September 24, 2023

Siemens Healthcare Diagnostics Inc.
Asha Gartland
Regulatory Affairs Specialist
511 Benedict Ave
Tarrytown, NY 10591

Re: K220265
Trade/Device Name: ADVIA Centaur® NT-proBNPII (PBNPII)
Regulation Number: 21 CFR 862.1117
Regulation Name: B-Type Natriuretic Peptide Test System
Regulatory Class: Class II
Product Code: NBC
Dated: November 18, 2022
Received: November 18, 2022

Dear Asha Gartland:

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,

Marianela Perez-torres -S

Marianela Perez-Torres, Ph.D.
Acting Director
Division of Chemistry
and Toxicology Devices
OHT7: Office of In Vitro Diagnostics
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K220265

Device Name
ADVIA Centaur® NT-proBNPII (PBNPII)

Indications for Use *(Describe)*
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.

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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This 510(k) Summary is being submitted in accordance with the requirements of 21 CFR 807.92 and the Safe Medical Device Act of 1990.

The assigned 510(k) Number is: K220265

1. Date Prepared

September 22nd , 2023

2. Applicant Information

Contact: Asha Gartland
Regulatory Affairs Specialist

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511 Benedict Avenue
Tarrytown, NY 10591-5097

Phone: 845-327-8296

Email asha.gartland@siemens-healthineers.com

3. Regulatory Information

Table 1. Regulatory Information for ADVIA Centaur® NT-proBNPII (PBNPII) Assay

Trade Name	ADVIA Centaur® NT-proBNPII (PBNPII)
Common Name	Test, Natriuretic Peptide
Classification Name	B-type natriuretic peptide test system
FDA Classification	Class II
Review Panel	Clinical Chemistry (75)
Product Code	NBC
Regulation Number	21 CFR 862.1117

4. Predicate Device Information

Predicate Device Name: Roche Elecsys proBNP II assay

510(k) Number: K072437

5. Intended Use / Indications 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.

6. Special Conditions for Use Statement

For Prescription Use

7. Device Description

Component	Volume	Ingredients
ADVIA Centaur PBNPII Primary Reagent ReadyPack (included in assay kit)		
Lite Reagent	7.5 mL/pack	Monoclonal sheep anti-human NT-proBNP F(ab')2 fragment antibody (~0.36 µg/mL) labeled with acridinium ester in buffer; bovine serum albumin (BSA); bovine gamma globulin; preservatives
Solid Phase Reagent	20.0 mL/pack	Monoclonal sheep anti-human NT-proBNP antibody (~2 µg/mL) labeled with biotin bound to streptavidin magnetic particles (~220 mg/L) in buffer; BSA; bovine gamma globulin; sheep gamma globulin; preservatives
Ancillary Well Reagent	7.5 mL/pack	Buffer; BSA; bovine gamma globulin; sheep gamma globulin; preservatives
ADVIA Centaur PBNPII Calibrator (included in assay kit)		
ADVIA Centaur PBNPII Low and High Calibrators	2.0 mL/vial Lyophilized	After reconstitution, low or high levels of NT-proBNP antigen; buffer; BSA; preservatives

8. Comparison of Technological Characteristics with the Predicate Device

	Candidate Device	Predicate
Item	**ADVIA Centaur** **NT-proBNP (PBNPII) assay**	**Roche Elecsys proBNP II assay (K072437)**
Intended 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.	Immunoassay for the in vitro quantitative determination of N-terminal pro-Brain natriuretic peptide in human serum and plasma. This assay is used as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure. The test may also serve as an aid in the assessment of increased risk of cardiovascular events and mortality in patients at risk for heart failure who have stable coronary artery disease.
Indications for Use	Same as Intended Use (Candidate)	Same (for Predicate)
Similarities		
Measurement	Quantitative	Same
Technology	Chemiluminescence	Same
Sample type	Plasma and Serum	Same
Standardization	Traceable to synthetic human NT-proBNP (1-76) through internal standard	Same
Calibration	2 levels	Same
Calibrators	Lyophilized	Same
Hook Effect	No hook effect up to 300,000 pg/mL	Same
Differences		
Operating Principle	1-Step Sandwich immunoassay	2-Step Sandwich immunoassay
Assay Range	35-35,000 pg/mL	5-35,000 pg/mL

