142	4.2	2.9%	3.5	2.5%	1.0	0.7%	0.6	0.4%	4.9	3.4%	7.4	5.2%
Control	420	11.4	2.7%	8.8	2.1%	3.8	0.9%	3.3	0.8%	8.6	2.0%	17.5	4.2%
Control	4842	118.0	2.4%	105.1	2.2%	32.3	0.7%	30.9	0.6%	91.3	1.9%	187.9	3.9%
serum	139	4.4	3.1%	1.9	1.3%	1.4	1.0%	0.0	0.0%	4.5	3.2%	6.7	4.8%
serum	319	7.3	2.3%	4.3	1.3%	2.5	0.8%	0.0	0.0%	8.0	2.5%	12.0	3.8%
serum	482	11.9	2.5%	4.9	1.0%	3.8	0.8%	0.0	0.0%	10.6	2.2%	17.0	3.5%
serum	809	17.2	2.1%	12.3	1.5%	5.7	0.7%	4.1	0.5%	15.6	1.9%	27.1	3.4%
serum	1611	35.3	2.2%	26.2	1.6%	0.0	0.0%	7.2	0.4%	30.0	1.9%	53.7	3.3%
serum	10230	281.8	2.8%	160.2	1.6%	61.2	0.6%	62.6	0.6%	216.3	2.1%	399.4	3.9%
serum	19230	630.3	3.3%	181.4	0.9%	98.0	0.5%	117.4	0.6%	391.7	2.0%	779.1	4.1%
serum	28557	834.3	2.9%	248.9	0.9%	139.2	0.5%	0.0	0.0%	702.2	2.5%	1127.2	3.9%

2. Linearity:

The linearity performance of the ADVIA Centaur® NT-proBNPII (PBNPII) assay run on the ADVIA Centaur XP system was establish in a study following the recommendations of CLSI EP06, 2nd Edition. Samples for testing were comprised of two linearity panels each with 10 concentration levels. Each linearity panel was a dilution series prepared by intermixing known volumes of high and low sample pools of native human serum. The low pool was a non-zero sample. In the study, each sample (of the 20 total) was assayed in replicates of seven on one instrument using each of three reagent lots. The linearity was analyzed separately for each reagent lot. Using a weighted linear regression model, the difference between the mean observed value and the value predicted by the weighted linear regression model was derived. At each concentration, the deviation from linearity was less than 10%. The sponsor concluded that the assay yields a linear response over the claimed NT-proBNP measuring range of 35 to 35,000 pg/mL.

Sample Dilution

Serum and plasma samples with concentrations up to 63,128 pg/mL can be measured after a 5-fold dilution or 10-fold dilution. The percent recovery of diluted samples ranged from 80.5% to 87.2%.

3. Analytical Specificity/Interference:

The analytical specificity performance of the ADVIA Centaur® NT-proBNPII (PBNPII) was established by conducting a cross-reactivity study and interference testing for endogenous and exogenous substances, consistent with CLSI EP07, 3rd Edition and CLSI EP37, 1st Edition.

Endogenous substances
Interference from endogenous substances was assessed using serum samples with NT-proBNP at approximate concentrations of 125 pg/mL and 2000 pg/mL. Each of the two samples was further divided into two aliquots for a control sample (with no added interferent) and test sample (with added interferent). For screening, each sample was assayed in replicates of 8 using three lots of reagent packs on one instrument. No significant interference, defined by the sponsor as within ±10% difference in the mean for the test sample versus the mean of the control sample, was observed at the following concentrations:

Substance	Highest concentration tested at which no significant interference is observed
Albumin	6.00 g/dL
Cholesterol	500 mg/dL
Conjugated Bilirubin	60 mg/dL
Unconjugated Bilirubin	60 mg/dL
Creatinine	30.0 mg/dL
Hemoglobin	1000 mg/dL
Human anti-mouse antibodies (HAMA)	800 µg/L
Immunoglobulin G (IgG)	5.00 g/dL
Lipemia (Intralipid®)	3000 mg/dL
Protein, total	11.1 g/dL
Rheumatoid factor (RF)	1500 IU/mL
Triglyceride	1000 mg/dL

Exogenous substances
Interference from exogenous substances was assessed using samples with NT-proBNP concentrations of 125 pg/mL and 2000 pg/mL following the same procedure as for endogenous substances. No significant interference, defined by the sponsor as within ±10% difference in the mean for the test sample versus the mean of the control sample was observed at the following concentrations:

Substance	Highest concentration tested at which no significant interference is observed
Abciximab	21.0 µg/mL
Acetaminophen	20.0 mg/dL
Allopurinol	2.50 mg/dL
Amiodarone	2.0 mg/dL
Acetylcysteine	15.0 mg/dL
Amiodarone	4.2 mg/dL
Ampicillin	7.50 mg/dL
Amlodipine Besylate	4.00 µg/mL
Ascorbic Acid	5.00 mg/dL
Atenolol	1.00 mg/dL

