April 12, 2024

Beckman Coulter Inc.
Kate Oelberg
Senior Staff Quality and Regulatory Affairs
1000 Lake Hazeltine Drive
Chaska, Minnesota 55331

Re: K232164
Trade/Device Name: Access NT-proBNP
Regulation Number: 21 CFR 862.1117
Regulation Name: B-Type Natriuretic Peptide Test System
Regulatory Class: Class II
Product Code: NBC
Dated: March 15, 2024
Received: March 15, 2024

Dear Kate Oelberg:

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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 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,

Paula V. Caposino -S

Paula Caposino, Ph.D.
Acting Deputy 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)*
K232164

Device Name
Access NT-proBNP

Indications for Use *(Describe)*
The Access NT-proBNP assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of N-terminal pro B-type natriuretic peptide levels in human serum and plasma using the automated DxI Access Immunoassay Analyzers to aid in the following:
1. diagnosis of patients suspected of having acute heart failure in the Emergency Department
2. assessment of heart failure severity
3. risk stratification of patients with heart failure
4. risk stratification of patients with acute coronary syndrome

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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510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

510(k) Number: K232164 **Date Prepared:** April 12, 2024

Submitter Name and Address:
Beckman Coulter, Inc
1000 Lake Hazeltine Drive
Chaska, MN 55318

Primary Contact:
Kate Oelberg
Senior Staff Quality and Regulatory Affairs
Phone: (612) 431-7315
Email: kmoelberg@beckman.com

Alternate Contact:
Rachel Clark
Staff Regulatory Affairs Specialist
Email: rclark01@beckman.com
Phone: (336) 327-2336

Trade Device Name: Access NT-proBNP
Common Name: Access NT-proBNP
Classification name: B-Type natriuretic peptide test system
Classification Regulation: 21 CFR 862.1117
Classification Product Code*:* NBC

Predicate Device: Elecsys® proBNP II - k072437

Reference Device: VITROS® NT-proBNP II – k201312

Device Description

The Access NT-proBNP assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of N-terminal pro B-type natriuretic peptide levels in human serum and plasma using the automated DxI 9000 Access Immunoassay Analyzers to aid in the following: 1) diagnosis of patients suspected of acute heart failure in the Emergency Department, 2) assessment of heart failure severity, 3) risk stratification of patients with heart failure, 4) risk stratification of patients with acute coronary syndrome.

The Access NT-proBNP is a two-site immunoenzymatic (sandwich) assay. Paramagnetic particles coated with monoclonal anti-NT-proBNP antibody and monoclonal anti-NT-proBNP antibody conjugated to alkaline phosphatase are added to a reaction vessel along with a surfactant-containing buffer and serum or plasma sample. The human NT-proBNP binds to the anti-NT-proBNP antibody on the solid phase, while the anti-NT-proBNP antibody–alkaline phosphatase conjugate reacts with a different antigenic site on the NT-proBNP molecule. After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of analyte in the sample. Analyte concentration is automatically determined from a stored calibration.

Other items required to use the assay include calibrators, Lumi-Phos PRO, and wash buffer. The Access NT-proBNP reagent packs, Access NT-proBNP calibrators, along with the Access wash buffer, and Lumi-Phos PRO are designed for use on the DxI 9000 Access Immunoassay Analyzers in a clinical laboratory setting.

Intended use

The Access NT-proBNP assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of N-terminal pro B-type natriuretic peptide levels in human serum and plasma using the automated DxI Access Immunoassay Analyzers to aid in the following:

1. diagnosis of patients suspected of having acute heart failure in the Emergency Department
2. assessment of heart failure severity
3. risk stratification of patients with heart failure
4. risk stratification of patients with acute coronary syndrome

Table 1: Device Comparison

Device Characteristics	**New Device** Access NT-proBNP	**Predicate Device** Elecsys® NT-pro BNP II k072437	**Reference Device** VITROS® NT-proBNP II k201312	**Comment**
Intended Use / Indications for Use	Rx ONLY For *in vitro* diagnostic use only. The Access NT-proBNP assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of N-terminal pro B-type natriuretic peptide levels in human serum and plasma using the automated DxI Access Immunoassay Analyzers to aid in the following: 1. diagnosis of patients suspected of having acute heart failure in the Emergency Department 2. assessment of heart failure severity 3. risk stratification of patients with heart failure 4. risk stratification of patients with acute coronary syndrome	Rx ONLY For *in vitro* diagnostic use only. For the quantitative determination of N terminal pro-Brain natriuretic peptide in human serum and plasma. Elecsys® proBNP II 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. The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobas e immunoassay analyzers.	Rx ONLY For *in vitro* diagnostic use only. For the quantitative measurement of N-terminal pro Brain Natriuretic Peptide (NT-proBNP) in human serum and plasma (K_2 EDTA or Lithium Heparin) using VITROS 3600 Immunodiagnostic System to aid in the diagnosis of heart failure. The test can also be used in the assessment of heart failure severity in patients diagnosed with heart failure.	Similar
Analyte Measured	NT-proBNP	NT-proBNP	NT-proBNP	Same
Antibody	Monoclonal anti-NT-proBNP	Monoclonal anti-NT-proBNP	Monoclonal anti-NT-proBNP	Same