	Candidate Device	Predicate
Item	**ADVIA Centaur NT-proBNP (PBNPII) assay**	**Roche Elecsys proBNP II assay (K072437)**
Sample Volume	20 µL	15 µL
LoB	13 pg/mL	LoB<LoD
LoD	20 pg/mL	5.00 pg/mL
LoQ	35 pg/mL	50.0 pg/mL
Detection Antibody	Monoclonal sheep anti-human NT-proBNP F(ab')2 fragment antibody (~0.36 µg/mL) labeled with acridinium ester in buffer	Monoclonal anti-NT-proBNP antibody (sheep) labeled with ruthenium complex 1.1 µg/mL in buffer
Capture Antibody	Monoclonal sheep anti-human NT-proBNP antibody (~2 µg/mL) labeled with biotin bound to streptavidin magnetic particles (~220 mg/L) in buffer	Biotinylated monoclonal anti-NT-proBNP antibody (mouse) 1.1 µg/mL in buffer
Precision (Serum) (Total CV)	6.7% @ 116 pg/mL 4.0% @ 271 pg/mL 2.3% @ 380 pg/mL 2.1% @ 806 pg/mL 2.0% @ 1,597 pg/mL 2.8% @ 25,073 pg/mL 4.2% @ 144 pg/mL 2.9% @ 418 pg/mL 2.8% @ 4,778 pg/mL	4.6% @ 44.0 pg/mL 2.6% @ 126 pg/mL 1.8% @ 2,410 pg/mL 3.8% @ 33,606 pg/mL 2.8% @ 82.0 pg/mL 1.6% @ 2,318 pg/mL
Intended Use Population(s)	Emergency Department (ED) and Outpatient (OP)	Single Population
Clinical Cut-Off	ED Population Rule out HF: All ages <300 pg/mL Indeterminate <50 years ≥300 to ≤ 450 pg/mL 50–75 years ≥ 300 to ≤ 900 pg/mL >75 years ≥ 300 to ≤ 1800 pg/mL Rule-in HF < 50 years > 450 pg/mL 50–75 years > 900 pg/mL >75 years > 1800 pg/mL OP Population Rule out HF All ages <125 pg/mL	125 pg/mL for <75 years 450 pg/mL for ≥ 75 years

	Candidate Device	Predicate
Item	**ADVIA Centaur** **NT-proBNP (PBNPII) assay**	**Roche Elecsys proBNP II assay (K072437)**
Clinical Data Presentation	ED Population Likelihood Ratio – age dependent rule-out (negative), indeterminate and rule in (positive) cut offs OP Population Sensitivity and Specificity and Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for ages ≤75 and >75 years and sex	Sensitivity and Specificity vs age (<45, 45-54, 55-64, 65-74, ≥ 75 and <75 years) and sex

9. Performance Characteristics: ADVIA Centaur PBNPII assay

9.1 Precision

Precision was determined in accordance with CLSI Document EP05-A3. Samples were assayed in duplicate in 2 runs per day for 20 days. The following results were obtained:

		Repeatability			Within-Lab		
Specimen Type	**Mean of 80 reps pg/mL (pmol/L)**	**SD pg/mL (pmol/L)**	**% CV**	**Acceptable Criteria (%CV)**	**SD pg/mL (pmol/L)**	**% CV**	**Acceptable Criteria (%CV)**
Serum 1	116 (13.7)	6.1 (0.720)	5.3	≤5.5	7.8 (0.920)	6.7	≤8
Serum 2	271 (32.0)	9.6 (1.13)	3.5	≤5.5	10.8 (1.27)	4.0	≤8
Serum 3	380 (44.8)	5.4 (0.637)	1.4	≤5.5	8.9 (1.05)	2.3	≤8
Serum 4	806 (95.1)	15.3 (1.81)	1.9	≤7	16.7 (1.97)	2.1	≤10
Serum 5	1597 (188)	25.7 (3.03)	1.6	≤7	31.6 (3.73)	2.0	≤10
Serum 6	25,073 (2959)	416.4 (49.1)	1.7	≤7	690.1 (81.4)	2.8	≤10
QC 1	144 (17.0)	5.6 (0.661)	3.9	≤5.5	6.1 (0.720)	4.2	≤8
QC 2	418 (49.3)	8.7 (1.03)	2.1	≤5.5	12.1 (1.43)	2.9	≤8
QC 3	4778 (564)	93.0 (11.0)	1.9	≤7	134.7 (15.9)	2.8	≤10

9.2 Reproducibility

Reproducibility was determined in accordance with CLSI Document EP05-A3. Samples (N=90) were assayed in duplicate in 2 runs per day for 5 days at 3 sites.