Substance	Highest concentration tested at which no significant interference is observed
Atorvastatin	32.0 mg/dL
Bisoprolol	0.0258 mg/dL
Biotin	3510 ng/mL
Caffeine	10.8 mg/dL
Captopril	5.00 mg/dL
Chlordiazepoxide	1.00 mg/dL
Cinnarizine	3.00 mg/dL
Clopidogrel bisulfate	30.0 µg/mL
Cyclosporine	4000 ng/mL
Calcium dobesilate	6.00 mg/dL
Carvedilol	4.32 mg/dL
Cefoxitin	660 mg/dL
Chloramphenicol	7.80 mg/dL
Digitoxin	7.5 µg/dL
Digoxin	0.039 mg/dL
Diltiazem	120 µg/mL
Dipyridamole	30.0 µg/mL
Disopyramide	40.0 µg/mL
Dopamine	16.0 mg/dL
Doxycycline	1.80 mg/dL
Enalapril maleate	16.0 µg/mL
Erythromycin	13.8 mg/dL
Epinephrine	0.050 mg/dL
Furosemide	6.00 mg/dL
Gentamycin sulfate	3.51 mg/dL
Heparin	3.00 U/mL
Hydralazine	20.0 µg/mL
Hydrochlorothiazide	20.0 µg/mL
Indomethacin	16.0 µg/mL
Isosorbide dinitrate	6.00 mg/dL
Insulin	0.160 mg/dL
Lisinopril	16.0 µg/mL
Lovastatin	16.0 µg/mL
L-Thyroxine	60.0 µg/dL
L-dopa (Levodopa)	0.750 mg/dL
Lidocaine	8.00 mg/dL
Methyldopa	2.50 mg/dL
Milrinone lactate	2.40 µg/mL
Methylprednisolone	0.783 mg/dL
Metoprolol tartrate	15.0 mg/dL
Metronidazole	12.3 mg/dL
Molsidomine	0.018 mg/dL
Nicotine	0.100 mg/dL
Nifedipine	6.00 mg/dL
Nitrofurantoin	40.0 µg/mL

Substance	Highest concentration tested at which no significant interference is observed
Nitroglycerine	0.160 µg/mL
Oxazepam	12.0 µg/mL
Oxytetracycline	100 µg/mL
Phenytoin	5.00 mg/dL
Probenecid	200 µg/mL
Propranolol	0.150 mg/dL
Phenprocoumon	1.50 mg/dL
Phenobarbital	69.0 mg/dL
Phenylbutazone	32.1 mg/dL
Phenytoin	6.00 mg/dL
Pravastatin	0.021 mg/dL
Propafenone HCL	30.0 mg/dL
Quinidine	20.0 µg/mL
Retavase (reteplase)	3.33 mg/dL
Rifampicin (Rifampin)	4.80 mg/dL
Salicylic Acid	60.0 mg/dL
Simvastatin	32.0 µg/mL
Sotalol hydrochloride	0.510 mg/dL
Spironolactone	7.50 mg/dL
Streptokinase	150,000 U/L
Theophylline	4.00 mg/dL
Trimethoprim	64.0 µg/mL
Tolbutamide	150 mg/dL
Torsemide	1.50 mg/dL
Urokinase	150,000 U/L
Verapamil	96.0 µg/mL
Warfarin	8.00 mg/dL

Cross-reactivity

A study was conducted to evaluate the performance of the ADVIA Centaur NT-proBNPII (PBNPII) in the presence of cross reactants. In the study, two samples were prepared from human serum pools- low and high. Each serum pool was then spiked with cross-reactive substance to form a test sample or spiked with solvent to form a control sample. Each sample was assayed in replicates of 8. The % cross-reactivity was calculated as:

% cross-reactivity = 100% x (test conc. – control conc.) / cross-reactant conc.

Cross-reactant	Concentration	Control (pg/mL)	Test (pg/mL)	% Cross-reactivity
Adrenomedullin	1.0 ng/mL	3	8	ND
		126	127	0.1%
Aldosterone	0.6 ng/mL	3	2	ND
		139	143	0.7%
Angiotensin I	0.6 ng/mL	3	4	ND
		126	128	0.3%
Angiotensin II	0.6 ng/mL	9	18	ND
		143	147	0.7%
Angiotensin III	1.0 ng/mL	2	5	ND
		139	134	-0.5%
ANP28	3.1 µg/mL	2	1	ND
		139	138	0.0%
Arg-Vasopressin	1.0 ng/mL	9	11	ND
		143	144	0.1%
BNP32 (Natrecor®)	3.5 µg/mL	2	1	ND
		139	135	0.0%
CNP32	2.2 µg/mL	2	1	ND
		139	138	0.0%
DNP	1.0 ng/mL	2	1	ND
		139	138	-0.1%
Endothelin	20 pg/mL	2	7	ND
		139	138	-5.0%
proBNP (non-glycosylated)	3000 pg/mL	5	398	13%
		158	1060	30%
proBNP (glycosylated)	3000 pg/mL	5	43	1%
		158	732	19%
preproANP26-55	3.5 µg/mL	2	2	ND
		139	138	0.0%
preproANP56-92	1.0 ng/mL	2	2	ND
		139	137	-0.2%
preproANP104-123	1.0 ng/mL	3	4	ND
		126	124	-0.2%
Renin	50 ng/mL	2	5	ND
		141	123	0.0%
Urodilatin	3.5 µg/mL	2	2	ND
		141	124	0.0%
VNP	1.0 ng/mL	2	2	ND
		139	137	-0.2%

The results showed cross-reactivity of proBNP (glycosylated) and proBNP (nonglycosylated). Cross-reactivity of NT-proBNP assays to proBNP has been documented previously.