Device Characteristics	**New Device** Access NT-proBNP	**Predicate Device** Elecsys® NT-pro BNP II k072437	**Reference Device** VITROS® NT-proBNP II k201312	**Comment**
Sample Type	Human Serum and Plasma (Lithium Heparin and EDTA)	Human Serum and Plasma	Human Serum and Plasma	Same
Method	Automated Assay	Automated Assay	Automated Assay	Same
	The Access NT-proBNP assay is used in association with the automated DxI Access Immunoassay Analyzer	Elecsys and cobas e immunoassay analyzers	VITROS 3600 Immunodiagnostic System	Different
Format	Chemiluminescent	Electrochemiluminescent	Immunometric	Different
Assay Principle	Sandwich	Sandwich	Sandwich	Same
Measuring Range	10.0 ng/L – 35,000 ng/L (pg/mL)	5 – 35,000 pg/mL	20.0 -30,000 pg/mL	Similar
Traceability	The Access NT-proBNP Calibrator is traceable to manufacturer's working calibrators. Traceability process is based on EN ISO 17511	Standardized against the Elecsys NT-proBNP assay	Standardized against the Elecsys NT-proBNP II assay	There is no internationally recognized standard for NT-proBNP specific antibody. The Elecsys proBNP assay reference materials are proprietary to Roche Diagnostics.
High Dose Hook Effect	No high dose hook effect observed up to 400,000 ng/L (pg/mL)	Hook effect studies demonstrated no effect up to 300,000 pg/mL	no high dose hook effect up to a concentration of 300,000 pg/mL	Similar

<table>
<tr><th>Device Characteristics</th><th>New Device
Access NT-proBNP</th><th>Predicate Device
Elecsys® NT-pro BNP II
k072437</th><th>Reference Device
VITROS® NT-proBNP II
k201312</th><th>Comment</th></tr>
<tr>
<td>Reagent Storage and Stability</td>
<td>
<table>
<tr><th colspan="2">Access NT-proBNP
Reagent Stability</th></tr>
<tr><td>Unopened at 2 -10°C</td><td>Up to stated Expiration Date</td></tr>
<tr><td>After Opening at 2-10°C</td><td>61 days</td></tr>
<tr><td>On analyzer</td><td>61 days</td></tr>
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</td>
<td>
<table>
<tr><th colspan="2">Elecsys NT-proBNP II
Reagent Stability</th></tr>
<tr><td>Unopened at 2 -8°C</td><td>Up to stated Expiration Date</td></tr>
<tr><td>After Opening at 2-8°C</td><td>12 weeks</td></tr>
<tr><td>On analyzers</td><td>8 weeks</td></tr>
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<td>
<table>
<tr><th colspan="2">VITROS NT-proBNP II
Reagent Stability</th></tr>
<tr><td>Unopened 2-8°C</td><td>Expiration Date</td></tr>
<tr><td>Open on system</td><td>≤ 8 weeks</td></tr>
<tr><td>Opened 2-8°C</td><td>≤8 weeks</td></tr>
</table>
</td>
<td>Similar</td>
</tr>
<tr>
<td>Expected Values</td>
<td>See Table A. below</td>
<td>125 pg/mL for patients, 75 years;
450 pg/mL for patients ≥ 75 years</td>
<td>See Table B. below</td>
<td>Same for Access NT-proBNP and VITROS® NT-proBNP II
Different from Elecsys NT-proBNP II</td>
</tr>
</table>

Table A. Access NT-proBNP

Expected Values	All Subjects ng/L (pg/mL)			
Age (years)	**<50**	**50 - 75**	**>75**	**All ages**
N	267	256	152	675
Mean	48	94	158	90
SD	43	79	103	85
Median	37	69	129	64
IQR: 25th – 75th percentile	19 - 65	36 - 125	85 - 190	30 - 121
95th percentile ULN	118	273	413	252
97.5th percentile ULN	162	311	457	358
% <125 ng/L (pg/mL)	95.1%	75.0%	44.1%	76.0%