The following results are representative of the performance of the assay:

		Mean	Repeatability		Between Run		Between Day		Between Site		Reproducibility	
Sample ID	N	pg/mL (pmol/L)	SD pg/mL (pmol/L)	%CV	SD pg/mL (pmol/L)	%CV	SD pg/mL (pmol/L)	%CV	SD pg/mL (pmol/L)	%CV	SD pg/mL (pmol/L)	%CV
Serum A	90	141 (16.6)	4.1 (0.484)	2.9%	0 (0.000)	0.0%	0.8 (0.094)	0.6%	5.7 (0.673)	4.0%	7 (0.826)	5.0%
Serum B	90	324 (38.2)	7.6 (0.897)	2.4%	0 (0.000)	0.0%	2.6 (0.307)	0.8%	6.7 (0.791)	2.1%	10.5 (1.24)	3.2%
Serum C	90	489 (57.7)	8.5 (1.00)	1.7%	0 (0.000)	0.0%	4.9 (0.578)	1.0%	15 (1.77)	3.1%	18 (2.12)	3.7%
Serum D	90	824 (97.2)	14.7 (1.73)	1.8%	0 (0.000)	0.0%	9.8 (1.16)	1.2%	18.5 (2.18)	2.2%	25.5 (3.01)	3.1%
Serum E	90	1641 (194)	29.4 (3.47)	1.8%	13.9 (1.64)	0.8%	9.6 (1.13)	0.6%	35 (4.13)	2.1%	48.7 (5.75)	3.0%
Serum F	90	10428 (1231)	184.6 (21.8)	1.8%	49.7 (5.86)	0.5%	95.7 (11.3)	0.9%	374.3 (44.2)	3.6%	431.1 (50.9)	4.1%
Serum G	90	19469 (2297)	349.1 (41.2)	1.8%	147.4 (17.4)	0.8%	0 (0.000)	0.0%	643.1 (75.9)	3.3%	746.5 (88.1)	3.8%
Serum H	90	28860 (3405)	696.8 (82.2)	2.4%	0 (0.000)	0.0%	127.4 (15.0)	0.4%	736.1 (86.9)	2.6%	1021.6 (121)	3.5%
Control 1	90	146 (17.2)	4 (0.472)	2.8%	1.2 (0.142)	0.8%	1.7 (0.201)	1.2%	4.8 (0.566)	3.3%	6.6 (0.779)	4.5%
Control 2	90	430 (50.7)	9.3 (1.10)	2.2%	3.8 (0.448)	0.9%	1.9 (0.224)	0.4%	12.9 (1.52)	3.0%	16.5 (1.95)	3.8%
Control 3	90	4965 (586)	89 (10.5)	1.8%	42.9 (5.06)	0.9%	32.4 (3.82)	0.7%	129 (15.2)	2.6%	165.7 (19.6)	3.3%

9.3 Linearity

Linearity testing was performed in accordance with CLSI Document EP06-Ed2. The ADVIA Centaur PBNPII assay is linear for the measuring interval of 35–35,000 pg/mL (4.13–4130 pmol/L).

9.4 Detection Limit

The limit of blank (LoB), limit of detection (LoD), and the limit of quantitation (LoQ) were determined as described in CLSI protocol EP17-A2. The ADVIA Centaur PBNPII assay has an LoB of 13 pg/mL (1.53 pmol/L), an LoD of 20 pg/mL (2.36 (pmol/L), and an LoQ of 35 pg/mL (4.13 pmol/L).

9.5 Interference

Hemolysis, Icterus, Lipemia (HIL)

Interference testing was performed in accordance with CLSI Document EP07-ed3. The following substances do not interfere with the assay when present in serum at the concentrations indicated.

Bias due to these substances does not exceed 10% at NT-proBNP concentrations of 123–137 pg/mL (14.5–16.2 pmol/L) and 1612–1813 pg/mL (190–214 pmol/L).

Substance	Substance Test Concentration
Hemoglobin	1000 mg/dL
Bilirubin, conjugated	60.0 mg/dL
Bilirubin, unconjugated	60.0 mg/dL
Lipemia (Intralipid)	3000 mg/dL

Other Substances

The following substances do not interfere with the assay when present in serum at the concentrations indicated. Bias due to these substances does not exceed 10% at NT-proBNP concentrations of 116–163 pg/mL (13.7–19.2 pmol/L) and 1478–2225 pg/mL (174–263 pmol/L).