High dose hook effect
The ADVIA Centaur® NT-proBNPII (PBNPII) assay was evaluated for high dose hook effect using 10 concentration levels of NT-proBNP. The results support that the ADVIA Centaur® NT-proBNPII (PBNPII) assay does not show a high dose hook effect up to 300,000 pg/mL of NT-proBNP.

4. Assay Reportable Range:

   35 to 35,000 pg/mL

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

   Metrological traceability
   The metrological traceability of the ADVIA Centaur® NT-proBNPII (PBNPII) assay was reviewed and found acceptable.

   Sample Stability
   The sponsor provided data to support sample stability at different temperatures and conditions:

   - After centrifugation, serum specimens stored on the clot are stable for up to 24 hours at 2–8°C.
   - Separated samples are stable for up to 3 days at room temperature, and for up to 4 days at 2–8°C.
   - Separated samples are stable at ≤ -20°C for up to 12 months.

6. Detection Limit:
   The detection capability of the ADVIA Centaur® NT-proBNPII (PBNPII) run on the ADVIA Centaur XP system was evaluated for limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) following the recommendations in CLSI EP17-A2.

   LoB
   Samples for LoB testing consisted of four blank native human serum samples preselected for low NT-proBNP levels. In the study, LoB was determined separately for each of three reagent lots using one instrument. With each lot, the four samples were each assayed in 12 replicates per run, one run per day over 5 days for a total of 60 measurements per sample per reagent lot. The LoB was calculated non-parametrically. The LoB was calculated separately for each reagent lot and the highest value was taken as the LoB value; 13 pg/mL.

   LoD
   Samples for the LoD study consisted of 10 low NT-proBNP in native human serum and pooled human serum. In the study, LoD was determined separately for each of three reagent lots using one instrument. With each lot, the samples were each assayed in replicates of 8 per run, with one run per day over five days for a total of 40 measurements per sample per reagent lot. The parametric approach described in EP17-A2 was followed to determine the

LoD. The highest observed LoD of the three lots was the reported LoD for the assay; 20 pg/mL.

LoQ

Samples for the LoQ study consisted of 10 low NT-proBNP in native human serum and pooled human serum. In the study, LoQ was determined separately for each of three reagent lots using one instrument. With each lot, the samples were each assayed in replicates of 8 per run, with one run per day over five days for a total of 40 measurements per sample per reagent lot. For each reagent lot, the within-laboratory precision for each sample, expressed as %CV, was plotted against the mean concentration obtained for each sample. LoQ was determined by the concentration where a power function model fit to the data equaled 20% CV. The largest estimate across all reagent lots was 35 pg/mL.

The summary results for LoB, LoD and LoQ are shown below.

LoB	LoD	LoQ	Claimed Measuring Range
13 pg/mL	20 pg/mL	21 pg/mL	35 to 35,000 pg/mL

7. Assay Cut-Off:

See Section VII D.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Not Applicable: see clinical studies in Section C.

2. Matrix Comparison:

The assay is intended for use with serum and plasma (EDTA and lithium heparin).

A matrix equivalency study to serum (no gel barrier) was conducted to support use of the ADVIA Centaur® NT-proBNPII (PBNPII) run on the ADVIA Centaur XP system with additional specimen matrix types claimed in the product labeling: Serum (no gel barrier), SST serum tube (gel barrier), RST serum tube (gel barrier), K2 EDTA plasma, and lithium heparin plasma. In the study, 50 donor matched venous specimens of the aforementioned were collected. Each specimen was tested in singlicate using one lot of the reagent kit and one instrument, and the results compared to the mean of singlicate serum measurements. The results were analyzed by Passing-Bablok linear regression with the concentration from each donor's evaluation tube (y-axis) versus the mean concentration of the serum results (x-axis).

	Slope	Intercept	Concentration range, pg/mL	r
K2EDTA plasma	1.00	1	50 - 30134	1.000
Lithium heparin plasma	1.00	4	57 - 30390	0.999
BD Vacutainer SST™ Tube	1.00	-2	54 - 30122	1.000
BD Vacutainer RST™ Tube	1.00	4	53 - 30237	1.000

The study results support the sponsor's claim that serum and plasma (EDTA and lithium heparin) are acceptable sample types to be used with this assay.

C Clinical Studies:

1. Clinical Sensitivity:

   See Section VII C.3.

2. Clinical Specificity:

   See Section VII C.3.

3. Other Clinical Supportive Data:

   Clinical studies were performed in the emergency department and in outpatient settings.