Table B. VITROS® NT-proBNP II

VITROS Expected Values				
Age	**Gender**	**N**	**RI Lower Limit (pg/mL)**	**RI Upper Limit (pg/mL)**
22-<50	Female	129	<20.0	95.3
50-<75	Female	127	<20.0	221
≥75	Female	129	<20.0	296
22-<50	Male	131	<20.0	125
50-<75	Male	120	<20.0	299
≥75	Male	123	<20.0	326
Overall		756	<20.0	217

Standard /Guidance Document Referenced

CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Third Edition
CLSI EP06-2nd Edition-: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – 2nd Edition
CLSI EP07 3rd Edition – Interference Testing in Clinical Chemistry Approved Guideline

Summary of Non-Clinical Studies

Imprecision

The assay was designed to have within-laboratory imprecision as listed below:

- ≤ 4.0 ng/L (pg/mL) SD at concentrations ≤ 50 ng/L (pg/mL)
- ≤ 8.0% CV at concentrations > 50 ng/L (pg/mL)

A study based on CLSI EP05-A3 performed on the DxI 9000 Access Immunoassay Analyzer tested multiple samples in duplicate in 2 runs per day for a minimum of 20 days.

Table 2: Access NT-proBNP Imprecision, DxI 9000

Sample	N	Mean (ng/L)	Repeatability (Within Run)		Between Run		Between Day		Within Laboratory precision	
			SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV	SD (ng/L)	%CV
Sample 1	86	31	0.7	2.3	0.5	1.5	0.7	2.2	1.1	3.5
Sample 2	84	129	2.9	2.2	7.2	5.6	0.0	0.0	7.8	6.0
Sample 3	83	266	5.3	2.0	15.8	5.9	0.0	0.0	16.7	6.3
Sample 4	84	377	7.7	2.0	25.3	6.7	0.0	0.0	26.4	7.0
Sample 5	85	1,777	45.1	2.5	63.2	3.6	44.5	2.5	89.5	5.0
Sample 6	86	12,076	225.5	1.9	638.0	5.3	0.0	0.0	676.7	5.6
Sample 7	86	26,126	534.1	2.0	1,418.9	5.4	1.5	0.0	1516.1	5.8

High Dose Hook Effect

The study was performed using samples containing increasing concentrations of NT-pro antigen in a range greater than > 400,000 ng/L exceeding the dose of the S6 Calibrator. Access NT-proBNP assay has no high dose hook effect observed up to 400,000 ng/L.

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ)

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) studies were conducted on the DxI 9000 Access Immunoassay Analyzer following CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition*. The LoB study included multiple reagent lots and 3 instruments for 3 days. The LoD and LoQ studies included multiple reagent lots and 3 instruments up to 5 days.

Table 4: Access NT-proBNP LoB, LoD and LoQ

	Maximum Observed Result	Design Criteria
	ng/L (pg/mL)	ng/L (pg/mL)
Limit of Blank (LoB)	1.1	<10.0
Limit of Detection (LoD)	4.8	≤10.0
Limit of Quantitation (LoQ) ≤ 20% within-lab CV	4.8	≤10.0

Linearity

A full range and a low range study was performed following a protocol based on CLSI guideline EP06-ED2. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.* All native patient samples from each sample type were run on DxI 9000 Access Immunoassay analyzer. The results demonstrate the Access NT-

proBNP assay is within ± 10% for values > 50 ng/L and is within ± 5.0 ng/L for values ≤ 50 ng/L. The assay demonstrates acceptable non-linearity across the analytical measuring range (10.0 -35,000 ng/L).

Matrix Comparison

Lithium heparin plasma and serum are preferred sample types. EDTA plasma is also an acceptable sample type. A sample type comparison study was performed on the Access NT-proBNP assay. The study included sixty-eight (68) matched serum, lithium heparin and EDTA plasma samples spanning the assay measuring range that were analyzed in replicates of three (3). The results of the study demonstrate all sample types are suitable for use on the Access NT-proBNP assay.

Interfering Substances

Lithium heparin plasma samples that contained NT-proBNP concentrations of approximately 125 and 1,800 ng/L (pg/mL) were spiked with the substances listed in Table 5. The spiked samples were run on the DxI 9000 Access Immunoassay Analyzer. The values were calculated based upon CLSI EP07-A3 guidelines. The interference was determined by testing controls (with no interfering substance added) and matched test samples (with interfering substance added). None of the compounds tested were found to cause significant interference (as defined by a shift in dose > 10%) using the test concentrations provided in the following table.