Substance	Substance Test Concentration	Substance	Substance Test Concentration
Abciximab	21.0 µg/mL	L-dopa (Levodopa)	0.750 mg/dL
Acetaminophen	20.0 mg/dL	Lidocaine	8.00 mg/dL
Acetylcysteine	15.0 mg/dL	Lisinopryl	16.0 µg/mL
Allopurinol	2.50 mg/dL	Lovastatin	16.0 µg/mL
Amiodarone	20.0 42.0 µg/mL	L-Thyroxine	60.0 µg/dL
Amlodipine Besylate	4.00 µg/mL	Methyldopa	2.50 mg/dL
Ampicillin	5.30 7.50 mg/dL	Methylprednisolone	0.783 mg/dL
Ascorbic Acid	5.00 mg/dL	Metoprolol tartrate	15.0 mg/dL
Atenolol	1.00 mg/dL	Metronidazole	12.3 mg/dL
Atorvastatin	32.0 mg/dL	Milrinone lactate	2.40 µg/mL
Biotin	3510 ng/mL	Molsidomin (Placeholder)	0.018 mg/dL
Bisoprolol	0.258 µg/mL	Nicotine	0.100 mg/dL
Caffeine	6.00 10.8 mg/dL	Nifedipine	6.00 mg/dL
Calcium dobesilate	6.00 mg/dL	Nitrofurantoin	40.0 µg/mL
Captopril	5.00 mg/dL	Nitroglycerine	0.160 µg/mL
Carvedilol	4.32 mg/dL	Oxazepam	12.0 µg/mL
Cefoxitin	660 mg/dL	Oxytetracycline	100 µg/mL
Chloramphenicol	7.80 mg/dL	Phenobarbital	69.0 mg/dL
Chlordiazepoxide	1.00 mg/dL	Phenprocoumon (Placeholder)	1.50 mg/dL
Cholesterol	500 mg/dL	Phenylbutazone	32.1 mg/dL
Cinnarizine	3.00 mg/dL	Phenytoin	6.00 mg/dL

Clopidogrel bisulfate	30.0 µg/mL	Pravastatin	0.021 mg/dL
Creatinine	30.0 mg/dL	Probenecid	200 µg/mL
Cyclosporine	4000 ng/mL	Propafenone HCL	30.0 mg/dL
Digitoxin	75.0 ng/mL	Propanolol	0.150 mg/dL
Digoxin	390 ng/mL	Protein: Albumin	6.00 g/dL
Diltiazem	120 µg/mL	Protein: Total	11.1 g/dL
Dipotassium EDTA	9.00 mg/mL	Quinidine	20.0 µg/mL
Dipyridamole	30.0 µg/mL	Retavase (reteplase)	3.33 mg/dL
Diclofenac	60.0 µg/mL	Rheumatoid Factor	1500 IU/mL
Disopyramide	40.0 µg/mL	Rifampicin (Rifampin)	4.80 mg/dL
Dopamine	16.0 mg/dL	Salicylic Acid	60.0 mg/dL
Doxycycline hyclate	1.80 mg/dL	Simvastatin	32.0 µg/mL
Enalapril maleate	16.0 µg/mL	Sotalol hydrochloride	0.510 mg/dL
Epinephrine	0.050 mg/dL	Spironolactone	7.50 mg/dL
Erythromycin	13.8 mg/dL	Streptokinase	150,000 U/L
Furosemide	6.00 mg/dL	Sulfamethoxazole	320 µg/mL
Gentamycin sulfate	3.51 mg/dL	Theophylline	4.00 mg/dL
HAMA (Human Anti-Mouse Antibody)	800 ug/L	Tolbutamide	150 mg/dL
Heparin	330 U/dL	Torasemide	1.50 mg/dL
Hydralazine	20.0 µg/mL	Triglycerides	1000 mg/dL
Hydrochlorothiazide	20.0 µg/mL	Trimethoprim	64.0 µg/mL
Immunoglobulin G (IgG)	5.00 g/dL	Verapamil	96.0 µg/mL
Indomethacin	16.0 µg/mL	Urokinase	150,000 U/L
Insulin	0.160 mg/dL	Warfarin	8.00 mg/dL
Isosorbide dinitrate	6.00 mg/dL		

9.6 Cross-Reactivity

Cross-reactivity was determined in accordance with CLSI Document EP07-ed3. Cross-reactants were tested at NT-proBNP concentrations of 0 pg/mL (0 pmol/L) and 126–158 pg/mL (14.9–18.6 pmol/L).