   Emergency Department (ED)
   A clinical study across 30 sites in the United States was conducted to establish the clinical performance characteristics of the ADVIA Centaur NT-proBNPII (PBNPII) run on the ADVIA Centaur XP system. In the study, subjects 22 years and older presenting with signs and symptoms that raise clinical suspicion of heart failure (HF), such as dyspnea, that were not related to trauma, were enrolled. For each patient enrollment, a serum sample was collected for determination of their NT-proBNP concentration. Data supporting the stability of the samples for the storage time and condition were provided by the sponsor. A diagnosis of whether or not acute HF for each subject was assessed by an independent, central adjudication panel. Individuals in the population were African American (45.8%) and white (50.1%), with the remaining 4.2% represented by other races.

   From the 3128 subjects enrolled in the study, a total of 1148 subjects were adjudicated as acute HF and 1980 subjects were adjudicated as without acute HF.

	Subject with Acute Heart Failure (N=1148)	Subject Without Acute Heart Failure (N=1980)
Age Group		
<50	20.0% (230/1148)	34.2% (678/1980)
50-75	41.9% (481/1148)	41.4% (820/1980)
>75	38.1% (437/1148)	24.3% (482/1980)
Sex		
Female	41.5% (476/1148)	52.4% (1038/1980)
Male	58.5% (672/1148)	47.6% (942/1980)

   The pretest probability of HF (prevalence of HF in the study), posttest probabilities, likelihood ratios and the two-tailed 95% CIs of the test result versus adjudicated diagnosis were determined using the age-dependent positive cut-offs (450 pg/mL for subjects 22–<50 years old; 900 pg/mL for subjects 50–<75 years old; 1800 pg/mL for subjects ≥75 years old)

and age-independent negative (300 pg/mL) cutoff and are summarized in the following tables:

All subjects

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	209	123	332	63.0% (209/332)	57.5%,68.2%	5.01	4.25, 5.91
	Indeterminate	300 – ≤450	8	19	27	29.6% (8/27)	13.8%,50.2%	1.24	0.55, 2.80
	Negative	<300	13	536	549	2.4% (13/549)	1.3%,4.0%	0.07	0.04, 0.12
	Total		230	678	908	Pre-Test Risk of HF= 25.3% (230/908)			
50-75	Positive	>900	403	185	588	68.5% (403/588)	64.6%,72.3%	3.71	3.25, 4.24
	Indeterminate	300 – ≤900	54	160	214	25.2% (54/214)	19.6%,31,6%	0.58	0.43, 0.77
	Negative	<300	24	475	499	4.8% (24/499)	3.1%,7.1%	0.09	0.06, 0.13
	Total		481	820	1301	Pre-Test Risk of HF= 37.0% (481/1301)			
>75	Positive	>1800	375	174	549	68.3% (375/549)	64.2%,72.2%	2.38	2.10, 2.69
	Indeterminate	300 –≤1800	55	186	241	22.8% (55/241)	17.7%,27.7%	0.33	0.25, 0.43
	Negative	<300	7	122	129	5.4% (7/129)	2.2%,10.9%	0.06	0.03, 0.13
	Total		437	482	919	Pre-Test Risk of HF= 47.6% (437/919)			

Female subjects

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	71	54	125	56.8% (71/125)	47.6%, 65.6%	5.71	4.39, 7.43
	Indeterminate	300 – ≤450	4	12	16	25.0% (4/16)	7.3%, 52.4%	1.45	0.48, 4.38
	Negative	<300	9	299	308	2.9% (9/308)	1.3%, 5.5%	0.13	0.07, 0.24
	Total		84	365	449	Pre-Test Risk of HF = 18.7% (84/449)			
50-75	Positive	>900	155	81	236	65.7% (155/236)	59.2%, 71.7%	3.97	3.23, 4.89
	Indeterminate	300 – ≤900	28	69	97	28.9% (28/97)	20.1%, 39.0%	0.84	0.56, 1.26
	Negative	<300	14	259	273	5.1% (14/273)	2.8%, 8.5%	0.11	0.07, 0.19

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
	Total		197	409	606	Pre-Test Risk of HF = 32.5% (197/606)			
>75	Positive	>1800	170	91	261	65.1% (170/261)	59.0%, 70.9%	2.53	2.12, 3.01
	Indeterminate	300 –≤1800	21	97	118	17.8% (21/118)	11.4%, 25.9%	0.29	0.19, 0.45
	Negative	<300	4	76	80	5.0% (4/80)	1.4%, 12.3%	0.07	0.03, 0.19
	Total		195	264	459	Pre-Test Risk of HF= 42.5% (195/459)			