Table 5: Interfering Substances

Substance	Concentration	Substance	Concentration
(+)-cis-Diltiazem hydrochloride	120 ug/mL	Hydralazine	20 µg/mL
Acetaminophen	1456 umol/L	Hydrochlorothiazide	20 µg/mL
Alkaline Phosphatase	2000 U/L	Ibuprofen	2425 umol/L
Allopurinol	240 ug/mL	Indomethacin	36 µg/mL
Amiodarone	4.2 mg/dL	Intralipid	1600 mg/dL
Amlodipine besylate	4 ug/mL	Isosorbide dinitrate	0.593 mg/dL
Ampicillin	200 ug/mL	L-Ascorbic Acid	376 umol/L
Ascorbic acid	20 mg/dL	Levothyroxine	0.042 mg/dL
Atenolol	40 ug/mL	Lidocaine	1.5 mg/dL
Atorvastatin calcium trihydrate	32 ug/mL	Lisinopril x 2H2O	16 µg/mL
Bilirubin, conjugated	19 mg/dL	Losartan potassium	130 µmol/L
Bilirubin, unconjugated	15 mg/dL	Lovastatin	0.021 mg/dL
Biotin	30,000 ng/mL	Methyldopa sesquihydrate	100 ug/mL
Caffeine	10.8 mg/dL	Metoprolol hemitartrate	18.7 umol/L
Captopril	40 ug/mL	Naproxen sodium	2170 umol/L
Carvedilol	74 umol/L	Nicotine	1.6 µg/mL
Chloramphenicol	7.8 mg/dL	Nicotinic acid	40 µg/mL
Cholesterol	400 mg/dL	Nifedipine	36 ug/mL
Clopidogrel hydrogen sulfate	30 ug/mL	Nitrofurantoin	40 µg/mL
Creatinine	15 mg/dL	Oxazepam	12 µg/mL

Table 5: Interfering Substances

Substance	Concentration	Substance	Concentration
Cyclosporine	40 ug/mL	Oxytetracycline	100 µg/mL
Diclofenac sodium salt	60 ug/mL	Phenobarbital	69 mg/dL
Digitoxin	60 ug/mL	Phenytoin	6.00 mg/dL
Digoxin	0.0039 mg/dL	Probenecid	600 µg/mL
Disopyramide	1.68 mg/dL	Procainamide	4.80 mg/dL
Dobutamine	100 µg/mL	Propranolol	64 µg/mL
Dopamine hydrochloride	116 µg/mL	Quinidine	20 µg/mL
Dipyridamole	30 ug/mL	Ramipril	14.4 µmol/L
Enalaprilat dihydrate	16 ug/mL	Rheumatoid Factor	500 IU/mL
Erythromycin	13.8 mg/dL	Salicylic acid	200 ug/mL
Fenofibrate	45 µg/mL	Simvastatin	32 µg/mL
Fibrinogen	1000 mg/dL	Spironolactone	600 mg/dL
Furosemide	199 umol/L	Sulfamethoxazole	1.7 µmol/L
Hemoglobin	1000 mg/dL	Theophylline	6 mg/dL
Heparin	330 units/dL	Trasylol/Aprotinin	100 KIE/mL
Human anti-Mouse Antibodies (HAMA)	800 µg/L	Trimethoprim	64 µg/mL
Human gamma-globulin	30 g/L	Verapamil hydrochloride	96 ug/mL
Human Serum Albumin	60 g/L	Warfarin	7.5 mg/dL

Cross Reactivity

A study evaluated the potential for cross-reactivity of substances that are similar in structure to NT-proBNP. Lithium heparin samples that contain NT-proBNP concentrations of 125 ng/L (pg/mL) and 1,800 ng/L (pg/mL) were spiked with concentrations of the substances listed in Table 6. The spiked samples were run on the DxI 9000 Access Immunoassay Analyzer. The values were calculated based upon CLSI EP07-A3 guidelines. No significant cross-reactivity (>10%) was observed when the listed substances were tested at the indicated concentrations.