Cross-reactant	Cross-reactant Concentration	Cross-reactivity (%)
Adrenomedullin	1.00 ng/mL	Not Detectable < 1.0%
Aldosterone	0.600 ng/mL	Not Detectable < 1.0%
Angiotensin I	0.600 ng/mL	Not Detectable < 1.0%
Angiotensin II	0.600 ng/mL	Not Detectable < 1.0%
Angiotensin III	1.00 ng/mL	Not Detectable < 1.0%
ANP28	3.10 µg/mL	Not Detectable < 1.0%
Arg-Vasopressin	1.00 ng/mL	Not Detectable < 1.0%
BNP32	3.50 µg/mL	Not Detectable < 1.0%
CNP32	2.20 µg/mL	Not Detectable < 1.0%
DNP	1.00 ng/mL	Not Detectable < 1.0%
Endothelin	20.0 pg/mL	Not Detectable -5.0%
preproANP26-55	3.50 µg/mL	Not Detectable < 1.0%
preproANP56-92	1.00 ng/mL	Not Detectable < 1.0%
preproANP104-123	1.00 ng/mL	Not Detectable < 1.0%
proBNP (glycosylated)	3000 pg/mL	1.0% 19.0%
proBNP (non-glycosylated)	3000 pg/mL	13.0% 30.0%
Renin; human	50.0 ng/mL	Not Detectable < 1.0%
Urodilatin	3.50 µg/mL	Not Detectable < 1.0%
VNP	1.00 ng/mL	Not Detectable < 1.0%

9.7 Specimen Equivalency

Specimen equivalency was determined with the Passing-Bablok regression model in accordance with CLSI Document EP09c-ed3.

Tube (y) vs. Serum (x)	Regression Equation	Sample Interval pg/mL (pmol/L)	r	N
Plasma (Dipotassium EDTA) vs Serum (no gel barrier)	y = 1.00x + 1 pg/mL (y = 1.00x + 0.118 pmol/L)	50-30,134 (5.90-3556)	1.000	50
Plasma (Lithium heparin) vs Serum (no gel barrier)	y = 1.00x + 4 pg/mL (y = 1.00x + 0.472 pmol/L)	57-30,390 (6.73-3586)	0.999	50
BD Vacutainer® SST™ Tube vs Serum (no gel barrier)	y = 1.00x - 2 pg/mL (y = 1.00x - 0.236 pmol/L)	54-30,122 (6.37-3554)	1.000	50
BD Vacutainer® RST™ Tube vs Serum (no gel barrier)	y = 1.00x + 4 pg/mL (y = 1.00x + 0.472 pmol/L)	53-30,237 (6.25-3568)	1.000	50

9.8 Expected Values

9.8.1 Reference Study Group

Expected values were established non- parametrically on the ADVIA Centaur XP system in accordance with CLSI Document EP28-A3c on a population of 723 apparently healthy subjects (362 females and 361 males) without HF.

Sex	Age (years)	N	Mean pg/mL (pmol/L)	SD pg/mL (pmol/L)	Median pg/mL (pmol/L)	95th Percentile pg/mL (pmol/L)	% < 125 pg/mL	% < 300 pg/mL
Male	<50	120	56 (6.61)	95.0 (21.2)	< 35 (4.13)	124 (14.6)	N/A[a]	97.5
	50-75	121	78 (9.20)	136.4 (16.1)	< 35 (4.13)	322 (38.0)	N/A[a]	94.2
	>75	120	56 (6.61)	50.6 (5.97)	< 35 (4.13)	154 (18.2)	N/A[a]	98.3
Female	<50	122	57 (6.73)	33.1 (3.91)	37 (4.37)	133 (15.7)	N/A[a]	100
	50-75	120	77 (9.09)	124.0 (14.6)	40 (4.72)	192 (22.7)	N/A[a]	97.5
	>75	120	89 (10.5)	216.4 (25.5)	43 (5.07)	178 (21.0)	N/A[a]	97.5
Overall	Overall	723	69 (8.14)	124.9 (14.7)	< 35 (4.13)	163 (19.2)	92.0	97.5

[a] The cut-off value is not applicable for the age group indicated.