Male subjects

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	138	69	207	66.7% (138/207)	59.8%, 73.1%	4.29	3.47, 5.30
	Indeterminate	300 – ≤450	4	7	11	36.4% (4/11)	10.9%, 69.2%	1.23	0.36, 4.12
	Negative	<300	4	237	241	1.7% (4/241)	0.5%, 4.2%	0.04	0.01, 0.10
	Total		146	313	459	Pre-Test Risk of HF = 31.8% (146/459)			
50-75	Positive	>900	248	104	352	70.5% (248/352)	65.4%, 75.2%	3.45	2.91, 4.10
	Indeterminate	300 – ≤900	26	91	117	22.2% (26/117)	15.1%, 30.8%	0.41	0.27, 0.62
	Negative	<300	10	216	226	4.4% (10/226)	2.1%, 8.0%	0.07	0.04, 0.12
	Total		284	411	695	Pre-Test Risk of HF= 40.9% (284/695)			
>75	Positive	>1800	205	83	288	71.2% (205/288)	65.6%, 76.3%	2.22	1.86, 2.66
	Indeterminate	300 –≤1800	34	89	123	27.6% (34/123)	20.0%, 36.4%	0.34	0.24, 0.49
	Negative	<300	3	46	49	6.1% (3/49)	1.3%, 16.9%	0.06	0.02, 0.19
	Total		242	218	460	Pre-Test Risk of HF = 52.6% (242/460)			

Subjects WITH History of HF

Age Group (years)	NT-proBNP	Cut-off (pg/ml)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	157	63	220	71.4% (157/220)	64.9%, 77.2%	1.72	1.44, 2.05
	Indeterminate	300 – ≤450	5	8	13	38.5% (5/13)	13.9%, 68.4%	0.43	0.14, 1.29
	Negative	<300	12	49	61	19.7% (12/61)	10.6%, 31.8%	0.17	0.09, 0.30
	Total		174	120	294	Pre-Test Risk of HF = 59.2% (174/294)			
50-75	Positive	>900	312	94	406	76.8% (312/406)	72.4%, 80.9%	2.15	1.83, 2.54
	Indeterminate	300 – ≤900	44	49	93	47.3% (44/93)	36.9%, 57.9%	0.58	0.40, 0.85
	Negative	<300	20	101	121	16.5% (20/121)	10.4%, 24.4%	0.13	0.08, 0.20
	Total		376	244	620	Pre-Test Risk of HF = 60.6% (376/620)			
>75	Positive	>1800	265	86	351	75.5% (265/351)	70.7%, 79.9%	1.68	1.44, 1.95
	Indeterminate	300 –≤1800	30	63	93	32.3% (30/93)	22.9%, 42.7%	0.26	0.18, 0.38
	Negative	<300	4	14	18	22.2% (4/18)	6.4%, 47.6%	0.16	0.05, 0.47
	Total		299	163	462	Pre-Test Risk of HF = 64.7% (299/462)			

Subjects with NO History of HF

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	47	53	100	47.0% (47/100)	36.9%, 57.2%	8.94	6.84, 1.68
	Indeterminate	300 – ≤450	3	10	13	23.1% (3/13)	5.0%, 53.8%	3.02	0.86, 0.64
	Negative	<300	1	451	452	0.2% (1/452)	0.0%, 1.2%	0.02	0.00, 0.16
	Total		51	514	565	Pre-Test Risk of HF = 9.0% (51/565)			
50-75	Positive	>900	87	80	167	52.1% (87/167)	44.2%, 59.9%	5.73	4.62, 7.11
	Indeterminate	300 – ≤900	10	102	112	8.9% (10/112)	4.4%, 15.8%	0.52	0.28, 0.95
	Negative	<300	3	345	348	0.9% (3/348)	0.2%, 2.5%	0.05	0.02, 0.14
	Total		100	527	627	Pre-Test Risk of HF = 15.9% (100/627)			
>75	Positive	>1800	106	83	189	56.1% (106/189)	48.7%, 63.3%	2.83	2.31, 3.47

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
	Indeterminate	300 –≤1800	25	118	143	17.5% (25/143)	11.6%, 4.7%	0.47	0.32, 0.69
	Negative	<300	3	96	99	3.0% (3/99)	0.6%, 8.6%	0.07	0.02, 0.21
	Total		134	297	431	Pre-Test Risk of HF of HF = 31.1% (134/431)			

Subjects with eGFR <60 mL/min/1.73m2

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	72	39	111	64.9% (72/111)	55.2%, 73.7%	1.68	1.35, 2.08
	Indeterminate	300 – ≤450	3	3	6	50.0% (3/6)	11.8%, 88.2%	0.91	0.19, 4.35
	Negative	<300	1	27	28	3.6% (1/28)	0.1%, 18.3%	0.03	0.00, 0.24
	Total		76	69	145	Pre-Test Risk of HF = 52.4% (76/145)			
50-75	Positive	>900	176	82	258	68.2% (176/258)	62.2%, 73.9%	2.08	1.75, 2.48
	Indeterminate	300 – ≤900	19	36	55	34.5% (19/55)	22.2%, 48.6%	0.51	0.30, 0.86
	Negative	<300	7	78	85	8.2% (7/85)	3.4%, 16.2%	0.09	0.04, 0.18
	Total		202	196	398	Pre-Test Risk of HF = 50.8% (202/398)			
>75	Positive	>1800	260	105	365	71.2% (260/365)	66.3%, 75.8%	1.99	0.73, 2.30
	Indeterminate	300 –≤1800	22	88	110	20.0% (22/110)	13.0%, 28.7%	0.20	0.13, 0.31
	Negative	<300	0	34	34	0.0% (0/34)	NA	NA	NA
	Total		282	227	509	Pre-Test Risk of HF = 55.4% (282/509)			