Table 6: Access NT-proBNP Cross Reactivity

Substance	High Concentration	Substance	High Concentration
Adrenomedullin	1.0 ng/mL	CNP_{22}	2.2 ug/mL
Aldosterone	0.6 ng/mL	Endothelin I	2000 pg/mL
Angiotensin I	0.6 ng/mL	NT-proANP$_{1-30}$ (preproANP$_{26-55}$)	3.5 ug/mL
Angiotensin II	0.6 ng/mL	NT-proANP$_{31-67}$ (preproANP$_{56-92}$)	1.0 ng/mL
Angiotensin III	1.0 ng/mL	NT-proANP$_{79-98}$ (preproANP$_{104-123}$)	1.0 ng/mL
ANP_{28}	3.1 ug/mL	Renin	50 ng/mL
Arg-Vasopressin	1.0 ng/mL	Urodilatin	3.5 ug/mL
BNP_{32}	3.5 ug/mL		

Expected Values

Each laboratory should validate or establish its own reference intervals to assure proper representation of specific populations.

A multicenter prospective reference interval study was conducted to establish the upper limit of normal (ULN) for Access NT-proBNP in a population of apparently healthy adults. A total of 306 males and 369 females were included with 39.6% < 50, 37.9% from 50 to 75, and 22.5% > 75 years of age.

Subjects were surveyed and were excluded if they met any of the following criteria:

- Disease(s) of/or affecting the cardiovascular system
- Poorly controlled hypertension (defined as current blood pressure ≥ 140 mm Hg systolic, or ≥ 85 mm Hg diastolic)
- Currently taking medication for cardiovascular disease (except medications to control hypertension)
- Body-mass index (BMI) ≥ 30 kg/m^2
- Diabetes
- Chronic kidney disease.
- Other serious chronic disease(s) (e.g. cancer, COPD, HIV, lupus erythematosus, etc.)
- Acute bacterial or viral infection

Additional surrogate biomarkers were screened, and subjects were also excluded based on abnormal estimated glomerular filtration rate (eGFR) and high-sensitivity cardiac troponin (hsTnI). Descriptive statistics for NT-proBNP concentrations are shown in Table 9.

Table 7: Access NT-proBNP Healthy population ULN and descriptive statistics

	All Subjects ng/L (pg/mL)			
Age (years)	**<50**	**50 - 75**	**>75**	**All ages**
N	267	256	152	675
Mean	48	94	158	90
SD	43	79	103	85
Median	37	69	129	64
IQR: 25th – 75th percentile	19 - 65	36 - 125	85 - 190	30 - 121
95th percentile ULN	118	273	413	252
97.5th percentile ULN	162	311	457	358
% <125 ng/L (pg/mL)	95.1%	75.0%	44.1%	76.0%
	Males ng/L (pg/mL)			
Age (years)	**<50**	**50 - 75**	**>75**	**All ages**
N	132	111	63	306
Mean	33	68	130	66
SD	38	71	82	72
Median	23	48	115	41
IQR: 25th – 75th percentile	13 - 39	28 - 77	77 - 148	20 - 84
95th percentile ULN	84	188	243	188
97.5th percentile ULN	103	284	434	267
% <125 ng/L (pg/mL)	99.2%	87.4%	58.7%	86.6%
	Females ng/L (pg/mL)			
Age (years)	**<50**	**50 - 75**	**>75**	**All ages**
N	135	145	89	369
Mean	63	114	178	111
SD	42	80	111	89
Median	54	91	154	82
IQR: 25th – 75th percentile	32 - 80	54 - 155	93 - 216	49 - 149
95th percentile ULN	152	282	443	294
97.5th percentile ULN	178	317	457	370
% <125 ng/L (pg/mL)	91.1%	65.5%	33.7%	67.2%

Clinical Performance Evaluation

Clinical Sensitivity

The Access NT-proBNP assay is not intended to be used in isolation; results should be interpreted in conjunction with other diagnostic tests and clinical information.

A multicenter prospective study was conducted to validate clinical performance of the established diagnostic cutoffs and evaluate the clinical utility of the Access NT-proBNP assay on the DxI 9000 Immunoassay Analyzer as an aid in the diagnosis of adults aged 21 and older presenting to the Emergency Department with a clinical suspicion of acute heart failure. NT-proBNP concentrations were determined in samples from 2,384 patients presenting to the Emergency Department with clinical suspicion of acute heart failure (AHF). Final diagnoses were adjudicated by an independent committee of medical doctors who decided on presence or absence of acute heart failure. Adjudicators were blinded to the Access NT-proBNP assay results. The AHF incidence was 44.4% (1059/2384) consisting of 48.2% Females (1149/2384) and 51.8% (1235/2384) Males, 57.8% White or Caucasian (1377/2384), 35.7% Black or African American (850/2384), and 6.5% Asian (155/2384). Two subjects did not have their races reported.

Descriptive statistics were determined by age group for the enrolled population and are presented below.