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference interval for the diagnostic evaluation of patient results. Consider these values as guidance only.

*9.8.2 **Disease Study Group***

9.8.2.1 ED Population

Samples were obtained from 1148 patients (476 females and 672 males) that were adjudicated with a diagnosis of acute HF in the ED. ADVIA Centaur PBNPII values are presented for subjects with acute HF (ED Population- Disease Study Group) by subgroups based on age group and NYHA Functional Class. Each group of females and males was divided into three age groups as follows: < 50 years, 50-75 years and>75 years.

The data for the ED population with acute HF for combined male and female (All) is presented in this summary.

ED Population – All Subjects with Acute HF			
Age Group	**< 50 years**	**50–75 years**	**> 75 years**
Mean pg/mL (pmol/L)	6004 (708)	6820 (805)	8591 (1014)
SD pg/mL (pmol/L)	7601 (897)	8182 (965)	8984 (1060)
Median pg/mL (pmol/L)	3552 (419)	3677 (434)	5295 (625)
95th Percentile pg/mL (pmol/L)	25,401 (2997)	26,473 (3124)	34,451 (4065)
% > 300 pg/mL	94.3	95.0	98.4
% > 450 pg/mL	90.9	N/A*	N/A*
% > 900 pg/mL	N/A*	83.8	N/A*
% > 1800 pg/mL	N/A*	N/A*	85.8
N	230	481	437

* The cut-off value is not applicable for the age group indicated.

9.8.2.2 OP Population

Samples were obtained from 185 patients (102 females and 83 males) adjudicated with new onset of HF.

The data for the OP population with new onset of HF for combined male and female (All) is presented in this summary.

OP Population – All Subjects with Adjudicated New Onset HF		
Age Group	**≤ 75 years**	**> 75 years**
Mean pg/mL (pmol/L)	1313 (155)	2418 (285)
SD pg/mL (pmol/L)	3756 (443)	5536 (653)
Median pg/mL (pmol/L)	449 (53.0)	661 (78.0)
95th Percentile pg/mL (pmol/L)	4547 (537)	13,518 (1595)
% > 125 pg/mL	82.1	96.1
N	134	51

The NYHA classifications for the ED and OP population with acute HF for combined male and female (All) is presented in this summary.

NYHA Functional Class[a]	NYHA I	NYHA II	NYHA III	NYHA IV
Mean pg/mL (pmol/L)[b]	880 (104)	3340 (394)	7139 (842)	7466 (881)
SD pg/mL (pmol/L)	1161 (137)	6262 (739)	8480 (1001)	8277 (977)
Median pg/mL (pmol/L)	387 (46)	996 (118)	4018 (474)	4409 (520)
5th Percentile pg/mL (pmol/L)	135 (15.9)	73 (8.6)	261 (30.8)	449 (52.9)
95th Percentile pg/mL (pmol/L)	2612 (308)	17357 (2048)	29643 (3498)	30,824 (3637)
N	4[c]	265	573	474

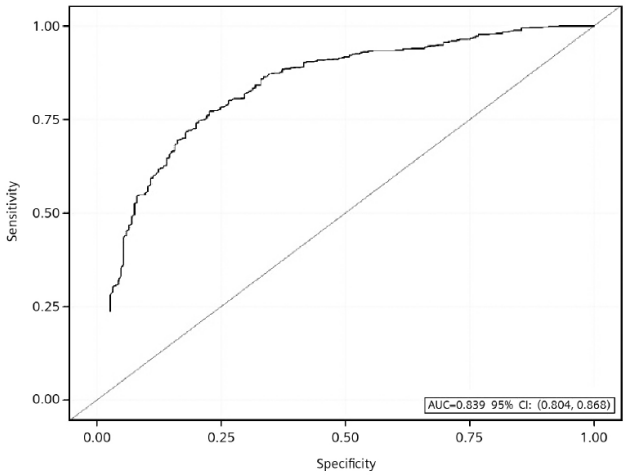
a Unable to determine NYHA classification for 16 subjects.

b p = <0.0001 for increasing mean NT-ProBNP concentration between NYHA Class II and NYHA Classes III and IV per Jonckheere-Terpstra. The mean NT-ProBNP concentration for NYHA Class III and Class IV are not statistically different.

c One male subject, identified as an outlier with an abnormally high NT-ProBNP concentration, was excluded from the NYHA I classification summary.