Subjects with eGFR ≥60 mL/min/1.73m^2

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	137	83	220	62.3% (137/220)	55.5%, 68.7%	6.22	5.07, 7.64
	Indeterminate	300 – ≤450	4	15	19	21.1% (4/19)	6.1%, 45.6%	1.01	0.34, 2.99
	Negative	<300	11	475	486	2.3% (11/486)	1.1%, 4.0%	0.09	0.05, 0.15

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
	Total		152	573	725	Pre-Test Risk of HF = 21.0% (152/725)			
50-75	Positive	>900	223	101	324	68.8% (223/324)	63.5%, 73.8%	4.87	4.04, 5.87
	Indeterminate	300 – ≤900	34	122	156	21.8% (34/156)	15.6%, 29.1%	0.61	0.43, 0.87
	Negative	<300	17	381	398	4.3% (17/398)	2.5%, 6.8 %	0.10	0.06, 0.16
	Total		274	604	878	Pre-Test Risk of HF = 31.2% (274/878)			
>75	Positive	>1800	113	67	180	62.8% (113/180)	55.3%, 69.9%	2.77	2.21, 3.47
	Indeterminate	300 –≤1800	32	97	129	24.8% (32/129)	17.6%, 33.2%	0.54	0.38, 0.77
	Negative	<300	7	86	93	7.5% (7/93)	3.1%, 14.9%	0.13	0.06, 0.28
	Total		152	250	402	Pre-Test Risk of HF = 37.8% (152/402)			

Subjects with BMI ≥30 kg/m2

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	147	69	216	68.1% (147/216)	61.4%, 74.2%	5.13	4.11, 6.40
	Indeterminate	300 – ≤450	7	10	17	41.2% (7/17)	18.4%, 67.1%	1.69	0.65, 4.35
	Negative	<300	13	323	336	3.9% (13/336)	2.1%, 6.5%	0.10	0.06, 0.16
	Total		167	402	569	Pre-Test Risk of HF = 29.3% (167/569)			
50-75	Positive	>900	217	67	284	76.4% (217/284)	71%, 81.2%	4.81	3.83, 6.05
	Indeterminate	300 – ≤900	46	86	132	34.8% (46/132)	26.8%, 43.6%	0.79	0.57, 1.10
	Negative	<300	23	272	295	7.8% (23/295)	5.0%, 11.5%	0.13	0.08, 0.19
	Total		286	425	711	Pre-Test Risk of HF = 40.2% (286/711)			
>75	Positive	>1800	111	38	149	74.5% (111/149)	66.7%, 81.3%	3.02	2.26, 4.04
	Indeterminate	300 –≤1800	30	61	91	33.0% (30/91)	23.5%, 43.6%	0.51	0.35, 0.74
	Negative	<300	5	52	57	8.8% (5/57)	2.9%, 19.3%	0.10	0.04, 0.24
	Total		146	151	297	Pre-Test Risk of HF = 49.2% (146/297)			

Subjects with BMI <30 kg/m^2

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	52	52	104	50.0% (52/104)	40.0%, 60.0%	4.77	3.75, 6.07
	Indeterminate	300 – ≤450	0	8	8	0.0% (0/8)	NA	NA	NA
	Negative	<300	0	188	188	0.0% (0/188)	NA	NA	NA
	Total		52	248	300	Pre-Test Risk of HF = 17.3% (52/300)			
50-75	Positive	>900	168	101	269	62.5% (168/269)	56.4%, 68.3%	3.45	2.92, 4.08
	Indeterminate	300 – ≤900	6	71	77	7.8% (6/77)	2.9%, 16.2%	0.18	0.08, 0.40
	Negative	<300	0	189	189	0.0% (0/189)	NA	NA	NA
	Total		174	361	535	Pre-Test Risk of HF = 32.5% (174/535)			
>75	Positive	>1800	240	131	371	64.7% (240/371)	59.6%, 69.6%	2.12	1.85, 2.42
	Indeterminate	300 –≤1800	21	107	128	16.4% (21/128)	10.5%, 24.0%	0.23	0.15, 0.35
	Negative	<300	1	65	66	1.5% (1/66)	0.0%, 8.2%	0.02	0.00, 0.13
	Total		262	303	565	Pre-Test Risk of HF = 46.4% (262/565)			

Subjects WITH Comorbidities (Diabetes, Hypertension, Kidney Disease/Renal Dysfunction)

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	173	89	262	66.0% (173/262)	59.9%, 71.7%	3.99	3.30, 4.82
	Indeterminate	300 – ≤450	7	13	20	35.0% (7/20)	15.4%, 59.2%	1.11	0.45, 2.72
	Negative	<300	11	290	301	3.7% (11/301)	1.8%, 6.4%	0.08	0.04, 0.14
	Total		191	392	583	Pre-Test Risk of HF = 32.8% (191/583)			
50-75	Positive	>900	374	160	534	70.0% (374/534)	66.0%, 73.9%	3.67	3.18, 4.23
	Indeterminate	300 – ≤900	52	141	193	26.9% (52/193)	20.8%, 33.8%	0.58	0.43, 0.78
	Negative	<300	24	405	429	5.6% (24/429)	3.6%, 8.2%	0.09	0.06, 0.14
	Total		450	706	1156	Pre-Test Risk of HF = 38.9% (450/1156)			
>75	Positive	>1800	351	155	506	69.4% (351/506)	65.1%, 73.4%	2.41	2.11, 2.76