Table 8: Descriptive statistics for Access NT-proBNP concentrations (ng/L [pg/mL]) in patients Adjudicated as (AHF+ and AHF-)

	Adjudicated Acute Heart Failure (positive)				Adjudicated Acute Heart Failure (negative)			
Age (years)	**All ages**	**<50**	**50 - 75**	**>75**	**All ages**	**<50**	**50 - 75**	**>75**
N	1044	308	440	296	1324	569	469	286
Mean	5377	4119	5659	6266	1077	716	1009	1905
SD	5511	4868	5442	6008	2358	2226	2282	2537
Median	3,776	2,466	4,111	4,291	218	106	204	926
IQR: 25^{th} – 75^{th} percentile	1406–7483	959–5745	1539–8222	2077–8394	63–904	39–347	72–670	335–2325
Min	<10	< 10	33	188	< 10	< 10	< 10	16
Max	34,973	34,973	33,611	33,866	23,996	23,996	23,968	16,253

Note: A lesser N is observed in this table compared to the clinical performance data tables since only results based on measured responses within the assay analytical measuring range are used to generate descriptive statistics tables.

Table 9: Access NT-proBNP Test positive, grey zone, negative counts in relation to the adjudicated diagnosis of acute heart failure within each age group and by age group.

Age (Years)	Access NT-proBNP Test Result	Adjudicated Diagnosis		Total
		HF	Non-HF	
< 50	Positive	279	127	406
	Grey Zone	12	25	37
	Negative	19	417	436
	Total	310	569	879

Age (Years)	Access NT-proBNP Test Result	Adjudicated Diagnosis		Total
		HF	Non-HF	
50 -75	Positive	380	105	485
	Grey Zone	47	96	143
	Negative	19	268	287
	Total	446	469	915
> 75	Positive	240	94	334
	Grey Zone	59	132	191
	Negative	4	61	65
	Total	303	287	590
All	Positive	899	326	1225
	Grey Zone	118	253	371
	Negative	42	746	788
	Total	1059	1325	2384

The pretest probability of acute heart failure (prevalence of heart failure in the study based on the subject adjudicated diagnosis), posttest probabilities, likelihood ratios and the two-tailed 95% confidence interval of the Access NT-proBNP test result were determined across the age groups using the age-independent rule-out (300 ng/L) cutoffs and age-dependent rule-in (450 ng/L for subjects <50 years old; 900 ng/L for subjects 50-75 years old; 1800 ng/L for subjects >75 years old). *Table 10* displays data for all subjects by age group.

Table 10: Access NT-proBNP of all subjects (LiHep samples)

ALL Subjects Age, Prevalence, Test Result			Posttest Probability of HF		Posttest Probability of Non-HF		Likelihood Ratio and CI	
Age Group (Years)	**Pretest Probability of HF (Prevalence of HF in Study) (n/N)**	**Access NT-proBNP Test Result Interpretation**	**Estimate (%)**	**95% CI * (%)**	**Estimate (%)**	**95% CI* (%)**	**Likelihood Ratio Positive (HF)**	**95% CI**
< 50 years	35.3% (310/879)	Positive	68.7% (279/406)	(64.1-73.0%)	-	-	4.03	(3.44, 4.72)
		Grey Zone	32.4% (12/37)	(19.6-48.5%)	67.6% (25/37)	(51.5-80.4%)	0.88	(0.45, 1.73)
		Negative	-	-	95.6% (417/436)	(93.3-97.2%)	0.08	(0.05, 0.13)
50-75 years	48.7% (446/915)	Positive	78.4% (380/485)	(74.5-81.8%)	-	-	3.81	(3.20, 4.52)
		Grey Zone	32.9% (47/143)	(25.7-40.9%)	67.1% (96/143)	(59.1-74.3%)	0.51	(0.37, 0.71)
		Negative	-	-	93.4% (268/287)	(89.9-95.7%)	0.07	(0.05, 0.11)
>75 years	51.4% (303/590)	Positive	71.9% (240/334)	(66.8-76.4%)	-	-	2.42	(2.03, 2.88)
		Grey Zone	30.9% (59/191)	(24.8-37.8%)	69.1% (132/191)	(62.2-75.2%)	0.42	(0.33, 0.55)
		Negative	-	-	93.8% (61/65)	(85.2-97.6%)	0.06	(0.02, 0.16)
All Subjects	44.4% (1059/2384)	Positive	73.4% (899/1225)	(70.8-75.8%)	-	-	3.45	(3.13, 3.80)
		Grey Zone	31.8% (118/371)	(27.3-36.7%)	68.2% (253/371)	(63.3-72.7%)	0.58	(0.48, 0.71)
		Negative	-	-	94.7% (746/788)	(92.9-96.0%)	0.07	(0.05, 0.09)

*Wilson Score confidence intervals **log method confidence intervals

Sensitivity and specificity are also calculated and plotted in separate receiver operation curves (ROC) for both an overall age-independent analysis and individual age-dependent groups separately. Area under the curve (AUC) is also reported with 95% 2-sided confidence intervals. The ROC results for the Rule-Out sensitivity and 1-specificity data are provided in Table 12.