OP Population – Receiver Operating Characteristic Curve

The Receiver Operating Characteristic (ROC) curve presents the clinical sensitivity and specificity for the enrolled 185 subjects diagnosed with new onset HF and 848 subjects without HF. The area under ROC curve for the ADVIA Centaur PBNPII assay is 0.839 with a 95% confidence interval of 0.804 to 0.868.



9.9 Dilution Recovery

Samples that exceed the high end of the measuring interval may be diluted 1:5 and 1:10 with ADVIA Centaur Multi-Diluent 1 using automated dilution. The percent recovery of diluted samples up to 63,128 pg/mL (7449 pmol/L) ranged from 80.5% to 88.2% with a mean recovery of 83.9 %.

9.10 High Dose Hook

High NT-proBNP concentrations can cause a paradoxical decrease in the RLUs (high-dose hook effect). In this assay, patient samples with NT-proBNP concentrations above the measuring interval and as high as 300,000 pg/mL (35,400 pmol/L) will report >35,000pg/mL (4130 pmol/L).

9.11 Stability

The ADVIA Centaur NT-proBNP (PBNPII) reagents and calibrators are stable until the date printed on the box label when stored at 2-8°C.

The onboard stability and calibration interval of the ADVIA Centaur NT-proBNP (PBNPII) reagents is 36 days. The ADVIA Centaur PBNPII Calibrators are stable for 48 hours at 2-8°C and 31 days at ≤ -20°C after reconstitution. The Calibrators are stable onboard at Room Temperature for 6 hours.

9.12 Clinical Performance

9.12.1 ED Population

A total of 3128 subjects with signs and symptoms of acute HF who presented to the ED, were prospectively enrolled in a multi-site clinical evaluation of the ADVIA Centaur PBNPII assay. Diagnosis and severity of HF were determined by an independent central adjudication panel of expert clinicians (Cardiologists).1148 subjects were adjudicated as acute HF and 1980 subjects were adjudicated as without HF.

Clinical results were evaluated and Post-test risk (%), Positive Likelihood ratio (LR+), and respective two-sided confidence intervals (CI) were computed. Subgroup analyses were performed by using age group and sex.

Clinical Agreement between ADVIA Centaur PBNPII Results and Adjudicated Diagnosis Entire ED Population by Age Group with combined male and female (All) is presented in this summary:

Adjudicated Diagnosis									
Age Group (years)	**NT-proBNP**	**Rule-in Cutoff (**pg/ml)	**Positive**	**Negative**	**Total**	**Post-test Risk (%)**	**95% CI Post-test Risk (%)**	**LR+**	**95% CI LR+***
<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 = 25.3% (230/908)			

Adjudicated Diagnosis									
Age Group (years)	**NT-proBNP**	**Rule-in Cutoff (**pg/ml)	**Positive**	**Negative**	**Total**	**Post-test Risk (%)**	**95% CI Post-test Risk (%)**	**LR+**	**95% CI LR+***
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 = 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 = 47.6% (437/919)			

*Two-sided 95% score intervals will be presented for the percent risk and positive likelihood ratio estimates.

9.12.2 OP Population

A total of 1033 OP subjects with signs and symptoms of new onset HF were prospectively enrolled in a multi-site clinical evaluation of the ADVIA Centaur PBNPII assay. The clinical performance was assessed using a single cut-off value of 125 pg/mL.
Diagnosis and severity of HF were determined by an independent central adjudication panel of expert clinicians (Cardiologists).185 subjects were adjudicated as new onset HF and 848 subjects were adjudicated as without HF.

Diagnostic accuracy was computed as the Clinical Sensitivity, Clinical Specificity, Negative Predictive (NPV), and Positive Predictive (PPV).

The OP population clinical performance for All subjects is presented below:

Cut off Value	Sensitivity	Specificity	PPV	NPV
125 pg/mL	86.0% (159/185) (80.1%, 90.6%) *	64.3% (545/848) (60.9%, 67.5%) *	34.4% (159/462) (30.1%, 39.0%) *	95.5% (545/571) (93.4%, 97.0%) *

*Confidence Interval

The OP population clinical performance by sex and age group is presented 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%

*CI=Confidence Interval

10. Conclusions

ADVIA Centaur NT-proBNP II (PBNPII) assay is substantially equivalent in analytical performance to the currently marketed predicate device, the Roche Elecsys proBNP II assay cleared under 510(k) Number: K072437.