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
	Indeterminate	300 –≤1800	52	168	220	23.6% (52/220)	18.2%, 29.8%	0.33	0.25, 0.44
	Negative	<300	7	114	121	5.8% (7/121)	2.4%, 11.6%	0.07	0.03, 0.14
	Total		410	437	847	Pre-Test Risk of HF = 48.4% (410/847)			

Subjects WITHOUT Comorbidities (Diabetes, Hypertension, Kidney Disease/Renal Dysfunction)

Age Group (years)	NT-proBNP	Cut-off (pg/mL)	Adjudicated Diagnosis		Total	Post-test Risk (%) of HF	95% CI Post-test Risk (%) of HF	LR+	95% CI LR+
			Positive	Negative					
<50	Positive	>450	29	31	60	48.3% (29/60)	35.2%, 61.6%	7.72	5.44, 10.94
	Indeterminate	300 – ≤450	1	6	7	14.3% (1/7)	0.4%, 57.9%	1.38	0.17, 11.06
	Negative	<300	2	227	229	0.9% (2/229)	0.1%, 3.1%	0.07	0.02, 0.28
	Total		32	264	296	Pre-Test Risk of HF = 10.8% (32/296)			
50-75	Positive	>900	25	23	48	52.1% (25/48)	37.2%, 66.7%	4.23	2.90, 6.16
	Indeterminate	300 – ≤900	2	18	20	10.0% (2/20)	1.2%, 31.7%	0.43	0.11, 1.75
	Negative	<300	0	64	64	0.0% (0 /64)	NA	NA	NA
	Total		27	105	132	Pre-Test Risk of HF = 20.5% (27/132)			
>75	Positive	>1800	22	18	40	55.0% (22/40)	38.5%, 70.7%	2.10	1.44, 3.08
	Indeterminate	300 –≤1800	3	17	20	15.0% (3/20)	3.2%, 37.9%	0.30	0.10, 0.93
	Negative	<300	0	8	8	0.0% (0/8)	NA	NA	NA
	Total		25	43	68	Pre-Test Risk of HF = 36.8% (25/68)			

The sponsor included the following statements in their instructions for use concerning the performance of their device in ED settings in certain clinical subgroups:

• Patients with BMI ≥30 kg/m2 had a higher rate of false negatives compared to those patients with BMI <30 kg/m2. Of the total false negatives (44/1148), 41 (93%) came from patients with BMI ≥30 kg/m2, 1 (2.2%) came from a patient with a BMI <30 kg/m2, and 2 (4.4%) were from patients with unknown BMI.

• Patients with eGFR <60 mL/min/1.73m2 had a higher rate of false positives compared to those patients with eGFR ≥60 mL/min/1.73m2. Of the 492 total patients with eGFR <60 mL/min/1.73m2 adjudicated as no acute HF, 226 (45.9%) had PBNPII concentrations ≥ ASC. Of

the 1427 total patients with eGFR ≥60 mL/min/1.73m2 adjudicated as no acute HF, 251 (17.6%) had PBNPII concentrations ≥ ASC. Sixty-one (61) patients adjudicated as no acute HF (3.1%), had unknown eGFR.

• Patients with a history of HF had a higher rate of false positives compared to those patients with no history of HF. Of the 527 total patients with a history of HF adjudicated as no acute HF, 243 (46.1%) had PBNPII concentrations ≥ ASC. Of the 1338 total patients with no history of HF adjudicated as no acute HF, 216 (16.1%) had PBNPII concentrations ≥ ASC. Of the 1980 patients adjudicated as no acute HF, 115 (5.8%) had unknown history of HF.

Variation in NT-proBNP concentrations due to high BMI, low GFR, and history of HF are extensively discussed in published literature on Natriuretic Peptides.

Outpatient (OP)

A clinical study across 28 OP sites in the United States was conducted to establish the clinical performance characteristics of the ADVIA Centaur® NT-proBNPII (PBNPII) run on the ADVIA Centaur XP system. In the study, subjects 22 years and older presenting with signs and symptoms that raise clinical suspicion of heart failure (HF), such as dyspnea, that were not related to trauma, were enrolled in the study. For each patient, a serum sample was collected for determination of their NT-proBNP concentration. Data supporting the stability of the samples for the storage time and condition were provided by the sponsor. A diagnosis of new onset of HF or not was assessed by an independent, central adjudication panel. Individuals in the population were African American (19.7%) and white (78.4%), with the remaining 1.8% represented by other races. The clinical performance of the device using cutoff of 125 pg/mL was evaluated. From the 1033 subjects enrolled in the study, a total of 185 subjects were adjudicated as new onset HF and 848 subjects were adjudicated as without HF. The clinical performance of the device is summarized below:

Group		Sensitivity	Specificity	PPV	NPV
Males ≤75 years	Estimate	85.5% (53/62)	68.9% (179/260)	39.6% (53/134)	95.2% (179/188)
	95% CI	74.2%, 93.1%	62.8%, 74.4%	31.2%, 48.4%	91.1%, 97.8%
Females ≤75 years	Estimate	79.2% (57/72)	70.8% (335/473)	29.2% (57/195)	95.7% (335/350)
	95% CI	67.5%, 87.8%	67.0%, 74.9%	23.0%, 36.2%	93.0%, 97.6%
Males >75 years	Estimate	90.5% (19/21)	37.2% (16/43)	41.3% (19/46)	88.9% (16/18)
	95% CI	69.6%, 98.8%	22.8%, 51.7%	27.0%, 56.8%	65.3%, 98.6%
Females >75 years	Estimate	100% (30/30)	20.8% (15/72)	34.5% (30/87)	100% (15/15)
	95% CI	88.4%,100%	2.2%, 32.0%	24.6%, 45.4%	78.2%, 100%

Group		Sensitivity	Specificity	PPV	NPV
BMI <30 kg/m^2	Estimate	88.2% (67/76)	60.6% (238/393)	30.2% (67/222)	96.4% (238/247)
	95% CI	(87.7%, 99.6%)	(63.5%, 75.0%)	(31.9%, 49.1%)	(96.1%, 99.9%)
BMI ≥30 kg/m^2	Estimate	84.4% (92/109)	67.5% (303/449)	38.7% (92/238)	94.7% (303/320)
	95% CI	(76.2%, 90.6%)	(62.9%, 71.8%)	(32.4%, 45.2%)	(91.6%, 96.9%)

Group		Sensitivity	Specificity	PPV	NPV
Comorbidities present	Estimate	86.4% (153/177)	60.7% (396/652)	37.4% (153/409)	94.3% (396/420)
	95% CI	(80.5%, 91.1%)	(56.9%, 64.5%)	(32.7%, 42.3%)	(91.6%, 96.3%)
Comorbidities not present	Estimate	75.0% (6/8)	76.0% (136/179)	12.2% (6/49)	98.6% (136/138)
	95% CI	(34.9, 96.8%)	(69.0%, 82.0%)	(4.6%, 24.8%)	(94.9%, 99.8%)

Group		Sensitivity	Specificity	PPV	NPV
eGFR <60 mL/min/1.73 m^2	Estimate	100.0% (33/33)	32.7% (18/55)	47.1% (33/70)	100.0% (18/18)
	95% CI	(89.4%, 100.0%)	(20.7%, 46.7%)	(35.1%, 59.5%)	(81.5%, 100.0%)
eGFR ≥60 mL/min/1.73 m^2	Estimate	96.4% (4/56)	69.5% (182/262)	40.3% (54/134)	98.9% (182/184)
	95% CI	(87.7%, 99.6%)	(63.5%, 75.0%)	(31.9%, 49.1%)	(96.1%, 99.9%)

D Clinical Cut-Off:

The sponsor describes the following cut-offs for patients presenting to ED settings where HF is suspected:

Age Group (Years)	PBNPII Results (pg/mL)	Interpretation
All	<300	Negative: Heart Failure Unlikely
<50 50-75 >75	≥ 300 - ≤ 450 ≥ 300 - ≤ 900 ≥ 300 - ≤ 1800	Gray Zone: Result Indeterminate – Consider other reasons for NT-proBNP elevation
<50 50-75 >75	> 450 > 900 > 1800	Positive: Heart Failure Likely

For patients presenting to outpatient facilities where HF is suspected (but has not been previously diagnosed), the following cut-off is described:

Age Group (Years)	PBNPII Results (pg/mL)	Interpretation
All	< 125	Negative: Heart Failure Unlikely
All	≥ 125	Positive: Heart Failure Likely

E Expected Values/Reference Range:

The expected values of NT-proBNP in healthy adults was establish in a study conducted in accordance with CLSI EP28-A3c.

In the study, serum levels of NT-proBNP were assayed with the ADVIA Centaur® NT-proBNPII (PBNPII) on a total of 723 apparently healthy subjects (362 females and 361 males) without HF. These apparently healthy subjects were self-reported without heart failure or disease. The results were subgrouped by gender, with each group of females and males was stratified into three age groups of: < 50 years, 50–75 years, and > 75 years. The data was analyzed by a non-parametric method and summarized as follows.

Sex	Age years	N	Mean pg/mL	SD pg/mL	Median pg/mL	95th Percentile pg/mL
Male	<50	120	56	95.	< 35	124
	50-75	121	78	136.4	< 35	322
	>75	120	56	50.6	< 35	154
Female	<50	122	57	33.1	37	133
	50-75	120	77	124.0	40	192
	>75	120	89	216.4	43	178
Overall	Overall	723	6	124.9	< 35	163

VIII Proposed Labeling:

The labeling does support the finding of substantial equivalence for this device.

IX Conclusion:

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