Table 11: The Area Under the Curve (AUC) for Rule-Out and Rule-In cutoffs with Upper / Lower CIs

Age Group	Area Under the Curve	Standard Error	Lower 95% CI	Upper 95% CI
All Subjects (Rule-Out)	0.8692	0.00729	0.8549	0.8835
< 50 years (Rule-In)	0.8919	0.0115	0.8694	0.9143
50-75 years (Rule-In)	0.8802	0.0113	0.8581	0.9024
> 75 years (Rule-In)	0.8122	0.0175	0.7779	0.8465

Access NT-proBNP Correlation to New York Heart Association (NYHA) functional classification in patients diagnosed with acute HF

There was an even distribution of classifications across the 1043 subject group adjudicated to acute HF with a clinical ED site NYHA evaluation and represents the accurate performance estimates for this claim. The population consisted of 450/1043 (43.14%) females and 593/1043 (56.86%) males. The descriptive statistics for the Access NT-proBNP results (ng/L) were determined across gender and are summarized in Table 12.

The JT test of trending was conducted on the 1043 all-subject group, resulting in a Z statistic of 4.1991 and a one-sided p-value <0.0001 indicating a significant trend relationship between NT-proBNP values and NYHA classification.

The JT test of trending was conducted on the 450 Female sub-group, resulting in a Z statistic of 3.2729 and a one-sided p-value 0.0005, indicating significant trend relationship between NT-proBNP values and NYHA classification.

The JT test of trending was conducted on the 593 Male sub-group, resulting in a Z statistic of 2.7120 and one-sided p-value 0.0033 indicating significant trend relationship between NT-proBNP value and NT-proBNP values and NYHA classification.

Table 12: Descriptive statistics of the clinical enrollment ED site NYHA classification in the subjects adjudicated as acute Heart Failure

Clinical ED Site NYHA Evaluation						
Group	**Statistics**	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**	**All HF**
All Subjects	N	91	271	485	196	1043
	Mean (ng/L)	3485	4718	5656	6460	5374
	SD (ng/L)	3499	4539	5939	6087	5513
	Median (ng/L)	2350	3547	3717	5073	3773
	5th Percentile (ng/L)	425	345	382	185	360
	95th Percentile (ng/L)	11643	13291	18446	18290	16302
Female	N	37	112	213	88	450

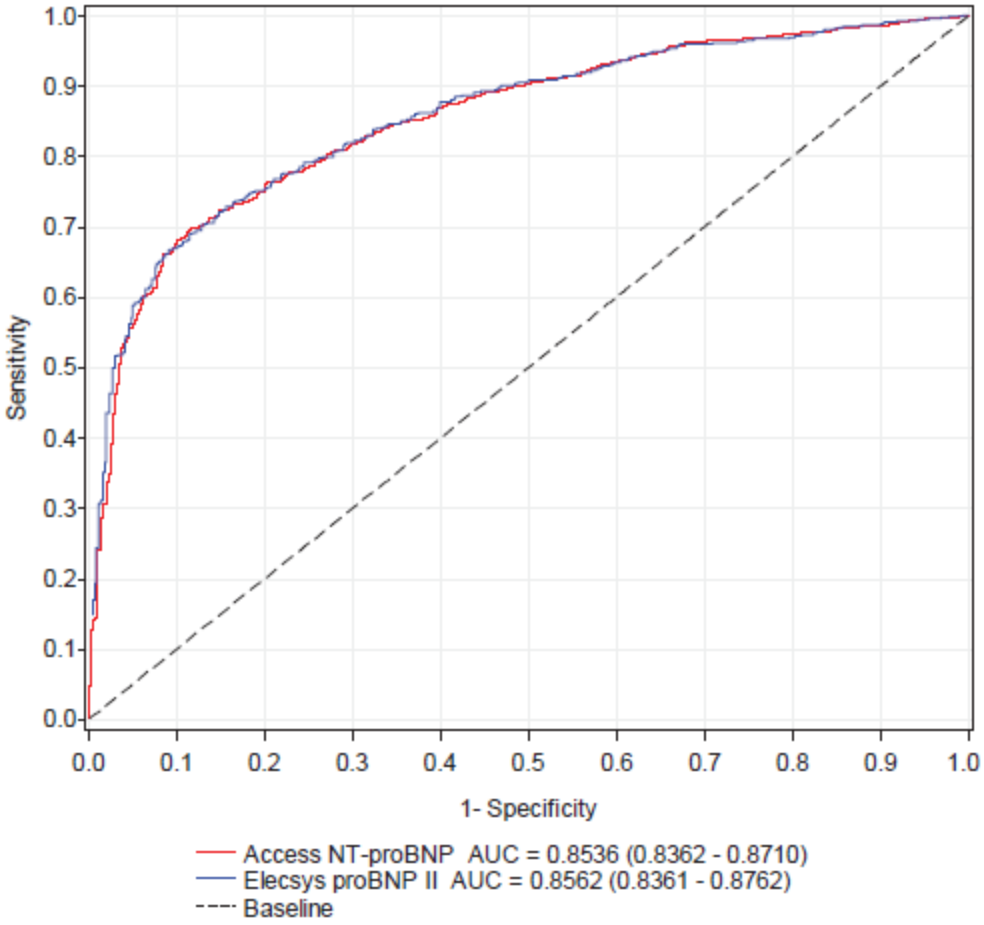
Clinical ED Site NYHA Evaluation						
Group	**Statistics**	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**	**All HF**
	Mean (ng/L)	2282	4659	5297	7206	5264
	SD (ng/L)	1857	4465	5987	7144	5795
	Median (ng/L)	1546	3698	3173	4533	3342
	5th Percentile (ng/L)	343	294	291	150	272
	95th Percentile (ng/L)	7384	12706	17152	26226	16481
Male	N	54	159	272	108	593
	Mean (ng/L)	4309	4761	5938	5852	5458
	SD (ng/L)	4093	4604	5896	5020	5293
	Median (ng/L)	2948	3422	4173	5149	4044
	5th Percentile (ng/L)	425	432	606	379	443
	95th Percentile (ng/L)	12527	13402	20869	14584	16047

Note: A lesser N is observed in this table compared to the clinical performance data tables since only results based on measured responses within the assay analytical measuring range are used to generate descriptive statistics tables.

Comparison to Other Commercially Available NT-proBNP Assays

Samples from the prospective multicenter study were also run on the Elecsys proBNP II assay (Roche Diagnostics) and Receiver Operating Characteristic (ROC) curves were generated for each assay, which are presented in the figure below. Area under the curve (AUC) for Access NT-proBNP was 0.8536 (95% CI: 0.8362 - 0.8710), demonstrating comparable diagnostic accuracy to the Roche Elecsys proBNP II assay [0.8562 (95% CI: 0.8361 - 0.8762)].

Figure 1: ROC Curves for Beckman Coulter Access NT-proBNP and Roche Elecsys proBNP II



Risk Stratification of Patients with Heart Failure and Acute Coronary Syndrome

An objective and systematic analysis of recent peer-reviewed literature and clinical practice guidelines was conducted to verify clinical performance supporting use of NT-proBNP for risk stratification. Prognostic utility was assessed in the following patient groups:

- Patients with heart failure
- Patients with Acute Coronary Syndrome

Based on peer-reviewed scientific papers, guidelines for an assay measuring the same analyte, and results from clinical performance studies, the measurement of NT-proBNP is recommended as an aid in risk stratification for patient groups listed in the previous paragraph. Studies have consistently demonstrated elevated NT-proBNP concentrations are correlated with increased incidence of cardiovascular events, mortality and composite outcomes.[1,2,3]

Conclusion

This submission provides clinical and nonclinical data to assure that the Access NT-proBNP assay is safe and effective for the stated intended use and is substantially equivalent to the cleared predicate and reference devices.

References

1. N-Terminal Pro-Brain Natriuretic Peptide and Other Risk Markers for the Separate Prediction of Mortality and Subsequent Myocardial Infarction in Patients with Unstable Coronary Artery Disease, GUSTO IV Substudy, James, S.K. et al, Circulation 2003108: 275-281.
2. N-Terminal Pro-Brain Natriuretic Peptide on Admission for Early Risk Stratification of Patients with Chest Pain and No ST-Segment Elevation, Jernberg, T. et al. Journal of the American College of Cardiology Vol 40, No. 3, 2002: 437-445.
3. N-Terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure. Fisher, C. et al. Heart 2003; 89:879-881.